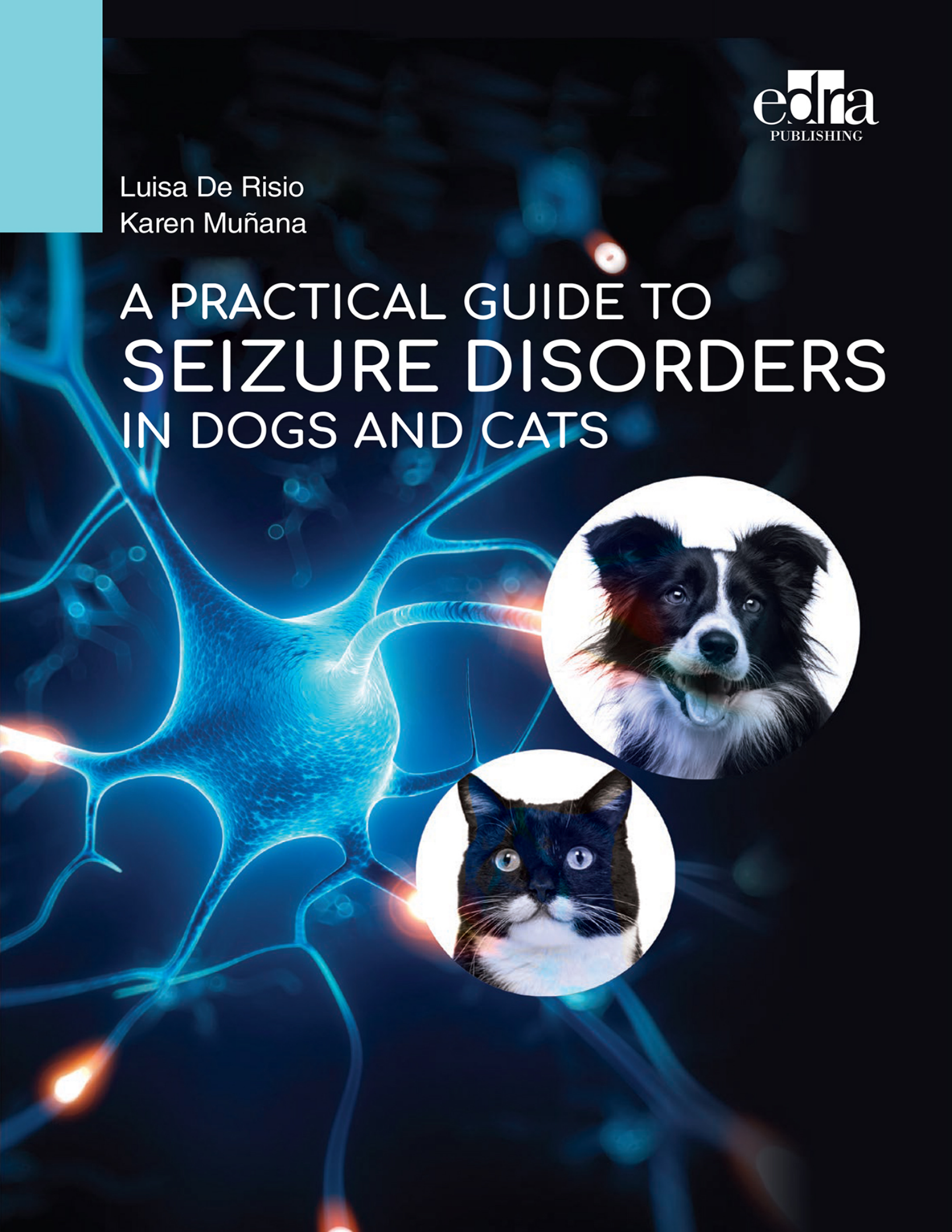
Luisa De Risio
Karen Muñana

A PRACTICAL GUIDE TO SEIZURE DISORDERS IN DOGS AND CATS



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Luisa De Risio, Karen Muñana
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Preface

Seizure disorders are commonly encountered in small animal practice. The goal of this book is to provide a comprehensive, evidence-based resource to assist in the successful management of recurrent seizures in dogs and cats. Practical information on every aspect of seizure management is presented and is supported with a review of the available literature.

The book's format is designed to provide a logical, clinically relevant approach to the seizure patient, with in-depth information on the broad range of topics involved in the diagnosis and treatment of seizure disorders in dogs and cats. The first five chapters describe the clinical and diagnostic approach to the seizure patient, and include thorough descriptions of seizure classification with video case examples, canine idiopathic epilepsy, the genetics of epilepsy, feline epilepsy and quality of life. There are separate chapters devoted to advanced imaging and electroencephalography, both of which contain numerous images to complement the discussion of the material. The remaining chapters focus on epilepsy treatment and include a review of general treatment guidelines and pharmacological principles, as well as a comprehensive review of antiseizure drugs, adjunctive therapies for drug-resistant epilepsy, and the management of cluster seizures and status epilepticus in dogs and cats.

The 19 book chapters are authored by veterinary specialists from around the globe. Algorithms are included throughout the book, and each chapter contains a summary of key points, providing easy access to information to support clinical decision making and patient care. Our aim was to create a comprehensive reference that would be of value to primary care veterinarians, veterinary students, interns, residents, and veterinary specialists alike.

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The Clinical and Diagnostic Approach to the Seizure Patient

01

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When presented with a patient with a history of seizures, the clinician needs to determine the nature and the cause of the paroxysmal events. Episodic abnormalities of behavior, mentation, muscle tone, posture and/or movements may or may not be seizural in origin. A systematic approach including an accurate medical history, a thorough understanding of the episode phenomenology, physical and neurological examination and relevant diagnostic investigations can help establish if the episodes are seizures, either epileptic or reactive, or a nonepileptic paroxysmal event. Sometimes clarifying the nature of the paroxysmal events can be challenging even after extensive diagnostic investigations. Reaching a diagnosis of the nature of the paroxysmal events and of their etiology is important to establish the most appropriate treatment and prognosis and set achievable expectations of the pet's caregiver from the onset. This has a significant impact on the pet's and caregiver's quality of life (see Chapter 3).

TERMINOLOGY

The following definitions have been developed based on several human and veterinary references,[1–4] which can be consulted for additional details on seizure-related terminology.

The term **seizure** refers to any sudden, short-lasting and transient event (i.e., episodic abnormality of behavior, mentation, muscle tone, posture and/or movements). It does not imply that the event is epileptic in nature.

- A **reactive seizure** is a seizure occurring as a response of a healthy brain to a transient alteration in function due to a metabolic, nutritional or exogenous toxic disorder. Normal cerebral function can be restored when the disturbance is rectified. The terms "provoked seizure" or "acute symptomatic seizure" have been used as synonyms for reactive seizure.
- An **epileptic seizure** is a transient occurrence of signs (motor, autonomic or behavioral) due to abnormal excessive and/or synchronous epileptic neuronal activity in the brain, which can be caused by a variety of underlying etiologies (such as idiopathic and structural epilepsy). The excessive and/or synchronous epileptic activity of neurons and neuronal networks in the brain is usually self-limiting. The resulting clinical signs can vary. Motor signs can involve part (focal epileptic seizure) or all (generalized epileptic seizure) of the body.

Epilepsy is defined as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is practically applied as the occurrence of two or more unprovoked epileptic seizures at least 24 hours apart.

- **Structural epilepsy** refers to epilepsy caused by intracranial/cerebral structural pathology including vascular, inflammatory/infectious, traumatic, anomalous/developmental, neoplastic and degenerative diseases.
- **Idiopathic epilepsy (IE)** has been defined as epilepsy of known genetic or presumed genetic origin in animals with an anatomically normal brain. The term IE has also been used to refer to epilepsy in which the nature of the underlying cause is as yet unknown following exclusion of structural epilepsy and reactive seizures in dogs with epileptic seizure onset between 6 months and 6 years of age. A similar age range may apply to cats. The subclassification of IE is detailed in Chapter 2, Fig. 2.1.

Motor seizures involve musculature in any form. The motor event could consist of an increase or decrease in muscle contraction to produce a

movement.

- **Tonic:** characterized by a sustained increase in muscle contraction lasting a few seconds to minutes.
- **Dystonic:** characterized by sustained contractions of both agonist and antagonist muscles that can produce abnormal movements and/or postures.
- **Myoclonic** (adjective); **myoclonus** (noun): sudden, brief (<100 milliseconds) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (Video 1.1).
- **Clonic:** characterized by myoclonus that is regularly repetitive, involves the same muscle groups, at a frequency of ~2–3 contractions per second, and is prolonged. Appears as rhythmical jerking movements caused by repeated contraction and relaxation of the muscles involved.
- **Tonic-clonic:** characterized by a sequence consisting of a tonic phase followed by a clonic phase. Variants such as clonic-tonic-clonic seizures may be seen.
- **Atonic:** characterized by a sudden loss or diminution of muscle tone with no apparent preceding myoclonic or tonic event that lasts 1 to 2 seconds and involves the head, trunk, jaw, or limb musculature. Atonic seizures have also been referred to as "drop attacks" when the sudden and general loss of muscle tone results in the animal's collapse (Video 1.2).
- **Automatism:** a more or less coordinated, repetitive, motor activity usually occurring when consciousness is impaired. The following adjectives are usually employed to further characterize the type of automatism:
  - **Oroalimentary:** characterized by lip smacking, chewing, licking, tooth grinding, or swallowing (Video 1.3)

Myoclonic seizure in a 7-year-old female neutered Shetland Sheepdog diagnosed with idiopathic epilepsy at 2 years of age.

Video 1.1.



Atonic seizure in a 2-year-old male Labrador Retriever mix. This dog also had generalized tonic-clonic seizures.

Video 1.2.



Oroalimentary automatism, rhythmic facial muscle contractions and hypersalivation in an 11-month-old, female Boxer. This dog was diagnosed with severe encephalitis.

Video 1.3.



Pedal automatism during a generalized seizure in an Italian Spinone with idiopathic epilepsy.

Video 1.4.



- **Pedal:** characterized by running movement (Video 1.4)

Convulsion: this is primarily a lay term used to indicate episodes of excessive, abnormal muscle contractions, usually bilateral, which may be sustained or interrupted.

Epileptic spasm: a sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not as sustained as in a tonic seizure (i.e., ~1 second). Selected muscles can be affected resulting in head nodding or grimacing. Epileptic spasms frequently occur in clusters.

Sensory seizure: a perceptual experience not caused by appropriate stimuli in the external world. A sensory seizure can be **hallucinatory** when it is characterized by a creation of composite perceptions without corresponding external stimuli involving visual, auditory, somatosensory, olfactory, and/or gustatory phenomena. For example, seeing things or hearing sounds that are not there (Video 1.5). Animals cannot report what they are experiencing, therefore sensory seizures are challenging to recognize unless the animal displays paroxysmal episodes of abnormal behaviors such as chasing imaginary objects. Sensory seizures can be challenging to differentiate from compulsive behavior disorders or episodes of pain.

Autonomic seizures are characterized by involvement of the autonomic nervous system, which manifests in companion animals as increased salivation, involuntary urination and/or defecation, mydriasis and vomiting.

Focal epileptic seizures are characterized by lateralized and/or regional signs (motor, autonomic or behavioral signs, alone or in combination). Motor signs may include facial muscle twitching (see Video 1.3), repeated jerking head movements, rhythmic blinking, or repeated rhythmic jerks of one extremity. Autonomic signs can include mydriasis, hypersalivation or vomiting. Behavioral signs can include a brief episode of altered behavior such as anxiousness, restlessness, unexplainable fear reactions or aggression. Consciousness can be impaired, although this may be challenging to ascertain. Focal seizures can evolve into generalized seizures.

Generalized epileptic seizures are characterized by involvement of both sides of the body (Videos 1.6 and 1.7). Generalized epileptic seizures can occur from the onset of the ictus, or can evolve from a focal epileptic seizure. Bilateral motor manifestations in dogs and cats with generalized epileptic seizures are most commonly tonic, clonic or tonic-clonic, but can also be myoclonic or atonic. With the exception of myoclonic seizures (see Video 1.1), consciousness impairment and autonomic signs (i.e., increased salivation, involuntary urination and/or defecation, mydriasis and vomiting) often occur in animals with generalized epileptic seizures.

- **Generalized tonic-clonic seizure** (formerly referred to as “grand mal” seizure): bilateral symmetrical tonic contraction followed by bilateral

clonic contractions of somatic muscles, usually associated with autonomic signs.

Suspected sensory (hallucinatory) seizure in a 4-year-old Border Collie cross. During the episode the dog does not respond to his owner who is repeatedly calling his name and trying to distract him. The dog continues to chase imaginary objects. The dog was neurologically normal (hearing and vision included) between episodes.

Video 1.5.



Generalized tonic-clonic seizure in a 1.5-year-old British Shorthair cat with unremarkable interictal neurological examination, laboratory investigations (on blood, urine and cerebrospinal fluid) and magnetic resonance imaging of the brain.

Video 1.6.



Generalized tonic-clonic epileptic seizures with loss of consciousness, hypersalivation and involuntary urination in a Boxer.

Video 1.7.



Cluster seizures are defined clinically as the occurrence of ≥2 seizures within a 24-hour period with complete recovery of consciousness between seizures.

Status epilepticus is defined clinically as >5 minutes of continuous seizure activity or ≥2 discrete seizures between which there is incomplete recovery of consciousness.

Reflex epileptic seizures are epileptic seizures that are objectively and consistently elicited by a specific stimulus (such as flashing or flickering lights, or a particular sound) or by activity (e.g., movement) of the patient.

Provocative factor: transient and sporadic endogenous or exogenous element capable of increasing epileptic seizure incidence in the patient with chronic epilepsy and evoking seizures in susceptible nonepileptic individuals.

PHASES ASSOCIATED WITH A SEIZURE

In dogs and cats with seizures, either epileptic or reactive in nature, the following three phases can be recognized: the prodrome, the ictus and the postictal phase (Fig. 1.1).

The **prodrome or preictal phase** lasts hours to days and it is not always observed by the pet owner. When present, it is characterized by a change in disposition that can manifest as reluctance to perform normal activities, restlessness, anxiousness, fearful behavior, attention-seeking, increased affection, withdrawal, hiding (particularly in cats) or uncharacteristic aggression. People with epilepsy may report experiencing days of irritability, withdrawal or other emotional aberrations during the prodrome. In an online cross-sectional survey of 229 owners of dogs with IE, nearly two-thirds (65%) of owners observed prodromal (preictal) signs in their dogs. The top three behavioral changes that were reported spontaneously (i.e., without prompts) as seizure predictors by the epileptic dog owners included restlessness (29%), clinginess (25%) and fearful behavior (12%).[5] When behavioral alterations are consistently identified by the pet owner prior to the ictus, they can represent an indicator of a forthcoming seizure and therefore provide a potential important therapeutic window for pulse therapy with fast-acting antiseizure drugs (ASDs) such as levetiracetam (see discussion of pulse therapy in Chapter 12).

The **ictus** lasts seconds to a few minutes (in self-limiting seizures) and is characterized by alterations of consciousness, behavior, motor activity, and

autonomic signs due to an imbalance between excitatory and inhibitory neurotransmission in the brain. The clinical manifestations of the ictus can be highly variable, sometimes making it challenging to determine the nature of the paroxysmal events without simultaneous electroencephalographic (EEG) evidence of seizure activity (see Chapter 7). The ictus may consist of a generalized epileptic seizure alone, a focal epileptic seizure alone, or a focal epileptic seizure which evolves into a generalized epileptic seizure. The focal onset of the seizure is often very brief and may not be detected or reported by the pet owner, unless specific questions are asked (see Fig. 1.2) and/or video footage is obtained from the very onset of the seizure. Consciousness is often impaired during the ictus in animals with generalized seizures and can also be affected with focal seizures. Autonomic manifestations such as involuntary urination, defecation, increased salivation, vomiting and mydriasis can occur in isolation or in association with motor and sensory signs. The ictus can also be characterized by abnormal behavior secondary to epileptic activity in the limbic system or in sensory areas of the brain (for example, the animal may experience what a person may describe as hallucinations).

The **postictal phase** occurs soon after the ictus and can last seconds to days and be characterized by one or more of the following clinical manifestations: disorientation, compulsive locomotion, blindness, inability to avoid obstacles, ataxia, proprioceptive deficits (e.g., spontaneous knuckling and delayed paw replacement response), repetitive vocalization, hunger, thirst, defecation, urination, fatigue, deep sleep, and uncharacteristic aggression.

Recognition of a pre- and/or postictal phase, occurrence of autonomic manifestations, rhythmic muscle contractions, oroalimentary and pedal automatisms, and impairment of consciousness can help to discriminate epileptic and reactive seizures from nonepileptic paroxysmal events. Epileptic seizures often arise in a spontaneous unpredictable fashion without detectable precipitating factors. However, in certain conditions they can be triggered by certain recognizable stimuli.[6–8] Epileptic seizures are generally self-limiting and last seconds to less than 5 minutes.

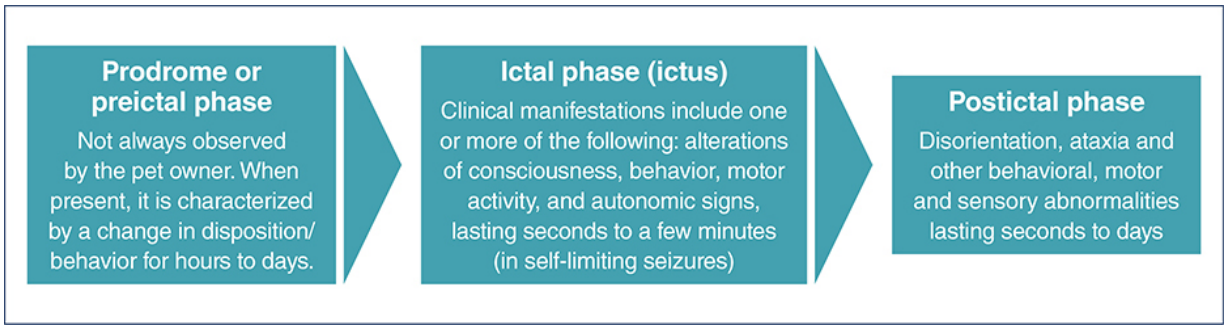


FIGURE 1.1. Phases associated with a seizure.

DISORDERS THAT CAN MIMIC SEIZURES AND DISCRIMINATORS

There are a range of conditions resulting in recurrent paroxysmal events that may be misdiagnosed as epileptic seizures. These include:

- Paroxysmal dyskinesias
- Syncope
- Compulsive behavior disorders
- Sleep disorders
- Episodic pain associated behavior
- Episodic vestibular dysfunction
- Neuromuscular disorders

Paroxysmal dyskinesias (PxDs) (also known as **movement disorders**) are a heterogeneous group of disorders in humans and animals characterized by recurrent episodes of sudden, abnormal, involuntary, sustained muscle contraction resulting in abnormal postures and movements (Videos 1.8, 1.9 and 1.10).[9–11] Consciousness remains normal during the episode and the animal may attempt to continue the activity it was performing prior to the episode onset (Videos 1.8 and 1.9). Typically autonomic, pre or postictal signs are not present. However, borborygmi, and sometimes also vomiting and diarrhea have been reported during or in the proximity of the episodes in Border Terriers with PxDs. Their duration can vary from seconds to hours (usually 2–30 minutes). The onset and end of

the movement disturbance are often abrupt. Episodes can occur in clusters over 24–48 hours.

Paroxysmal dyskinesias can be inherited or acquired and can be primary or secondary to various underlying disorders.[9] Patients with primary PxDs have normal neurological examinations between episodes. The clinical diagnosis is based on episode description, direct observation or video recording of episodes, and the exclusion of other neurological conditions by diagnostic investigations similar to those detailed below for the investigation of IE.

Episode of paroxysmal dyskinesia in a 2.5-year-old Border Terrier. Note that the dog is seeking the owner's reassurance despite the difficulty walking due to the appendicular and epaxial muscle spasticity.

Video 1.8.



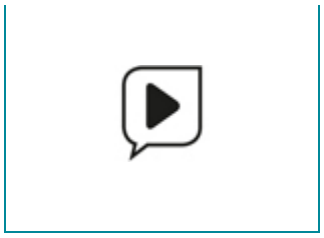
Episode of paroxysmal dyskinesia in a 3-year-old Norwich Terrier. Note the increased muscle tone in the appendicular, epaxial (particularly lumbar) and coccygeal muscles. The dog is still able to walk during most of the episode and go to his bed.

Video 1.9.



Episode of paroxysmal dyskinesia in a 2-year-old Labrador Retriever. The dog is unable to stand up but appears aware of the owner's reassurance.

Video 1.10.



Primary PxDs have been recognized with increasing frequency in various canine breeds and a characteristic age at onset, episode phenomenology, duration and frequency, clinical course, and response to treatment have been reported.[9] In the majority of PxDs described in dogs to date, ASDs are not efficacious in reducing episode frequency and severity. A retrospective study of Labrador Retrievers and Jack Russell Terriers with PxD reported a spontaneous decrease in episode frequency and duration in 86% Labradors and 57% Jack Russell Terriers.[12] The median follow-up time was 7 years and the dogs received no medications. Spontaneous remission occurred in 39% of Labradors and 22% of Jack Russell Terriers, and was lower in dogs with cluster episodes than those without. An association with gluten-sensitivity and remission following switching to a gluten-free diet has been reported in the Border Terrier.[13] A genetic basis of PxD has been identified in the Cavalier King Charles Spaniel,[14] the Soft-Coated Wheaten Terrier[15] and the Shetland Sheepdog[16]. Genetic testing may enable the clinician to achieve a rapid, noninvasive and cost-effective diagnosis of PxD in an increasing number of canine breeds in the future.

A detailed review of PxD as well as other events which can mimic epileptic seizures is beyond the scope of this chapter and can be found elsewhere.[4,9–11]

Syncope: transient loss of consciousness secondary to an abrupt reduction in blood flow and oxygen supply to the brain. Often associated with exercise or excitement. Muscle tone is characteristically flaccid (Video 1.11), but muscle rigidity or tonic-clonic movements can occur. Mucous membrane cyanosis and abnormalities of heart rate and rhythm may occur during the episode. The medical history and physical examination may reveal respiratory and/or cardiovascular signs. Episodes generally last ≤60 seconds. Seizure-like episodes characterized by collapse have been reported in cats with intermittent atrioventricular block.[17]

Compulsive behavior disorders. Compulsive behavior disorders can result in various types of episodic abnormal behavior including: aggression

directed at part of the pet's own body, other pets, people or objects; compulsive barking/meowing/whining/howling; circling, tail chasing, pacing (Video 1.12); self-licking, air or nose licking, flank sucking; staring at, chasing or attempting to catch shadows/imaginary objects. Consciousness is preserved; however, the animal may appear less responsive than normal. There are no autonomic, pre or postictal signs. Episodes can last seconds to hours. Animals can generally be distracted (by sound or tactile stimulus) to stop (at least transiently) the episode of abnormal behavior.

Sleep disorders

- **Narcolepsy-cataplexy:** consciousness is normal in animals that experience only cataplexy (i.e., sudden loss of postural tone and flaccid paralysis) and absent in animals that concurrently have narcolepsy (i.e., they suddenly fall asleep). There are no autonomic signs. The episodes, which can occur multiple times a day, are frequently induced by excitement such as eating or playing (Video 1.13) and can be reversed by verbal or tactile stimuli. Episodes last seconds to several minutes. Between episodes the animal often experiences excessive daytime sleepiness and fragmented sleep patterns.

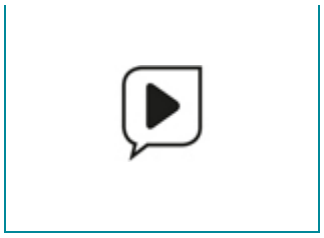
Suspected syncopal episode in an 8-year-old female neutered Goldendoodle with a history of episodic collapse and heart disease.

Video 1.11.



Compulsive behavioral disorder in 1-year-old female Cavalier King Charles Spaniel.

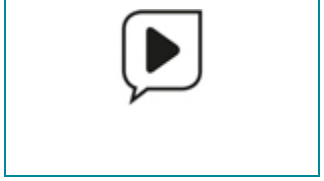
Video 1.12.



- **Rapid-eye-movement (REM) sleep disorder** (Video 1.14): abnormal and excessive manifestation of dream activity during the REM phase of sleep characterized by twitching, violent running movements, chewing, teeth grinding and vocalization. Most dogs can easily be woken up and are alert after arousal. These episodes can occur multiple times during sleep at night and during daytime naps. There are no autonomic signs. REM sleep disorder has been reported in dogs that recovered from tetanus.[18]
- As in people, it is likely that animals experience other types of sleep disorders that have not been characterized yet and may mimic epileptic seizure activity.

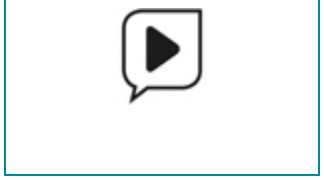
Episode of cataplexy-narcolepsy in a young Dogo Argentino, soon after playing and eating grass.

Video 1.13.



Rapid-eye-movement sleep behavior disorder in a 5-year-old Weimaraner. The episode is happening while the dog is sleeping at night.

Video 1.14.



Episodic pain-associated behavior: episodic pain caused by various conditions can result in paroxysmal episodes of abnormal behavior and posture. There are no autonomic signs and consciousness is preserved; however, due to the intense pain the animal may be mydriatic and less responsive than usual. Episodes can last seconds to hours and may occur multiple times a day. For example, a "stargazing" behavior manifested as upward extension of the head and neck has been observed in dogs (particularly of brachiocephalic breeds) with reflux esophagitis +/- gastritis[19, LDR's personal observation] (Video 1.15).

Episodic vestibular dysfunction is characterized by transient vestibular signs such as head tilt, nystagmus, ataxia and falling to the side. Attempts to stand up may be misinterpreted as limb paddling during an epileptic seizure (Video 1.16). Consciousness can be challenging to assess if the animal is distressed. Mydriasis can occur due to stress during the episode and vomiting can occur as part of the vestibular signs. Episodes can last seconds to hours.

Neuromuscular disorders can result in episodic loss of postural tone (collapse), typically following physical activity. The gait can become rigid and short-strided just before the collapse. The muscular contractions associated with myokimia can also be misinterpreted as a focal seizure (Video 1.17). Consciousness remains normal (unless impaired by respiratory compromise) and autonomic signs do not occur during neuromuscular collapse. Regurgitation, dysphagia, and dysphonia can occur anytime in animals with various neuromuscular disorders. Regurgitation should not be confused with vomiting and drooling excessive saliva due to dysphagia should not be confused with hypersalivation due to epileptic autonomic signs. Episode duration can vary from seconds to hours.

The disorders listed above should be considered during the investigation of the seizure patient. In people, there are conditions in which epileptic and nonepileptic paroxysmal events can coexist in the same individual. This may also be the case in veterinary patients.

Factors that can help in differentiating seizures, either epileptic or reactive, from nonepileptic paroxysmal episodes include:

Episode of "stargazing behavior" in a 1-year-2-month-old Pug. The episodes lasted seconds to a few minutes, occurred several times a day and resolved following treatment with omeprazole.

Video 1.15.



Vestibular signs in a dog with metronidazole toxicity.

Video 1.16.



Myokymia in a 7-year-old male neutered Chihuahua. The involuntary rippling movement of left facial muscles was reported to be continuous over several months, which helps to differentiate this from a focal seizure.

Video 1.17.



- Precipitating event or trigger
- Pre-event signs
- Event phenomenology
- Level of consciousness
- Autonomic signs
- Muscle tone (spastic vs. flaccid)
- Type of movements (rhythmic or not; oroalimentary/pedal automatisms or not)
- Lateralizing signs
- Willingness to continue the intended activity
- Ability to terminate the episode with verbal or tactile stimuli

- Duration
- Postevent signs

Generally, a pre- and postictal phase and autonomic signs do not occur during the nonepileptic paroxysmal events listed above. Except for syncope or other cardiovascular/respiratory disorders resulting in an abrupt reduction in oxygen supply to the brain, consciousness is unaffected.

An overview of "epilepsy imitators" in people can be found at www.epilepsydiagnosis.org/epilepsy-imitators.html. Interestingly, also in human neurology a thorough medical history is considered the key to a correct diagnosis along with video recordings of the paroxysmal events.

SYSTEMATIC DIAGNOSTIC APPROACH TO THE PATIENT WITH A SEIZURE DISORDER

Medical history

A detailed and accurate medical history is an essential element in the clinical management of the seizure patient (Fig. 1.2). In addition to the standard medical history information, seizure-disorder specific questions should be asked, including a detailed description of the paroxysmal event and what happens preceding and following the event. A standardized seizure disorder questionnaire can be provided to the pet owner prior to an elective consultation to enable completion at their convenience (Fig. 1.3). The clinician can review the questionnaire responses prior to the consultation and focus the discussion on the aspects that are most relevant to the individual patient. Alternatively, the seizure disorder questionnaire can be completed during the consultation with the support of veterinary professionals. Video footage of the clinical manifestations that occur during the paroxysmal event should be obtained whenever possible and carefully reviewed. Investing time in these fundamental steps can make a significant difference in the care of the seizure patient.

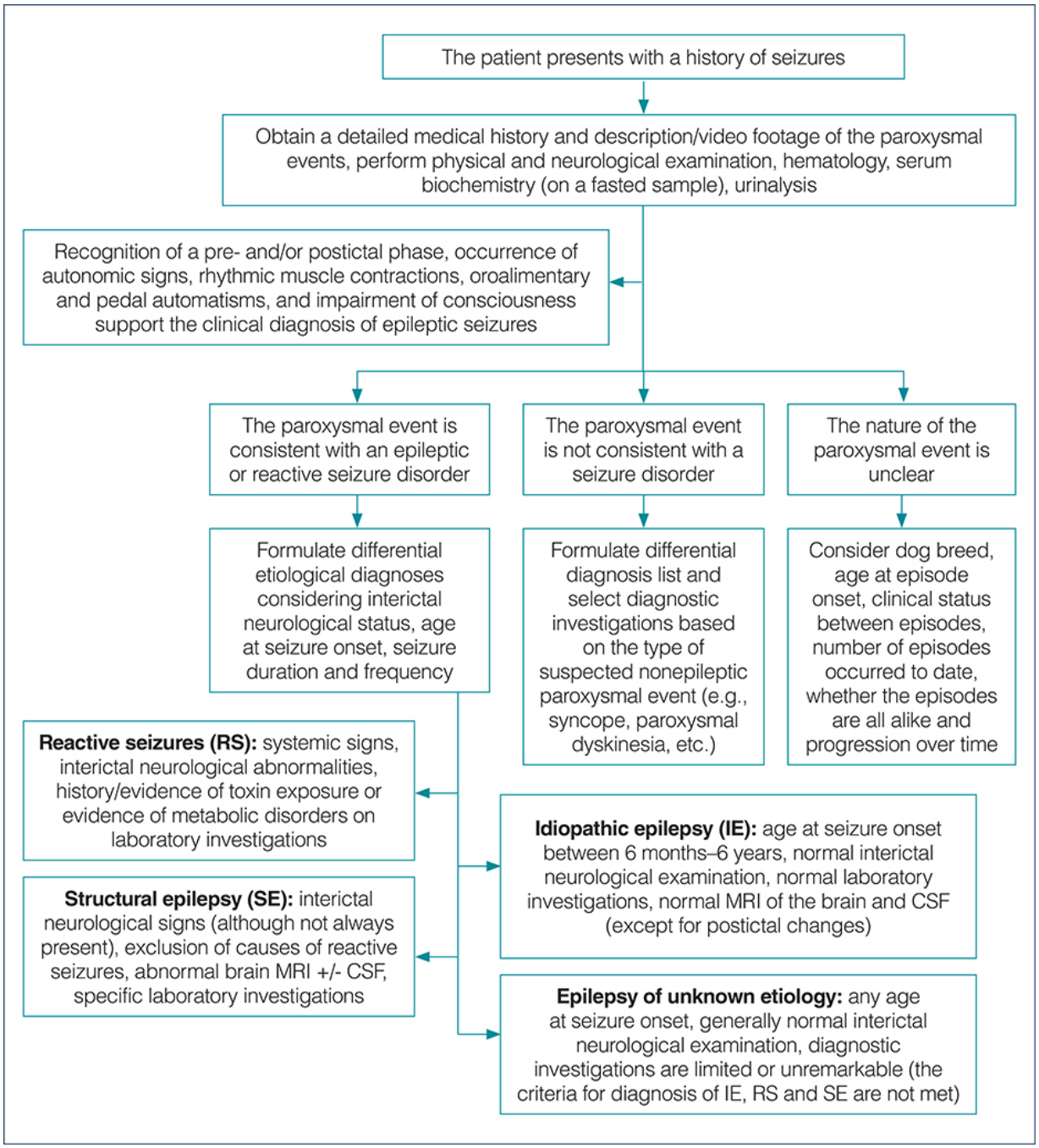


FIGURE 1.2. Algorithm outlining the clinical approach to the seizure patient.

Seizure disorder questionnaire

(modified from International Veterinary Epilepsy Task Force Epilepsy Questionnaire)

Owner name and surname:		
Pet's name:	Case number:	Date of birth (mm/dd/yyyy):
Species:	Breed:	Sex: ❑ M ❑ MN ❑ F ❑ FS
Body weight:	Diet:	

There are many possible causes of the episodes that your pet is experiencing. Please take the time to fill in this questionnaire, as the information it contains can be very helpful for your veterinarian in interpreting the events you are witnessing, and thereby help him/her to select the diagnostic investigations required to ascertain the cause of your pet's episodes, the most appropriate treatment and prognosis.
If several options are available, please select all that are appropriate.
The word "seizure" in this questionnaire refers to the episodes your pet is experiencing.
If available, please provide your veterinarian with:

- Video footage of the seizure (showing what happens during the seizure until your pet has fully recovered)
- A copy of the seizure diary (i.e., the dates and if possible also the time in which the seizures have occurred)
- If applicable, results of previous investigations (blood tests, urine test, MRI, CT, CSF analysis, others), details of medications administered and serum medication level testing.

Date of questionnaire completion (mm/dd/yyyy)

Regarding your pet's medical history:

Did your pet have birth complications? ❑ Yes ❑ No ❑ Not sure

Has your pet ever sustained head trauma? ❑ Yes ❑ No ❑ Not sure
If yes, specify the traumatic event and when it was sustained:

Has your pet ever had meningitis or encephalitis? ❑ Yes ❑ No ❑ Not sure
If yes, specify when and how it was diagnosed:

Does your pet suffer from any of the following conditions?
❑ Liver disease ❑ Low blood sugar ❑ Kidney disease
❑ Low potassium ❑ Low calcium ❑ Other condition (please specify)
❑ I am not aware that my pet suffers from any condition other than the seizures

Do you know of any relatives of your pet that suffer from seizures/epilepsy?
❑ Yes, please specify which relatives:
❑ No ❑ Not sure

Please provide the date of your pet's first seizure (mm/dd/yyyy)

If the date of your pet's first seizure is unknown, please specify your pet's age at the time of the first seizure in years and/or months ..... and/or select from the following ages
❑ <6 months ❑ 6 months–6 years ❑ >6 years

During the last 3 months, what is the average monthly seizure frequency for your pet?
❑ No seizures ❑ Less than 1 seizure per month ❑ 1–2 seizures per month
❑ 3–5 seizures per month ❑ 6–8 seizures per month ❑ Greater than 8 seizures per month

How many seizures does your pet usually have in a 24-hour period?

What is the greatest number of seizures your pet has had in a 24-hour period?

How often does your pet have more than one seizure per 24-hour period?
❑ Never ❑ Less than every 6 months ❑ Every 3–6 months
❑ Monthly ❑ Weekly ❑ Other frequency (specify):

Has your pet ever had status epilepticus (seizure lasting longer than 5 minutes or multiple seizures in 24 hours with incomplete recovery in between)?
❑ Yes ❑ No ❑ Not sure

If your dog is entire/intact female, does the seizure frequency increase during her season/when in heat?
❑ Yes ❑ No ❑ Not sure

When do the seizures occur:

Do the seizures occur: ❑ In the morning ❑ In the afternoon ❑ At night ❑ Any time

Do the seizures occur:
❑ At rest ❑ During sleep ❑ While waking up from sleep
❑ During/soon after excitement ❑ During/soon after regular physical activity/exercise
❑ During/soon after intense physical activity ❑ During/soon after a stressful event
❑ While eating ❑ Soon after a meal ❑ When a meal is due ❑ When startled
❑ During/soon after exposure to flashing lights ❑ During/soon after exposure to loud sounds
❑ During/soon after any other stimulus (specify which trigger)

Before the seizure:

Can you tell if your pet is going to have a seizure before the event? ❑ Yes ❑ No ❑ Not sure

If yes, which behavioral alterations are consistently observed prior to the seizure?
❑ Change in disposition ❑ Reluctance to perform normal activities ❑ Restlessness
❑ Anxiousness ❑ Fearful behavior ❑ Attention-seeking
❑ Increased affection ❑ Withdrawal ❑ Hiding
❑ Uncharacteristic aggression ❑ Other, please specify

If yes, how long do these behavioral alterations generally last before the seizure starts?
❑ <5 minutes ❑ 6–15 minutes ❑ 16–30 minutes ❑ 31–60 minutes ❑ >1 hour ❑ 1 day ❑ >1 day

The seizure itself:

Do all the seizures look the same? ❑ Yes ❑ No ❑ Not sure

Please describe what you see your pet doing immediately before, during and soon after the seizure(s).
If your pet displays more than one type of seizures, please describe the more common type of seizure first and then the other type/s.

During the seizure:

What is the very first thing that happens?

Is there a part of the body that is involved first? ❑ Yes ❑ No ❑ Not sure
If yes, which part is involved first?
❑ The head ❑ The hind limbs ❑ One hind limb (specify left or right)
❑ One front limb (specify left or right) ❑ One side of the body (specify left or right)

Does your pet display any of the following movements: lip smacking, chewing, licking, tooth grinding, or swallowing?
❑ Yes ❑ No ❑ Not sure

Does your pet display rhythmic twitching movements of his/her face muscles/ears/lips?
❑ Yes ❑ No ❑ Not sure

How is your pet's body? ❑ Stiff ❑ Floppy ❑ Normal

Does your pet fall to the floor? ❑ Yes ❑ No ❑ Not sure
If yes, is it always to the same side? ❑ Yes, to the …… ❑ No

Does your pet make paddling movements of the limbs? ❑ Yes ❑ No ❑ Not sure

Does your pet shake? ❑ Yes ❑ No ❑ Not sure

Do you think that your pet can hear you? ❑ Yes ❑ No ❑ Not sure

Do you think that your pet can see you? ❑ Yes ❑ No ❑ Not sure

Does your pet: ❑ Urinate ❑ Defecate ❑ Drool/froth

If your pet is engaged in an activity when the seizure starts (for example playing or walking) does your pet try to continue performing this activity at least during part of the seizure? ❑ Yes ❑ No ❑ Not sure

How long do the seizures generally last?

Have you timed them with a watch? ❑ Yes ❑ No

Soon after the seizure:

Does your pet appear:
❑ Normal ❑ Disoriented ❑ Restless
❑ Walking around aimlessly ❑ Anxious/agitated ❑ Fearful
❑ Attention-seeking/clingy ❑ Aggressive ❑ Withdrawn
❑ Hiding ❑ Wobbly/clumsy
❑ Very vocal (crying, whining, barking for no apparent reason) ❑ Hungry
❑ Thirsty ❑ Tired/exhausted ❑ Sleepy
❑ Deep asleep ❑ Staring into space ❑ Fly-catching/stargazing
❑ Unable to avoid obstacles/bumping into things ❑ Blind
❑ Other, please specify: ……

How long does it take for your pet to be standing and walking around after the seizure has ended?

How long does it take until your pet is completely back to normal after the seizure has ended?

How does your pet look on seizure-free days:

Does your pet appear completely normal during the days with no seizures? ❑ Yes ❑ No ❑ Not sure
If your pet displays clinical/behavioral abnormalities, which of the following have you observed:
❑ Personality/behavioral change. Specify which personality/behavioral abnormalities you have observed and since when:
❑ Sleep/wake cycle pattern change ❑ Less alert than usual
❑ Less active than usual ❑ More active than usual
❑ Unable to perform previously learned tasks ❑ Staring into space/corners
❑ Trying to catch imaginary objects/flies ❑ Often walking in circles
❑ Wandering aimlessly around the house ❑ Bumping into objects
❑ Pressing the head against walls/objects ❑ Abnormal gait
❑ Change in appetite ❑ Change in thirst
❑ Any other abnormality, please describe: ……

If your pet has already been prescribed any medication to treat the seizures, please complete the following section

Which of the following medications has been used to treat your pet's seizures? Include medications given in the past as well as those currently being administered.

❑ Phenobarbital ❑ Potassium bromide ❑ Imepitoin
❑ Gabapentin ❑ Zonisamide ❑ Levetiracetam
❑ Benzodiazepines (diazepam, midazolam or lorazepam) ❑ Other (please specify): .....

Which medications are currently being administered to your pet to treat the seizures?

Drug Name	Dosage	Frequency of administration	Route of administration	Date started (mm/dd/yy)	Drug serum level and date of testing if known/applicable

After initiation of the medications currently being administered, do you think the frequency of your pet's seizures has been:

❑ Increasing ❑ Unchanged ❑ Decreasing
❑ I am not sure if seizure frequency has changed after initiation of the above medication/s

After initiation of the medications currently administered, do you think the severity of your pet's seizures has been:

❑ Increasing ❑ Unchanged ❑ Decreasing
❑ I am not sure if seizure severity has changed after initiation of the above medication/s

When was your pet's last seizure (mm/dd/yyyy)?

Please rate the following regarding your pet's current condition while being treated with antiseizure medication/s:

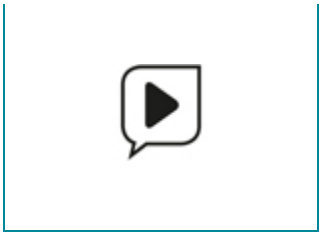
	Normal	Increased	Decreased
Appetite			
Thirst			
Frequency of urination			
Urination amount			
Frequency of defecation			
Amount of feces			
Activity level			
Alertness			

If you have any further information you would like to add, please do so here.

Thank you very much for your time.

FIGURE 1.3. Seizure disorder questionnaire.

Printable version available here.



Physical examination

A complete general physical examination can help identify abnormalities of body systems that can suggest an underlying etiology for the paroxysmal events or a concurrent condition that may affect diagnostic procedures and treatment selection. For example, detection of cardiovascular abnormalities may suggest the underlying etiology in a dog with paroxysmal events consistent with syncope or may indicate the need for further investigations (such as ECG and echocardiography) to ensure safe general anesthesia for magnetic resonance imaging (MRI) of the brain in a patient with epileptic seizures.

Ocular fundic examination should be performed to screen for hypertension, increased intracranial pressure, or ocular infections. Ocular fundic examination should be particularly thorough when vision impairment is one of the presenting clinical signs or infectious disorders with ocular involvement (such as feline infectious peritonitis and fungal disorders) are suspected.

Animals that present following a traumatic injury should be immobilized until vertebral instability has been ruled out. The initial assessment should be focused on vital organ function based on an emergency triage system.

Neurological examination

A thorough neurological examination is essential in the investigation of the seizure patient. Occurrence of epileptic seizures or reactive seizures per se indicates a forebrain neuroanatomical localization. Performing a full neurological examination is important to detect neurological deficits that are consistent with a forebrain localization and/or concurrent involvement of other nervous system regions, establish differential diagnoses, and select and interpret diagnostic investigations.

A detailed description of how to perform each section of the neurological examination can be found in any veterinary neurology

reference. The neurological examination findings should be recorded on a specific form (Fig. 1.4).

In this section, the focus will be on considerations to optimize execution of the neurological examination of the seizure patient. Every effort should be made to ensure that the animal is comfortable during the neurological examination. Responses of distressed animals may be challenging to interpret or lead to erroneous conclusions. With cats and anxious dogs, it often helps to perform short sections of the neurological examination and allow breaks in between. Careful assessment of mentation, behavior, posture, gait, postural reactions and cranial nerve function should precede any manipulation that could cause stress or discomfort such as spinal reflex assessment with the animal in lateral recumbency, pinching the skin or palpation to identify pain. Dogs often respond more naturally when taken outside the clinic, particularly if there is access to quiet green areas. Observing the animal where it is free to move in a relatively spacious enclosed space (e.g., large examination room for cats or fenced outdoor area for dogs) can help detect signs of forebrain disease that may not be apparent if the animal is on a lead or restrained. Toys can help motivate patients to walk, including cats that may have a tendency to hide in the consultation room. Sometimes, moving the carrier box to different areas of the room can encourage cats to walk as they attempt to hide in the carrier.

Clinical signs suggestive of forebrain disease that can be detected upon observation include: head turn, pleurothotonus (turning of the head, neck and trunk to one side), a tendency to turn to the same side when confronted with an obstacle, walking in circles, pacing, aimless/compulsive walking, collision of one side of the head or body with static objects as if the animal cannot see them, pressing the head against a wall or furniture, looking disoriented, or displaying any behavior that is unusual for that individual (based on the species, breed, age and feedback from the owner). Subtle changes in the pet's behavior may be detectable only by the pet owner in the animal's normal environment and this information should be obtained while taking the medical history. Inappropriate urination and/or defecation may occur at home. Interictal behavioral changes and seizures can be the only clinical abnormalities in animals with structural forebrain and certain metabolic disorders. In addition, behavioral changes (as persistent interictal abnormality) such as fear/anxiety, defensive aggression and abnormal perception[20–22] and cognitive dysfunction[23] have been reported in dogs with

IE (see Chapters 2 and 3 for further details). Behavior can also be affected by ASD treatment.

Upon "hands on" examination, abnormalities suggestive of forebrain disease include a decreased or absent menace response, facial hypoalgesia and postural reaction deficits. Proprioceptive placing (the paw replacement reaction) in particular can help detect subtle proprioceptive deficits. It is important to adequately support the animal's body weight when performing this test.

The neurological signs consistent with a forebrain neuroanatomical localization are summarized in Box 1.1.

DATE:	CLINICIAN'S NAME:
PET'S CASE NUMBER:	PET'S NAME:
BREED:	AGE:
SEX: ❑ M ❑ MN ❑ F ❑ FS	BODY WEIGHT:

OBSERVATION	
Mentation	❑ Normal ❑ Lethargic ❑ Obtunded ❑ Stuporous ❑ Comatose ❑ Delirium ❑ Disoriented ❑ Other (specify)
Behavior	❑ Normal ❑ Withdrawn ❑ Aggressive ❑ Other (specify)
Posture	❑ Normal ❑ Head tilt ❑ Head turn ❑ Pleurothotonus ❑ To the left ❑ To the right ❑ Opisthotonus ❑ Decerebrate rigidity ❑ Decerebellate rigidity ❑ Shilf-Sherrington posture ❑ Low head carriage ❑ Cervical ventroflexion ❑ Torticollis ❑ Spontaneous toe knuckling ❑ Wide-based stance ❑ Palmigrade ❑ Plantigrade Specify affected limb/s: ❑ Scoliosis ❑ Kyphosis ❑ Lordosis Specify affected spinal region:
Gait	❑ Normal ❑ Ataxia ❑ General proprioceptive ❑ Vestibular ❑ Cerebellar ❑ Paresis ❑ Paralysis ❑ Flaccid ❑ Spastic ❑ Lameness ❑ Circling to the left ❑ Circling to the right ❑ Circling to both sides
Limbs affected by gait abnormality	❑ All four limbs ❑ Thoracic limbs ❑ Pelvic limbs ❑ PL and TL on one side ❑ One limb (specify):..... ❑ Left ❑ Right
Paroxysmal events or involuntary movements witnessed during the examination	❑ Seizures ❑ Cataplexy ❑ Myoclonus ❑ Tremors ❑ Tetanus ❑ Myotonia ❑ Myokymia ❑ Neuromyotonia ❑ Other (specify) Indicate affected body part/s:

Grading of reactions and reflexes: 0 = no response; 1 = decreased response; 2 = normal response; 3 = exaggerated response; 4 = myotatic reflex with clonus; NE = not evaluated.
For strabismus: VL = ventrolateral; DL= dorsolateral; M = medial.
For nystagmus: H = horizontal; V = vertical; R = rotatory.

Cranial nerves					
	LEFT	RIGHT		LEFT	RIGHT
Olfaction (I)			Hearing (VIII)		
Vision (II)			Facial sensation (CN V)		
Menace response (II, VII)			Ophthalmic		
Pupil size (II, III, Sympathetic)			Maxillary		
PLR stimulating R (II, III)			Mandibular		
PLR stimulating L (II, III)			Masticatory muscles (CN V)		
Sympathetic innervation of the eye			Facial muscles (CN VII)		
Vestibulo-ocular reflex (VIII, III, IV, VI)			Palpebral reflex (CN V, VII)		
Strabismus, static (III, IV, VI)			Corneal reflex (CN V, VI, VII)		
Strabismus, positional (III, IV, VI, VIII)			Gag reflex (CN IX, X, XI)		
Nystagmus, resting (VIII, III, IV, VI)			Tongue atrophy/ deviation/ movement (CN XII)		
Nystagmus, positional (VIII, III, IV, VI)			Comments		

Postural reactions				
	L thoracic	R thoracic	L pelvic	R pelvic
Proprioceptive placing (paw replacement)				
Hopping				
Visual placing				
Tactile placing				
Hemi-standing/walking				
Wheelbarrow				
Extensor postural thrust				

Spinal nerve reflexes				
	L thoracic	R thoracic	L pelvic	R pelvic
Muscle size				
Muscle tone				
Extensor carpi radialis				
Patellar				
Cranial tibial				
Withdrawal				
Perineal	❑ Normal ❑ Decreased ❑ Absent ❑ Left ❑ Right			
Cutaneous trunci	❑ Normal ❑ Cut-off site ❑ Left ❑ Right			

Tail, micturition, defecation			
Tail	❑ Normal ❑ Paresis ❑ Paralysis ❑ Flaccid ❑ Spastic		
Micturition/ bladder	❑ Normal micturition ❑ Large and distended	❑ Urinary incontinence ❑ Easy to express	❑ Unknown ❑ Difficult to express
Defecation	❑ Normal defecation	❑ Fecal incontinence	❑ Unknown

Pain perception (nociception)					
	L thoracic	R thoracic	L pelvic	R pelvic	Other body site
Superficial nociception					
Deep nociception					
Specify affected dermatome/s					

Hyperalgesia on palpation/manipulation				
	Head	Spinal	Muscle	Other body site
Specify site				

Neurological examination	❑ NORMAL ❑ ABNORMAL
Neuroanatomical localization	
Forebrain	
Brain stem	
Central vestibular	
Peripheral vestibular	
Cerebellar	
Spinal	❑ C1-C5 ❑ C6-T2 ❑ T3-L3 ❑ L4-S1 ❑ S1-S3-Cd
Lesion distribution	❑ Lateralized to the left ❑ Lateralized to the right ❑ Bilateral symmetrical ❑ Other distribution (specify)
Neuromuscular	❑ Mononeuropathy ❑ Polyneuropathy ❑ Myopathy ❑ Junctionopathy Specify nerve/s/ limbs

DIFFERENTIAL DIAGNOSES

DIAGNOSTIC INVESTIGATIONS
❑ Hematology
❑ Serum biochemistry
❑ Fasting bile acids
❑ Bile acid stimulation tests
❑ Urinalysis
❑ T4, free T4, TSH
❑ Other laboratory investigations (specify)
❑ MRI (specify body region/s)
❑ CSF ❑ Cerebellomedullary cistern ❑ Lumbar
❑ EEG
❑ Other diagnostic investigation (specify)

FIGURE 1.4. Neurological examination form.

Printable version

available here.



BOX 1.1. Neurological signs that can occur alone or in combination in dogs and cats with forebrain disease.

- Epileptic seizures
- Behavioral changes
- Altered level of consciousness
- Hemineglect syndrome: lack of awareness of stimuli on one side of space (contralateral to the lateralized forebrain lesion)
- Head turn or turning of head, neck and body (pleurothotonus); tendency to turn/walk in circles (generally towards the side of the lateralized forebrain lesion)
- Pressing the head against solid objects (e.g., walls or furniture)
- Typically normal gait; may see mild hemi/tetra ataxia and/or paresis
- Facial (or full body) hypoalgesia (when unilateral this is contralateral to the lateralized forebrain lesion)
- Decreased/absent menace response (when unilateral this is contralateral to the lateralized forebrain lesion)
- Blindness with dilated pupils unresponsive to light with diencephalic lesions affecting optic chiasm or optic tracts
- Decreased or absent postural reactions in all four limbs or in the thoracic and pelvic limbs contralateral to the lateralized forebrain lesion
- Head or referred cervical hyperesthesia (spontaneous or upon palpation)
- Generalized hyperesthesia can occur with certain thalamic lesions
- Clinical signs consistent with dysfunction of the hypothalamo–hypophyseal system

Neurological examination abnormalities associated with the postictal period

Dogs and cats examined shortly after a seizure can present with neurological deficits (e.g., obtundation, general proprioceptive ataxia, delayed postural reactions, menace response deficits or blindness) associated with:

- The postictal phase (i.e., a transient decrease in forebrain activity lasting minutes to several hours).
- Hypoxic or excitoxic cerebral injury secondary to severe or prolonged seizures.

Whenever possible, the neurological examination should be repeated after at least 1 week of seizure freedom to investigate if neurological deficits have resolved, improved or worsened. Concurrent administration of ASDs can affect the clinical assessment.

Neurological examination abnormalities associated with antiseizure drugs

Obtundation, ataxia (particularly in the pelvic limbs) and sometimes also decreased postural reactions can be observed in dogs and cats as adverse effects of certain ASDs following loading, prior to achievement of steady state, following accidental overdosing, or following changes in disposition of the ASD resulting in higher serum concentrations. In these animals the neurological examination should be repeated after steady state has been achieved and when the serum ASD concentration has returned within the reference range.

Differential etiological diagnoses

After taking the medical history and performing the physical and neurological examination, the clinician can develop the differential etiological diagnosis list. This list represents an essential step in selecting and interpreting the diagnostic investigations. Seizure etiologies can be broadly classified as shown in Figure 1.5. Etiological diagnoses of reactive seizures and structural epilepsy are listed in Boxes 1.2 and 1.3, respectively.

Combining the following parameters can be helpful in establishing the most probable differential diagnosis group (i.e., IE, structural epilepsy, reactive seizures) in animals presenting with seizures:

1. Age at seizure onset
2. Breed (dogs)/pedigree status (cats)
3. Presence, onset and course of other clinical abnormalities in addition to the seizures (e.g., interictal neurological deficits, clinical signs suggestive of other organ system disease or exposure to toxins).

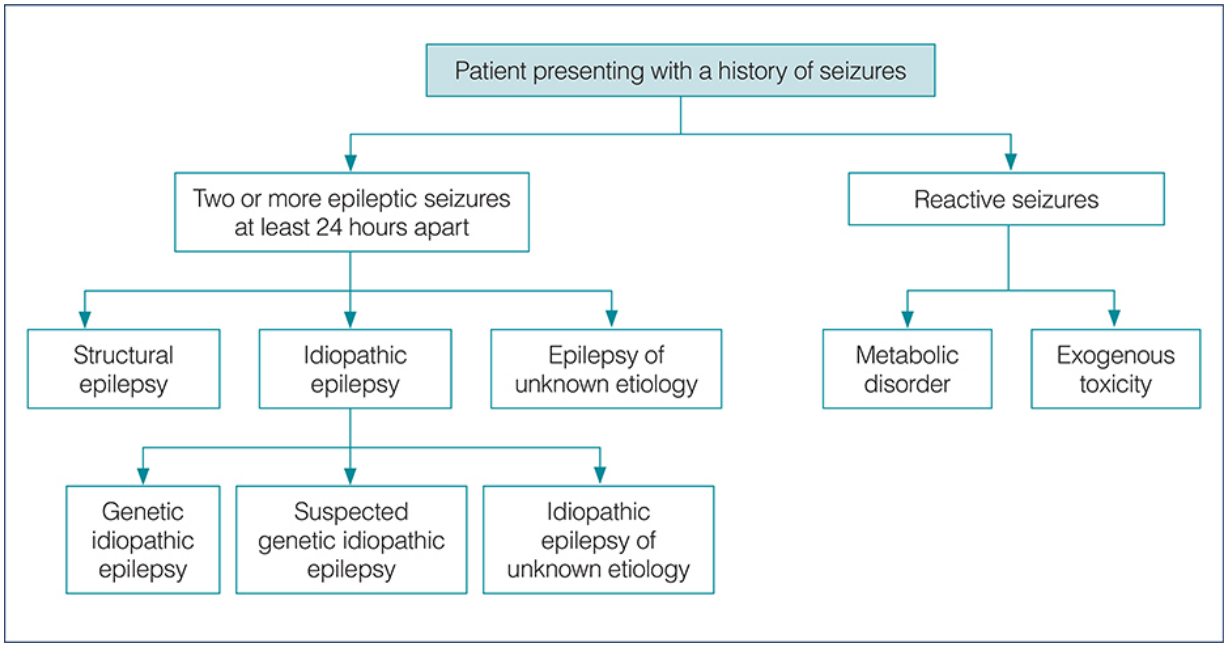


FIGURE 1.5. Etiological classification of seizure disorders.

4. Seizure phenomenology, frequency and progression.

The International Veterinary Epilepsy Task Force (IVETF) combined and analyzed data from two previous studies[24,25] to investigate the association between age at seizure onset and a diagnosis of structural or IE in dogs. The analysis included 236 dogs with structural epilepsy and 372 dogs with IE. Dogs between 6 months and 6 years of age at epileptic seizure onset were significantly more likely to be affected by idiopathic rather than structural epilepsy.[4]

In a retrospective study of 110 cats with recurrent epileptic seizures, results of binomial logistic regression analyses showed that being a pedigree cat, an age at seizure onset >7 years, abnormal interictal neurological examination, and ictal vocalization were associated with a diagnosis of structural epilepsy rather than IE.[26] Cats with an abnormal neurological examination had nearly three times increased odds of being diagnosed with structural epilepsy than IE. In this study, cats were diagnosed with IE if they had a history of two or more unprovoked epileptic seizures occurring at least 24 hours apart, no clinically significant abnormalities on minimum database blood tests and urinalysis, and unremarkable MRI of the brain and cerebrospinal fluid (CSF) analysis. The diagnosis of structural epilepsy was based on the history of recurrent

seizures and results of hematology, serum biochemistry, CSF analysis and/or morphological changes of the brain as identified by MRI.[26]

Dogs of breeds with a genetic predisposition to IE (see Chapters 2 and 4), a history of epilepsy in genetically related dogs, an age at epileptic seizure onset between 6 months and 6 years of age and a normal interictal neurological examination are more likely to have IE than other seizure disorders. Certain canine breeds may present specific epilepsy syndromes as a result of a known genetic mutation (e.g., Lafora disease/progressive myoclonic epilepsy in miniature Wirehaired Dachshunds, juvenile myoclonic epilepsy in Rhodesian Ridgeback dogs, see Chapter 4).

The presence of interictal forebrain signs (unrelated to the postictal period or ASDs) suggests an underlying structural, metabolic or toxic etiology. However, a normal interictal neurological examination per se does not rule out structural epilepsy as focal lesions in particular areas of the forebrain (referred to as "clinically silent regions") such as the olfactory bulb, frontal and pyriform lobes can result in epileptic seizures without any other neurological signs. Magnetic resonance imaging abnormalities relevant for epileptogenesis, including olfactory or frontal lobe neoplasia, were identified in 2% (1/46) and 27% (8/30) of interictally normal epileptic dogs younger and older than 6 years of age, respectively.[27]

In a retrospective study of 51 dogs presenting with status epilepticus as the first manifestation of a seizure disorder, 45% had structural epilepsy, 31% had reactive seizures and 24% had IE.[28] Dogs with IE had a reduced risk of developing status epilepticus at seizure onset compared to dogs with structural epilepsy or reactive seizures.

Further details on reactive seizures, structural and IE can be found in the following sections.

Reactive seizures

Reactive seizures etiologies are summarized in Box 1.2.

In animals with reactive seizures, the medical history and clinical presentation may lead to suspicion of a particular etiology (for example, exposure to a specific toxin or systemic signs suggestive of a metabolic condition). The neurological examination often reveals deficits consistent with diffuse, bilateral and often symmetrical forebrain involvement.

In a retrospective study, 11% (96/877) of dogs with seizures had a metabolic or toxic disorder as the underlying etiology.[29] Nearly 50% (47/96)

of dogs had generalized seizures with loss of consciousness and 41% (39/96) presented in status epilepticus.

BOX 1.2. Reactive seizures etiologies.

Exogenous toxic disorders

- 5-hydroxytryptophan
- Amphetamine and amphetamine-like compounds
- Animal-related poisoning (toad, spider, bee and wasp venom)
- Caffeine and other methylxanthines
- Detergents and disinfectants
- Ethylene glycol
- Lead and other heavy metals
- Marijuana (THC)
- Metaldehyde
- Metronidazole (cats)
- Mycotoxins (penitrem A, roquefortine)
- Poisonous plants
- Pyrethrins/pyrethroids, organophosphates, chlorinated hydrocarbons carbamate
- Selective serotonin reuptake inhibitors
- Sodium monofluoroacetate (compound 1080)
- Strychnine, bromethalin

Metabolic disorders

- Electrolyte imbalance
  - Hypocalcemia
  - Hypo- or hypernatremia
- Hepatic disease
  - Congenital and acquired portosystemic shunt
  - Microvascular dysplasia
  - Hepatic lipidosis
  - Neoplasia
  - Inflammation
- Hyperglycemia
- Hypertension
- Hypoglycemia
  - Insulin-secreting tumor
  - Severe sepsis
  - Iatrogenic insulin overdose
  - Hypoadrenocorticism
  - Xylitol ingestion
- Hypothyroidism
- Hypoxia
- Polycythemia
- Renal disease
  - Acute renal failure
  - End-stage chronic renal failure

Nutritional disorders

- Thiamine (vitamin B1) deficiency

Metabolic disorders can present with an acute, subacute, or chronic onset and can be progressive, or relapsing and remitting. Systemic clinical abnormalities can often be detected on general physical examination. In a retrospective study including 96 dogs with reactive seizures, the most frequent metabolic disorder was hypoglycemia (32%, 31/96 dogs) secondary to insulinoma, other tumor type, insulin overdosage, lactation, and hunting dog or juvenile hypoglycemia. The mean blood glucose concentration of all dogs with hypoglycemia at the time of presentation was 2.19 mmol/L or 39 mg/dL (range 0.55–3.5 mmol/L or 10–63 mg/dL; reference range 3.9–6.1 mmol/L or 70–110 mg/dL). Hypocalcemia (mean ionized calcium concentration of 0.61 mmol/L; reference range 1.25–1.47 mmol/L) was the most frequent (50%, 5/10 dogs) electrolyte disorder.[29]

Animals with intoxications typically have an acute (<24 hours) onset of neurological signs often preceded or accompanied by vomiting, diarrhea, salivation, bronchoconstriction, bradycardia or tachycardia, and hyperthermia. With several types of toxins, muscle tremors and fasciculations are frequently the initial clinical signs followed by seizures, ataxia, excitation and hyperactivity or obtundation progressing to stupor and coma. Chronic exposure to lead can result in recurrent seizures as the sole or predominant clinical abnormality.

In a retrospective study including 394 dogs, individuals with reactive seizures secondary to intoxication had a significantly higher risk of presenting in status epilepticus at seizure onset than dogs with other seizure etiologies.[28]

For further details on diagnosis and treatment of specific reactive seizure etiologies the reader can consult other textbooks.[30]

Structural epilepsy

Structural epilepsy can be caused by a variety of conditions (Box 1.3). Disease onset and course vary depending on the underlying etiology.[31]

An epileptic seizure may be the only initial sign of structural forebrain disease. The prevalence of abnormal neurological examination findings in dogs with structural epilepsy varies amongst studies most likely as a result of differences in the location, extent and type of cerebral pathology as well as disease stage at the time of the neurological examination.

BOX 1.3. Structural epilepsy etiologies.

Vascular

- Cerebrovascular accidents
  - Ischemic
  - Hemorrhagic

Inflammatory (noninfectious)

- Meningoencephalitis of unknown origin (MUO)
  - Granulomatous meningoencephalomyelitis
  - Necrotizing leukoencephalitis
  - Necrotizing meningoencephalomyelitis

Infectious

- Algal
  - *Prototheca wickerhamii*
  - *Prototheca zopfii*
- Bacterial

Aerobic/facultative anaerobic organisms	Anaerobic organisms
Bartonella spp. *Brucella* canis *Corynebacterium* spp. *Escherichia coli* *Klebsiella* sp. *Nocardia* spp. *Pasturella* spp. *Proteus* spp. *Pseudomonas* spp. *Salmonella* spp. *Staphylococcus* spp. *Streptococcus* spp. Other aerobic organisms	*Actinomyces* spp. *Bacteroides* spp. *Eubacterium* spp. *Fusobacterium* spp. *Peptostreptococcus* spp. Other anaerobic organisms

- Fungal
  - *Aspergillus* spp.
  - *Blastomyces dermatitidis*
  - *Cladophialophora bantiana*
  - Other *Cladophialophora* spp.
  - *Coccidioides* spp.
  - *Cryptococcus gattii*
  - *Cryptococcus neoformans*
  - Other *Cryptococcus* spp.
  - *Histoplasma capsulatum*
  - *Phoma eupyrena*
- Parasitic
  - *Dirofilaria immitis* (microfilaria or aberrant adult migration)
  - Aberrant larval migration (larva migrans) of:
    - *Cuterebra* spp.
    - *Tenia serialis*
    - *Toxocara canis*
    - *Toxocara cati*
    - *Baylisascaris procyonis*, other ascaride species
- Protozoal
  - *Neospora caninum*
  - *Toxoplasma gondii*
- Rickettsial
  - *Anaplasma phagocytophilum*
  - *Ehrlichia canis*
  - *Ehrlichia ewingii*
  - *Mycoplasma edwardii*
  - *Neorickettsia helminthoeca*
  - *Rickettsia rickettsia*
- Viral
  - Arbovirus (central European tick-borne encephalitis)

- Borna virus
- Canine distemper virus
- Canine herpesvirus
- Feline coronavirus (feline infectious peritonitis)
- Feline immunodeficiency virus
- Feline leukemia virus
- Feline panleukopenia virus
- Feline paramyxovirus
- Parvovirus
- Pseudorabies virus
- Rhabdovirus (rabies)
- West Nile virus

Traumatic

- Traumatic brain injury

Anomalous/developmental

- Agenesis or dysgenesis of the corpus callosum
- Cerebral neuronal heterotopias or dysplasias
- Exencephaly
- Holoprosencephaly
- Hydranencephaly
- Hydrocephalus
- Lissencephaly
- Meningocele
- Meningoencephalocele
- Polymicrogyria
- Porencephaly

Neoplastic

Primary	Secondary
Meningioma	Hemangiosarcoma
Astrocytoma (glioblastoma multiforme)	Lymphoma
Oligodendroglioma	Pituitary tumors
Gliomatosis cerebri	Carcinomas/adenocarcinomas (mammary, prostatic, pancreatic, pulmonary)
Ependymoma	Nasal tumors (e.g., adenocarcinoma, squamous cell carcinoma, chondrosarcoma, neuroesthesioblastoma)
Choroid plexus tumors	Histiocytic sarcoma
Primitive neuroectodermal tumors (neuroblastoma, medulloblastoma, gangliocytoma)	Calvarial osteosarcoma and multilobulated tumor of bone (multilobulated osteochondrosarcoma)
Primary CNS lymphoma	Malignant melanoma
Primary CNS histiocytic sarcoma (malignant histiocytosis)	Others

Degenerative

- Leukodystrophies

- Lysosomal storage diseases
  - Progressive myoclonic epilepsy (Lafora disease) (see Chapter 4)
  - Fucosidosis
- Mitochondrial encephalopathies
- Multisystem neuronal degenerations/abiotrophies
- Organic acidurias
  - L-2-hydroxyglutaric aciduria (see Chapter 4)
- Spongy degenerations

A retrospective study including 99 dogs ≥5 years of age at epileptic seizure onset reported that an abnormal neurological examination had 74% sensitivity and 62% specificity to predict structural epilepsy, with positive and negative predictive values of 79%, and 55%, respectively.[32]

In a cross-sectional retrospective study of dogs with histopathologically confirmed primary or secondary intracranial neoplasia, an epileptic seizure was the first sign of intracranial disease observed by the owners in 76% (31/41) of dogs.[33] The median age at epileptic seizure onset was 8.8 years. Dogs with frontal lobe neoplasia were more likely to develop epileptic seizures than dogs with neoplasia in other intracranial locations. Risk factors for development of epileptic seizures in these dogs with intracranial neoplasia included MRI findings consistent with the presence of neoplastic tissue in the frontal lobe, marked gadolinium enhancement of the neoplastic tissue and MRI findings of subfalcine and/or subtentorial cerebral herniation.[33]

In a retrospective study including dogs ≥7 years old at the time of the first epileptic seizure, neurological deficits consistent with an intracranial neuroanatomic localization were detected at the time of initial evaluation in 116 of 169 (69%) of dogs with structural epilepsy.[34]

A retrospective study including 404 dogs with epileptic seizures due to intracranial disorders investigated the association between neurological examination findings and age at seizure onset with a diagnosis of structural epilepsy or IE.[25] All dogs had a history of two or more epileptic seizures and underwent comprehensive investigations including a neurological examination, hematology, serum biochemistry profile, dynamic bile acid testing, imaging of the brain with 1.5-Tesla MRI, and CSF analysis. Thirty three percent (35/105) of dogs with structural epilepsy had a normal neurological examination interictally. Of the dogs with forebrain signs on neurological examination, 47% of dogs with lateralized structural cerebral lesions had asymmetrical neurological deficits and 55% of dogs with

symmetrical structural brain lesions had symmetrical neurological deficits. Dogs with abnormal neurological examinations interictally were 16.5 times more likely to have an asymmetrical structural brain lesions and 12.5 times more likely to have a symmetrical structural brain lesions than dogs with no abnormalities on diagnostic investigations.[25]

Idiopathic epilepsy

The main differential diagnosis in dogs with recurrent epileptic seizures, an age at seizure onset between 6 months and 6 years, and no abnormalities on physical and neurological examinations is IE. Similar criteria have been used to diagnose IE in cats. Breed predisposition and a history of IE/recurrent epileptic seizures in genetically related dogs further supports the index of suspicion. Idiopathic epilepsy is a diagnosis of exclusion.

The IVETF has proposed three levels of diagnostic evaluation (Tiers 1–3) requiring progressively more advanced diagnostic investigations resulting in increasing diagnostic confidence for the diagnosis of canine IE[4] (Box 1.4). Canine IE is discussed in detail in Chapter 2. Feline seizure disorders, including IE, are presented in Chapter 5.

Epilepsy of unknown etiology

The term "epilepsy of unknown etiology", "cryptogenic epilepsy" and "probably symptomatic epilepsy" have been used to refer to animals that do not fulfill any of the criteria previously described for reactive seizures, structural epilepsy and IE. In these patients, the underlying seizure etiology cannot be identified despite extensive diagnostic investigations. In a retrospective study including 214 dogs with an onset of epileptic seizures at ≥7 years of age that underwent MRI of the brain following exclusion of reactive seizures, 169 (79%) dogs were diagnosed with structural epilepsy and 45 (21%) dogs were diagnosed with epilepsy of unknown etiology (cryptogenic epilepsy).[34] In addition to MRI of the brain, these dogs underwent laboratory investigations on blood, urine and CSF. The median age at epileptic seizure onset for dogs with epilepsy of unknown etiology was 9.0 years (range, 7.3 to 16 years) and was significantly less than the age at epileptic seizures onset for dogs with structural epilepsy (median, 10.3 years; range, 7 to 18.4 years). Twenty-three (51%) dogs with epilepsy of unknown etiology had isolated seizures only, 21 (47%) had cluster seizures, and only 1 (2%) dog had an episode of status epilepticus.[34]

The term epilepsy of unknown etiology has also been used to refer to animals in which the cause of the recurrent epileptic seizures is unknown due to limited diagnostic investigations. Some authors have used the term "epilepsy of unknown etiology" also to refer to dogs and cats with IE and no evidence of a genetic basis for the condition. To avoid confusion, we have used the term "idiopathic epilepsy of unknown etiology" to refer to dogs with an age at epileptic seizure onset between 6 months and 6 years, ≥2 epileptic seizures at least 24 hours apart, unremarkable diagnostic investigations as detailed in Box 1.4, no identified causative gene or genetic predisposition, no family members with IE and no increased (i.e., >2%) IE prevalence in the breed (see Chapter 2, Fig. 2.1).

BOX 1.4. Three tier levels of diagnostic confidence for the diagnosis of idiopathic epilepsy in dogs as proposed by the International Veterinary Epilepsy Task Force.

Tier 1 confidence level requires:

- A history of two or more unprovoked epileptic seizures occurring at least 24 hours apart.
- Age at epileptic seizure onset between 6 months and 6 years.
- Unremarkable interictal clinical and neurological examinations (except for neurological abnormalities associated with the postictal phase or antiseizure drugs).
- No abnormalities relevant for epileptogenesis on minimum database blood tests and urinalysis.
- *Minimum database blood tests* include: hematology and serum biochemistry profile (sodium, potassium, chloride, calcium, phosphate, alanine aminotransferase, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, total protein, albumin, glucose, cholesterol, triglycerides, and fasting bile acids and/or ammonia).
- *Urinalysis* includes specific gravity, protein, glucose, pH, and sediment cytology.
- Additional laboratory parameters should be investigated depending on the index of disease suspicion.

Tier 2 confidence level requires:

- All the parameters listed in Tier 1.
- Unremarkable fasting and postprandial bile acid concentrations.
- No abnormalities relevant for epileptogenesis on magnetic resonance imaging and cerebrospinal fluid analysis.

Tier 3 confidence level includes:

- All the parameters listed in Tier 1 and 2.
- Identification of ictal or interictal electroencephalographic abnormalities.

Diagnostic investigations

Diagnostic investigations must be selected and their results interpreted based on the neuroanatomical diagnosis and differential etiological diagnosis list.

Laboratory investigations

Hematology, comprehensive serum biochemistry and urinalysis should be performed in all dogs and cats presenting with seizure disorders. Whenever possible, the blood sample should be obtained after fasting (12 hours for adult dogs and cats) and after a seizure free period of at least 1 week. Hepatic enzymes can be increased shortly after seizure activity because of the effects of hypoxia and hypotension. Additional discretionary laboratory parameters should be selected based on the suspicion index of specific seizure etiologies and/or concurrent disorders. These laboratory investigations include:

- A bile acid stimulation test (i.e., 12-hour fasting and 2-hour postprandial total serum bile acid concentrations) and/or fasting serum ammonia concentration anytime hepatic encephalopathy secondary to a portosystemic shunt or hepatic dysfunction is suspected.
- A bile acid stimulation test is also advisable as baseline before initiation of phenobarbital (see Chapter 10).
- Total T4 (TT4), free T4 (fT4), and thyroid stimulating hormone (TSH) when thyroid disorders are suspected or when a baseline function is desirable before initiating phenobarbital (see Chapter 10).
- Fructosamine, glucose curve and/or glucose-to-insulin ratio when hypoglycemia secondary to insulinoma is suspected.
- Insulin levels when glucose concentration is <3.33 mmol/L or 60 mg/dL in dogs with suspected insulinoma.
- Ionized calcium when hypocalcemia is suspected.
- Vitamin B12 when cobalamin malabsorption is a differential diagnosis.
- Testing for specific toxins or toxicological screening when toxin exposure is suspected. When the source of intoxication is known or highly suspected, toxicological testing can be focused on specific toxins (e.g., lead, metaldehyde, strychnine, mycotoxins). Feed or suspect bait material, gastric content from vomitus or lavage fluids, blood or urine (for urinary-excreted toxins) can be submitted to the laboratory for analysis of suspected neurotoxins or toxicological screen.
- Serology/polymerase chain reaction (PCR) antigen testing for regional infectious disorders anytime these are suspected.
- Quantification of amino acids and organic acids and determination of glycosaminoglycans, oligosaccharides, purines, and pyrimidines in serum, CSF and urine when inborn errors of metabolism are suspected.

- Genetic testing (on EDTA blood or buccal mucosa swabs) when a seizure disorder with a known genetic mutation is suspected (i.e., benign familial juvenile epilepsy in the Lagotto Romagnolo, progressive myoclonic epilepsy in miniature Wirehaired Dachshunds, L-2-hydroxyglutaric aciduria in Staffordshire Bull Terriers; see Chapter 4, Table 4.1).

Other investigations

Noninvasive blood pressure measurement should be performed in any dog and cat older than 6 years of age and when hypertension is suspected in animals of any age.

Abdominal ultrasonography or computed tomography (CT) are indicated in the investigation of the following conditions: portosystemic shunt or hepatic disease, renal disease, adrenal disease, insulinoma, primary or metastatic neoplasia, and infectious disorders with potential multiorgan involvement. Radiography or CT of the thorax should be performed when neoplastic disease or certain infectious disorders (i.e., fungal and bacterial infections, *Toxoplasma gondii* infection) are suspected.

Magnetic resonance imaging of the brain

Magnetic resonance imaging is the diagnostic imaging modality of choice for evaluation of the brain in the epileptic patient. It is indicated anytime structural epilepsy is suspected and to support the diagnosis of IE. The IVETF[4] has suggested performing MRI of the brain (eventually followed by CSF analysis) in dogs with one or more of the following findings:

- Age at seizure onset <6 months or >6 years
- Persistent interictal neurological abnormalities consistent with an intracranial neurolocalization
- Status epilepticus or cluster seizures
- A previous presumptive diagnosis of IE and inadequate epileptic seizure control following ASD monotherapy
- To achieve a Tier II level diagnostic confidence of IE in dogs

Similar criteria may apply to cats; however, the age at IE onset in cats is less well characterized than in dogs.

The IVETF has proposed a standardized veterinary epilepsy–specific MRI protocol to optimize anatomic detail and facilitate detection of subtle

lesions in cerebral areas susceptible of generating and perpetuating epileptic seizures such as the frontal and temporal lobes.[35] One feature of the IVETF MRI protocol is that the angles of the transverse and dorsal planes are respectively parallel and perpendicular to the long axis of the hippocampus identified in the sagittal plane. The details of the IVETF MRI protocol for both low and high field MRI scanners are presented in Chapter 6 (see Tables 6.1 and 6.2).

Quality of the MRI examination

The quality of the MRI examination is affected by various factors. Slice thickness and sequences influence the ability to detect cerebral lesions. Thinner slices increase the likelihood of lesion detection. A slice thickness of 3 mm or less in at least two planes is recommended for examination of the epileptic brain as lesions smaller than 5 mm may be missed with a larger slice size. Slice thickness should be proportional to the brain volume to achieve images with adequate diagnostic quality. Animals with a smaller brain volume require thinner slices.[35] Magnetic resonance imaging machines with a field strength under 1.5 Tesla are considered insufficient for the imaging of human epilepsy patients. A high magnetic field strength (1.5 Tesla and above) provides improved signal-to-noise ratio and spatial resolution, which allows shorter imaging times for a given resolution and/or higher resolution for a given imaging time. Other important factors in obtaining optimal image quality include the MRI operator's understanding of MRI physics, cerebral anatomy knowledge and practical experience.

The experience of the clinician who interprets the MRI of the seizure patient is also an important factor in the detection of epileptogenic lesions. A study in people compared the results of a standard brain MRI protocol reported by non-epilepsy-expert radiologists, a standard MRI evaluated by epilepsy-expert-radiologists, and an epilepsy specific MRI read by epilepsy-expert-radiologists in 123 consecutive patients undergoing epilepsy surgery evaluation.[36] Standard MRI was usually performed before referral for epilepsy surgery evaluation, which involved following an epilepsy-specific MRI protocol to obtain images that were then interpreted by an expert. Validation of radiological findings was performed by correlation with postoperative histological examination. Neuropathological diagnoses (n = 90) were predicted correctly in 22% of standard MRIs reported by non-epilepsy-expert radiologists, 40% of the same standard MRI reassessed by

epilepsy-expert-radiologists and in 89% of epilepsy specific MRIs interpreted by epilepsy-expert-radiologists.[36]

Epileptic seizure-induced intraparenchymal cerebral MRI signal changes

Epileptic seizure activity can cause intraparenchymal cerebral signal changes consistent with cytotoxic and vasogenic edema, which are detectable on MRI performed within 14 days of the last epileptic seizure.[37,38] These signal changes occur in specific anatomical areas of the forebrain; they can be unilateral or bilateral, local or remote to the epileptogenic focus, and are partially or completely reversible (see Chapter 6, Fig. 6.3). A retrospective study including 81 dogs with IE and seizure-induced MRI signal changes reported that the forebrain lesions were T2-hyperintense with no suppression of signal on FLAIR in all dogs, T1-isointense in 68% (55/81), T1-hypointense in 32% (26/81), contrast enhanced in 15% (12/81) and had local mass effect in 28% (23/81) of dogs.[38] All dogs underwent high field MRI (1.5 or 3 Tesla) within 1 week of the last seizure, with the majority of dogs (79%) having had seizures in the 48 hours prior to the MRI. Most dogs presented with cluster seizures (53%) or in status epilepticus (19%). The intraparenchymal cerebral signal changes were bilateral in 88% (71/81) of dogs and symmetrical in 85% (69/81). The most commonly affected areas were the hippocampus (39 dogs), cingulate gyrus (33 dogs), and piriform lobes (32 dogs). Diffusion weighted imaging (DWI) characteristics were a mixed-pattern of restricted, facilitated, and normal diffusion. Perfusion weighted imaging (PWI) showed either hypoperfusion (6/9 dogs) or hyperperfusion (3/9 dogs).[38]

In a previous study in 3 dogs following ASD treatment only, these seizure-induced signal changes had partly or completely resolved on a repeat MRI performed 10 to 16 weeks after the initial study. Histological examination of the affected temporal cortex, hippocampus and piriform lobe revealed edema, neovascularization, reactive astrocytosis, and acute neuronal necrosis.[37]

In animals with intraparenchymal cerebral signal changes that are suspected to be the result rather than the cause of the epileptic seizures, repeating the MRI of the brain after a period of seizure control, along with repeated neurological examination and, if indicated, CSF analysis, may help to differentiate epileptic seizure–induced MRI changes from inflammatory

or neoplastic epileptogenic structural lesions. Seizure-induced acute parenchymal changes can evolve into permanent abnormalities such as focal neuron cell loss and gliosis potentially leading to an epileptogenic lesion visible on MRI.

Advanced MRI modalities

Advances in veterinary MRI will improve understanding of the pathogenesis, etiology, treatment and prognosis of epilepsy in dogs and cats. There is a growing number of veterinary studies investigating different MRI techniques in epileptic patients.

Magnetic resonance imaging volumetry is used to compare the size and shape of brain structures. A retrospective study comparing 100 dogs with presumptive IE and 41 nonepileptic dogs showed that dogs with IE had greater hippocampal asymmetry than nonepileptic dogs.[39] However, due to the retrospective nature of the study, the authors were unable to evaluate if the subset of dogs with IE and hippocampal asymmetry (approximately 40%) had increased refractoriness to ASD therapy. Volumes of the right and left hippocampi were measured using image processing software. There was no significant difference in overall hippocampal volume between dogs with IE and nonepileptic dogs.

Diffusion weighted imaging evaluates the diffusibility (i.e., movement and distribution) of water molecules in a given time within a specific location and can detect abnormalities of microscopic structures. Seizure-induced cytotoxic edema, due to intracellular ictal-driven excitotoxic mechanisms, appears hyperintense on DWI and as a reduction in apparent diffusion coefficient (ADC) values. An increase in ADC values is commonly associated with vasogenic edema formation or progressive neuronal loss. In a prospective study that included 17 dogs with IE, interictal diffusion-weighted MRI (1.0 Tesla) showed that the dogs with IE had a significantly increased ADC in the amygdala and in the semioval center compared with the healthy control group.[40] It was hypothesized these changes could be secondary to neuronal cell loss or gliosis.

Magnetic resonance spectroscopy (MRS) measures the concentration of metabolites within a sample volume by analyzing the chemical shift of protons, usually H1 protons (referred to as H1-MRS) and displaying the shift as a spectrogram. A prospective study compared the interictal metabolic activity of the temporal lobe in 27 client-owned dogs with IE and

10 control healthy dogs with single-voxel H1-MRS.[41] The N-acetylaspartate (NAA)-to-creatine (NAA/Cr), NAA-to-choline (NAA/Cho), choline-to-creatine (Cho/Cr), and choline-to-NAA (Cho/NAA) ratios were determined in both hemispheres and compared to controls. No significant differences in all metabolite ratios were identified between dogs with IE and the control group. The time span from the last seizure to MRS acquisition significantly correlated with NAA/Cho and Cho/NAA ratio.[41]

Further details on MRI and other advanced imaging modalities can be found in Chapter 6.

Cerebrospinal fluid analysis

The main diagnostic value of CSF analysis in animals presenting with a history of epileptic seizures is to investigate structural brain disease, particularly inflammatory/infectious central nervous system (CNS) disorders. In a retrospective study in which both MRI and CSF analysis were performed in 256 dogs with various neurological disorders, CSF abnormalities were more common than MRI abnormalities only in dogs with inflammatory CNS disease.[42] Most CSF abnormalities were nonspecific and an etiological diagnosis was determined in only 2% of CSF samples. In a systematic review, up to 7% of dogs with meningoencephalitis of unknown origin (MUO) had no abnormalities on MRI of the brain and were diagnosed with MUO due to CSF abnormalities.[43]

Results of CSF routine analysis (red blood cell [RBC] count, total nucleated cell count [TNCC], cytological analysis and protein concentration) must be interpreted in the context of the animal's signalment, medical history, neuroanatomic diagnosis and results of other diagnostic investigations including blood tests and diagnostic imaging. Abnormalities of routine CSF analysis are relatively sensitive indicators of CNS disease; however, they are rarely specific for underlying etiologies. The type of TNNC observed on cytology may be suggestive of a particular etiology or disease group. Cerebrospinal fluid total protein concentration is frequently increased in many disease processes that cause CSF pleocytosis. However, the CSF protein concentration can be elevated without a concurrent increase in CSF TNNC (albuminocytological dissociation) due to alterations in the blood–brain barrier or intrathecal globulin production. Occasionally, bacteria, *Ehrlichia* morulae, fungi, protozoa, parasites, *Prototheca* spp., canine distemper virus inclusion bodies, or neoplastic cells (e.g.,

lymphoblasts) can be identified on microscopic examination of CSF. Investigations for specific pathogens can be performed on CSF (such as PCR, antigen or antibody testing) and may result in an etiological diagnosis. Quantification of organic acids, amino acids and other metabolites in CSF as well as urine and serum can help achieve a diagnosis of inborn errors of metabolism.

Measurement of lactate concentration in CSF has been investigated as a potentially useful biomarker of CNS disease in dogs. In a study including 118 dogs with seizure disorders, dogs with inflammatory and neoplastic disease had significantly higher lactate concentrations than dogs with IE or epilepsy of unknown etiology.[44] A lactate concentration above the established reference interval (>2.5 mmol/L) was 100% specific for predicting structural epilepsy, although sensitivity was low, being only 21%. There was a significant difference in CSF lactate concentrations between dogs with generalized seizures compared to those with focal seizures. No differences in lactate concentrations were identified in relation to the seizure presentation (i.e., single seizures, cluster seizures or status epilepticus), time interval from the last seizure to CSF collection, or number of seizures within the 72 hours prior to CSF collection.[44]

Cerebrospinal fluid abnormalities such as mild pleocytosis and/or increased total protein concentration can occur as a result of epileptic seizure activity.[45] A retrospective study in 124 dogs with IE identified an association between CSF TNNC and the time interval between the last seizure and CSF collection. The longer the time interval, the lower the CSF TNNC. No association was found between CSF protein concentration and time of CSF collection, as well as between the occurrence of cluster seizures and either the CSF TNCC or protein concentration.[45] The time to resolution of CSF abnormalities associated with the epileptic seizure is unknown. In dogs with a tier II diagnosis of IE, the IVETF has recommended to repeat CSF analysis following a seizure free interval of at least 6 weeks, when routine analysis of CSF collected after recent seizure activity is abnormal, investigations for infectious disorders on CSF and serum are negative and brain MRI is unremarkable or shows epileptic seizure–induced changes.[4]

Two recent retrospective studies concluded that performing CSF analysis does not increase the likelihood of detecting an underlying cause in dogs with suspected IE based on recurrent epileptic seizures, a normal

interictal neurological examination, unremarkable complete blood count and serum biochemistry analysis, and normal MRI of the brain.[46,47] In these studies, mild CSF abnormalities were detected in 11–15% of dogs with suspected IE. The first study included 200 dogs with a presumptive diagnosis of IE following exclusion of reactive seizures and structural cerebral abnormalities on MRI. Most dogs underwent CSF collection from the cerebellomedullary cistern. Cerebrospinal fluid analysis was abnormal in 30 (15%) dogs. Mild mononuclear pleocytosis was detected in 47% (14/30) dogs (median TNCC of 6 cells/μL) and total protein concentration was increased in 73% (22/30) dogs (median total protein concentration of 40 mg/dL). Both pleocytosis and increased CSF protein concentration were detected in 20% (6/30) of dogs. The time interval between the last epileptic seizure and CSF analysis was less than 2 days in 27% (8/30) of dogs, more than 7 days in 53% (16/30) of dogs and unreported in the remaining 6 dogs. No association was identified between the presence of CSF abnormalities and the type or number of epileptic seizures or the time interval between the last epileptic seizure and CSF collection.[46] Most of these dogs (77%, 20/26) showed a reduction in epileptic seizure occurrence with ASD treatment and no interictal neurological deficits with a median follow-up time of 32 months. Four dogs were lost to follow up, 3 died due to unrelated causes and 3 were euthanized due to poorly controlled epilepsy.[46] The second study included 82 dogs aged between 6 months and 6 years at seizure onset that were presented with a history of 2 or more epileptic seizures at least 24 hours apart, a normal neurological examination, no evidence of toxic or metabolic seizure etiologies, and a normal MRI of the brain (including contrast administration).[47] Results of cerebellomedullary cistern CSF analysis were abnormal in 11% (9/82) of dogs. Of these, 56% (5/9) had albuminocytological dissociation (TP range 32–58 mg/dL), 33% (3/9) had mild increases in TNNC (6–10 cells/μL), and 11% (1/9) had mild increases in both total protein concentration and TNCC (36 mg/dL and 7 cells/μL, respectively). Cytology in all dogs with an elevated TNCC revealed mononuclear pleocytosis. Of the 9 dogs with abnormal CSF, the time interval between the last seizure and CSF collection was less than 24 hours in 1 (11%) dog, less than 1 month in 5 (56%) dogs, and >1 month in the remaining 3 (33%) dogs.[47] Seven of the 9 dogs with abnormal CSF results underwent serology or CSF PCR for *Toxoplasma gondii* or *Neospora caninum* and results were all negative. One dog with increased total protein

(36 mg/dL) and TNCC (7 cells/μL) values on initial CSF analysis underwent a second CSF collection after 1 month of seizure freedom and CSF analysis was normal. At data collection end, of the 9 dogs with abnormal CSF analysis, 5 dogs (56%) had well controlled seizures, whereas 4 dogs (45%) were deceased. Three of the 4 deaths were related to epilepsy.[47]

Further details on collection, sample handling, analysis and interpretation of CSF can be found elsewhere.[48,49]

Electroencephalography

Electroencephalography is the recording of spontaneous electrical activity generated by pyramidal neurons in the cerebral cortex. In human medicine, EEG is a standard diagnostic procedure in the epileptic patient and plays an important role in the classification of seizure types (focal versus generalized onset), the diagnosis of epilepsy syndromes, monitoring nonconvulsive status epilepticus, localization of the epileptogenic focus, prediction of seizure recurrence, and monitoring effects of ASD therapy. In veterinary medicine, the clinical use of EEG is increasing, although predominantly restricted to academic institutions. Limiting factors to the clinical applicability of EEG in veterinary medicine include patient cooperation, muscle artifacts, length of recording, equipment availability, expertise and validated standardized methods in obtaining and interpreting the EEG tracings.

In dogs and cats, EEG can be obtained during sedation or general anesthesia, although this may limit the ability to capture epileptic events; or it can be obtained in awake patients preferably with simultaneous video recording (video-EEG). Video-EEG technology has advanced to include small portable wireless videosynchronized systems. Wireless video-EEG has been shown to help clarify the nature of paroxysmal events in 72% of unsedated dogs.[50] Depending on the EEG protocol used, different EEG abnormalities detection rates have been reported in epileptic dogs and cats, ranging from 20% to 86%.[50–56]

Details on acquisition and interpretation of EEG are presented in Chapter 7.

TAKE-HOME MESSAGES

- A thorough medical history, a detailed description (and whenever possible video footage) of the paroxysmal event along with a physical and neurological examination are key steps to establish if the paroxysmal events the animal is experiencing represent epileptic seizures, reactive seizures or other nonepileptic paroxysmal events.
- Various paroxysmal events such as PxDs can mimic seizure disorders. Clinical discriminators can be used to differentiate between seizures, either epileptic or reactive, and nonepileptic paroxysmal conditions.
  - Recognition of pre- and/or postictal signs and occurrence during the ictus of autonomic manifestations, impairment of consciousness, and rhythmic muscle contractions (including lip smacking, chewing, licking, tooth grinding) support a clinical diagnosis of epileptic seizures.
- Recognition of prodromal (preictal) signs can provide a useful therapeutic window for preemptive ASD administration to abort impending seizure activity.
- In the seizure patient, the differential diagnosis list can be developed combining information on:
  - Patient's age at seizure onset
  - Seizure phenomenology, frequency and progression
  - Presence, onset and course of interictal neurological abnormalities
  - Presence, onset and course of clinical signs suggestive of other organ system disease or exposure to toxins
- A systematic diagnostic approach can help identify the underlying cause of the seizure disorder, appropriate treatment and prognosis.
- Minimum database laboratory investigations in dogs and cats with seizure disorders include hematology, comprehensive serum biochemistry (including fasting bile acids and electrolytes) and urinalysis.
- Magnetic resonance imaging is indicated anytime structural epilepsy is suspected and to support the diagnosis of IE. The quality of the MRI images is affected by the magnet strength, the MRI protocol as well as the experience and expertise of the operators acquiring and interpreting the images.

- ✔ In animals with intraparenchymal cerebral signal changes that are suspected to be the result rather than the cause of the epileptic seizures, repeating the MRI of the brain after a period of seizure control, along with repeated neurological examination and, if indicated, CSF analysis, may help to differentiate epileptic seizure–induced MRI changes from inflammatory or neoplastic epileptogenic structural lesions.
- ✔ Cerebrospinal fluid analysis is indicated to investigate structural brain disease, particularly inflammatory/infectious central nervous system disorders.
- ✔ Wireless video-EEG in unsedated dogs may help to differentiate epileptic versus nonepileptic paroxysmal events.

REFERENCES

1. Blume WT, Luders HO, Mizrahi E et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia.* 2001; 42:1212–1218.
2. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*. 2014; 55(4):475–482.
3. Berendt M, Farquhar RG, Mandigers PJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res.* 2015; 28(11):182. doi: 10.1186/s12917-015-0461-2.
4. De Risio L, Bhatti S, Muñana K et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015; 28(11):148. doi: 10.1186/s12917-015-0462-1.
5. Finnegan SL, Volk HA, Asher L et al. Investigating the potential for seizure prediction in dogs with idiopathic epilepsy: owner-reported prodromal changes and seizure triggers. *Vet Rec.* 2020; 187(4):152. doi: 10.1136/vr.105307.
6. Brocal J, Lowrie M, Wamsley G et al. Epileptic seizures triggered by eating in dogs. *J Vet Intern Med.* 2020; 34(3):1231–1238. doi: 10.1111/jvim.15773.
7. Forsgård JA, Metsähonkala L, Kiviranta AM et al. Seizure-precipitating factors in dogs with idiopathic epilepsy. *J Vet Intern Med.* 2019; 33(2):701–707. doi: 10.1111/jvim.15402.
8. Lowrie M, Thomson S, Bessant C et al. Levetiracetam in the management of feline audiogenic reflex seizures: a randomised, controlled, open-label study. *J Feline Med Surg.* 2015; 19(2):200–206. http://doi.org/10.1177/1098612X15622806
9. Urkasemsin G, Olby NJ. Canine paroxysmal movement disorders. *Vet Clin North Am Small Anim Pract.* 2014; 44:1091–102.

10. Platt SR. Mimics of seizure activity: Disorders confused with epilepsy. Chapter 9. In: De Risio L, Platt SR (eds.). *Canine and feline epilepsy: diagnosis and management*. Wallingford: CABI; 2014. pp. 244–276.
11. Lowrie M, Garosi L. Classification of involuntary movements in dogs: Paroxysmal dyskinesias. *Vet J.* 2017; 220: 65–71.
12. Lowrie M, Garosi G. Natural history of canine paroxysmal movement disorders in Labrador retrievers and Jack Russell terriers. *Vet J.* 2016; 213:33–37. doi: 10.1016/j.tvjl.2016.03.007.
13. Lowrie M, Garden O, Hadjivassiliou et al. Characterization of paroxysmal gluten-sensitive dyskinesia in border terriers using serological markers. *J Vet Intern Med.* 2018; 32:775–781. doi: 10.1111/jvim.15038.
14. Forman OP, Penderis J, Hartley C et al. Parallel mapping and simultaneous sequencing reveals deletions in BCAN and FAM83H associated with discrete inherited disorders in a domestic dog breed. *PLoS Genet.* 2012;8:e1002462. doi: 10.1371/journal.pgen.1002462.
15. Kolicheski AL, Johnson GS, Mhlanga-Mutangadura T et al. A homozygous PIGN missense mutation in Soft-Coated Wheaten Terriers with a canine paroxysmal dyskinesia. *Neurogenetics*. 2017; 18(1):39–47. doi: 10.1007/s10048-016-0502-4.
16. Nessler J, Hug P, Mandigers PJJ et al. Mitochondrial PCK2 missense variant in Shetland Sheepdogs with paroxysmal exercise-induced dyskinesia (PED). *Genes (Basel)*. 2020 Jul; 11(7): 774. doi: 10.3390/genes11070774.
17. Penning VA, Connolly DJ, Gajanayake I et al. Seizure-like episodes in 3 cats with intermittent high-grade atrioventricular dysfunction. *J Vet Intern Med.* 2009; 23(1):200–205. doi: 10.1111/j.1939-1676.2008.0231.x.
18. Shea A, Hatch A, De Risio L et al. Association between clinically probable REM sleep behavior disorder and tetanus in dogs. *J Vet Intern Med.* 2018; 32:2029–2036. https://doi.org/10.1111/jvim.15320.
19. Poirier-Guay MP, Bélanger MC, Frank D. Star gazing in a dog: atypical manifestation of upper gastrointestinal disease. *Can Vet J.* 2014 Nov; 55(11):1079–1082.
20. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. *Epilepsy Behav*. 2011; 21(2):160–167. http://dx.doi.org/10.1016/j.yebeh.2011.03.018.
21. Jokinen TS, Tiira K, Metsähonkala L, et al. Behavioral abnormalities in Lagotto Romagnolo dogs with a history of benign familial juvenile epilepsy: a long-term follow-up study. *J Vet Intern Med.* 2015; 29(4):1081–1087. https://doi.org/10.1111/jvim.12611
22. Levitin H, Hague DW, Ballantyne KC et al. Behavioral changes in dogs with idiopathic epilepsy compared to other medical populations. *Front Vet Sci.* 2019; 6:396. doi: 10.3389/fvets.2019.00396.
23. Packer RMA, McGreevy PD, Salvin HE et al. Cognitive dysfunction in naturally occurring canine idiopathic epilepsy. *PLoS One.* 2018; 13(2): e0192182. https://doi.org/10.1371/journal.pone.0192182.
24. Pákozdy A, Leschnik M, Tichy AG et al. Retrospective clinical comparison of idiopathic versus symptomatic epilepsy in 240 dogs with seizures. *Acta Vet Hung.* 2008; 56:471–483.
25. Armașu M, Packer RMA, Cook S et al. An exploratory study using a statistical approach as a platform for clinical reasoning in canine epilepsy. *Vet J.* 2014; 202:292–296.
26. Stanciu GD, Packer RMA, Pakozdy A et al. Clinical reasoning in feline epilepsy: Which combination of clinical information is useful? *Vet J.* 2017; 225:9–12. doi: 10.1016/j.tvjl.2017.04.001.

27. SMITH PM, TALBOT CE, JEFFERY ND. Findings on low-field cranial MR images in epileptic dogs that lack interictal neurological deficits. *Vet J.* 2008; 176:320–325.
28. ZIMMERMANN R, HÜLSMEYER V, SAUTER-LOUIS C et al. Status epilepticus and epileptic seizures in dogs. *J Vet Intern Med.* 2009; 23:970–6.
29. BRAUER C, JAMBROSZY M, TIPOLD A. Metabolic and toxic causes of canine seizure disorders: a retrospective study of 96 cases. *Vet J.* 2011; 187:272–275.
30. DE RISIO L. Reactive Seizures. Chapter 4. In: DE RISIO L, PLATT SR. (eds). *Canine and feline epilepsy: diagnosis and management*. Wallingford: CABI; 2014. pp. 54–100.
31. DE RISIO L. Structural Epilepsy. Chapter 5. In: DE RISIO L, PLATT SR. (eds). *Canine and feline epilepsy: diagnosis and management*. Wallingford: CABI; 2014. pp. 101–206.
32. GHORMLEY TM, FELDMAN DG, COOK JR. Epilepsy in dogs five years of age and older: 99 cases (2006–2011). *J Am Vet Med Assoc.* 2015; 246(4): 447–450 http://dx.doi.org/10.2460/javma.246.4.447.
33. SCHWARTZ M, LAMB CR, BRODBELT DC et al. Canine intracranial neoplasia: clinical risk factors for development of epileptic seizures. *J Small Anim Pract.* 2011;52:632–637.
34. SCHWARTZ M, MUÑANA KR, NETTIFEE-OSBORNE J. Assessment of the prevalence and clinical features of cryptogenic epilepsy in dogs: 45 cases (2003-2011). *J Am Vet Med Assoc.* 2013; 42:651–657.
35. RUSBRIDGE C, LONG S, JOVANOVIK J et al. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol. *BMC Vet Res.* 2015; 28;11:194. doi: 10.1186/s12917-015-0466-x.
36. VON OERTZEN J, URBACH H, JUNGBLUTH S et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *J Neurol Neurosurg Psychiatry.* 2002;73(6):643–647.
37. MELLEMA LM, KOBLIK PD, KORTZ GD et al. Reversible magnetic resonance imaging abnormalities in dogs following seizures. *Vet Radiol Ultrasound.* 1999; 40:588–595.
38. NAGENDRAN A, MCCONNELL JF, DE RISIO L et al. Peri-ictal magnetic resonance imaging characteristics in dogs with suspected idiopathic epilepsy. *J Vet Intern Med*. 2021 Feb 9. doi: 10.1111/jvim.16058. Epub ahead of print.
39. ESTEY CM, DEWEY CW, RISHNIW M et al. A subset of dogs with presumptive idiopathic epilepsy show hippocampal asymmetry: a volumetric comparison with non-epileptic dogs using MRI. *Front Vet Sci*. 2017; 8(4):183. doi: 10.3389/fvets.2017.00183.
40. HARTMANN A, SAGER S, FAILING K et al. Diffusion-weighted imaging of the brains of dogs with idiopathic epilepsy. *BMC Vet Res.* 2017; 13(1):338. doi: 10.1186/s12917-017-1268-0.
41. OLSZEWSKA A, SCHMIDT MJ, FAILING K et al. Interictal single-voxel proton magnetic resonance spectroscopy of the temporal lobe in dogs with idiopathic epilepsy. *Front Vet Sci.* 2020; 24(7):644. doi: 10.3389/fvets.2020.00644.
42. BOHN AA, WILLS TB, WEST CL et al. Cerebrospinal fluid analysis and magnetic resonance imaging in the diagnosis of neurologic disease in dogs: a retrospective study. *Vet Clin Pathol.* 2006; 35(3):315–320. doi: 10.1111/j.1939-165x.2006.tb00138.x.
43. GRANGER N, SMITH PM, JEFFERY ND. Clinical findings and treatment of noninfectious meningoencephalomyelitis in dogs: a systematic review of 457 published cases from 1962 to 2008. *Vet J.* 2010; 184(3):290–297. https://doi.org/10.1016/j.tvjl.2009.03.031.
44. MARIANI CL, NYE CJ, RUTERBORIES L et al. Cerebrospinal fluid lactate concentrations in dogs with seizure disorders. *J Vet Intern Med.* 2020; 34(6):2562–2570. doi: 10.1111/jvim.15953.

45. GONÇALVES R, ANDERSON TJ, INNOCENT G et al. Effect of seizures on cerebrospinal fluid analysis in dogs with idiopathic epilepsy. *Vet Rec.* 2010; 166:497–498.
46. COELHO AM, MADDOX TW, SANCHEZ-MASIAN D et al. Diagnostic value of cerebrospinal fluid analysis in a population of dogs with suspected idiopathic epilepsy. *Vet Rec.* 2019; 185(17):539. doi: 10.1136/vr.105438.
47. GILBERT SE, CARDY TJ, BERTRAM S, TAYLOR-BROWN F. Diagnostic utility of cerebrospinal fluid analysis in dogs with suspected idiopathic epilepsy. *Aust Vet J.* 2020; doi: 10.1111/avj.13018.
48. DI TERLIZZI R, PLATT SR. The function, composition and analysis of cerebrospinal fluid in companion animals: part II - analysis. *Vet J.* 2009; 180(1): 15–32.
49. DE RISIO L. Clinical and Diagnostic Investigation of the Seizure Patient. Chapter 10. In: De Risio L, Platt SR. (eds). *Canine and feline epilepsy: diagnosis and management*. Wallingford: CABI; 2014. pp. 274–324.
50. JAMES FMK, CORTEZ MA, MONTEITH G et al. Diagnostic utility of wireless video-electroencephalography in unsedated dogs. *J Vet Intern Med.* 2017; 31(5):1469–1476. doi: 10.1111/jvim.14789.
51. JESEREVICS J, VIITMAA R, CIZINAUSKAS S et al. Electroencephalography findings in healthy and Finnish Spitz dogs with epilepsy: Visual and background quantitative analysis. *J Vet Intern Med.* 2007; 21:1299–1306.
52. JAGGY A, BERNARDINI M. Idiopathic epilepsy in 125 dogs: A long-term study. Clinical and electroencephalographic findings. *J Small Anim Pract.* 1998; 39:23–29.
53. BERENDT M, HOGENHAVEN H, FLAGSTAD A et al. Electroencephalography in dogs with epilepsy: Similarities between human and canine findings. *Acta Neurol Scand.* 1999; 99, 276–283.
54. PAKOZDY A, THALHAMMER JG, LESCHNIK M et al. Electroencephalographic examination of epileptic dogs under propofol restraint. *Acta Vet Hung.* 2012; 60:309–324.
55. BRAUER C, KASTNER SBR, KULKA AM et al. Activation procedures in the electroencephalograms of healthy and epileptic cats under propofol anaesthesia. *Vet Rec.* 2012a; 170:360.
56. BRAUER C, KASTNER SBR, ROHN K et al. Electroencephalographic recordings in dogs suffering from idiopathic and symptomatic epilepsy: Diagnostic value of interictal short time EEG protocols supplemented by two activation techniques. *Vet J.* 2012b; 193:185–192.

Canine Idiopathic Epilepsy

02

Andrea Fischer

Canine idiopathic epilepsy (IE) is one of the most common chronic neurological conditions in dogs, with an estimated prevalence of epilepsy of 0.6–0.75% in primary care veterinary practice[1,2] and 1–5.6% in referral veterinary hospital populations.[3–5] In neurology referral practice, IE constitutes 53% of all cases of epilepsy.[5,6] Prevalence of IE can be much higher in predisposed dog breeds and even higher in specific breeding lines. Breed prevalences as high as 17%, and up to 33% in predisposed breeding lines have been reported.[7,8] However, both purebred and mixed breed dogs can be affected.

Idiopathic epilepsy is a disease in its own right, in which the nature of the underlying cause is yet unknown. The age of onset is between 6 months and 6 years, and the interictal physical and neurological examination and blood tests are unremarkable. A genetic cause of IE is often suspected (see Chapter 4). In 2015, the International Veterinary Epilepsy Task Force (IVETF) suggested that IE in dogs be subclassified as follows (Fig. 2.1):[9]

- Genetic IE. Gene analysis has identified a causative gene for IE.
- Suspected genetic IE. A genetic etiology of IE is suspected when there are family members that are also affected by IE or a genetic risk factor has been identified. A genetic etiology may also be suspected if the prevalence of IE in the breed is higher than in the general canine population. The prevalence of epilepsy in the general dog population has been reported at less than 1%; a breed prevalence above 2% is therefore considered to be higher than normal. However, the prevalence of IE in a particular canine breed may fluctuate over time and with the breeding lines used.

- Idiopathic epilepsy of unknown etiology. The underlying cause of the IE is yet unknown despite extensive diagnostic investigations. There is no indication or suspicion of structural brain disease.

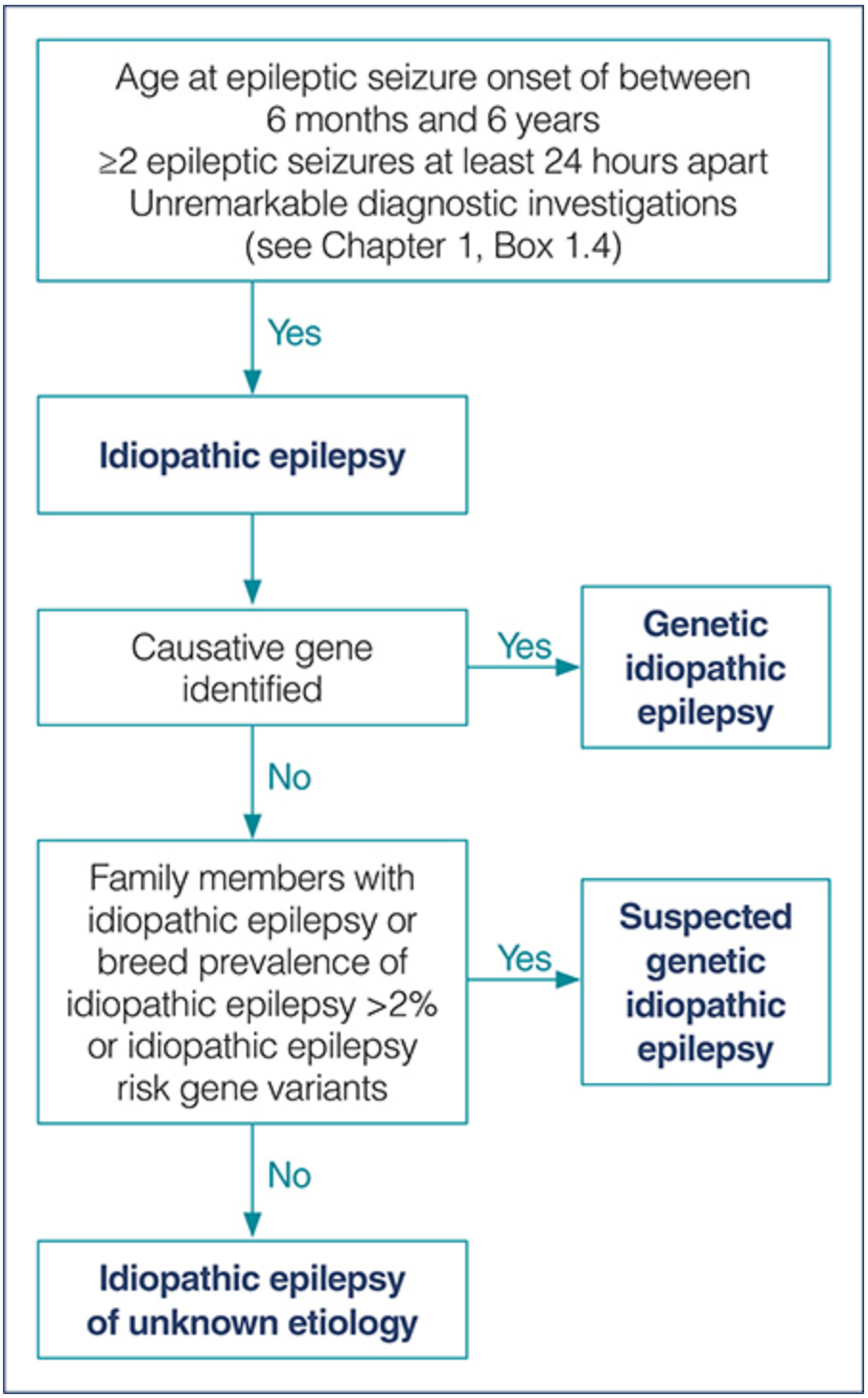


FIGURE 2.1. Classification of idiopathic epilepsy.

The IVETF terminology and consensus guidelines for the diagnosis of IE in dogs are presented in Chapter 1. The specific diagnostic steps (i.e., Tier 1, 2 and 3) to substantiate the clinical suspicion of IE and exclude structural epilepsy and reactive seizures are outlined in Chapter 1, Box 1.4 and described in the *Diagnostic Approach* section in this chapter.

TYPES OF EPILEPTIC SEIZURES

The two main types of epileptic seizures are generalized and focal seizures. Classification of epileptic seizures as generalized or focal is primarily based on the clinical signs and follows the current recommendations in humans. Idiopathic epilepsy in many dog breeds is characterized by the occurrence of both generalized and focal epileptic seizures. Focal epileptic seizures may or may not become generalized with bilateral tonic-clonic convulsions. Application of this type of clinical classification of epileptic seizures requires observations of the onset of the epileptic seizures and critical appraisal of any short episodes of abnormal motor, behavioral and autonomic signs. Yet the distinction between epileptic seizures and nonepileptic events such as paroxysmal dyskinesia (see Chapter 1) can be challenging because of overlapping clinical signs. Furthermore, different epileptic seizure types can occur in the same dog with IE. In human medicine, the initial approach to epileptic seizure classification is based on semiology and clinical signs at seizure onset. Electroencephalography (EEG) is widely used to determine the affected cerebral regions (focal versus generalized). Epileptic seizures can be further subdivided into motor or nonmotor epileptic seizures, and convulsive or nonconvulsive epileptic seizures.

Generalized epileptic seizures

Generalized epileptic seizures result from epileptic activity that involves networks in both cerebral hemispheres from the beginning of the seizure and is self-limiting. Dogs with generalized convulsive epileptic seizures show involvement of the head and both sides of the body immediately at the beginning of the seizure.

Generalized epileptic seizures are frequently **convulsive** and present as short and self-limiting convulsions in the form of generalized tonic, clonic or various combinations of tonic and clonic movements. These are often referred to as generalized tonic-clonic epileptic seizures. Autonomic signs (hypersalivation, urination, defecation, mydriatic pupils) and impairment of consciousness commonly occur. Convulsions are usually short and stop by themselves. The typical duration of a generalized convulsive epileptic seizure is less than 1–2 minutes (Videos 2.1 to 2.4).

A generalized epileptic seizure in a Border Terrier with idiopathic epilepsy. The dog is in lateral recumbency and shows convulsions of the whole body and the head. Convulsions appear as clonic movements and chewing movements. The dog is unconscious and saliva is coming out of the left side of the mouth. The onset of the epileptic seizure is not shown in this video.

Video 2.1.



Generalized epileptic seizure in a 4-year-old Border Collie–Australian Shepherd mixed-breed dog with idiopathic epilepsy. The epileptic seizure starts with clonic movements of the trunk. Then the dogs falls to the side and develops convulsions of the whole body. During the convulsions, the dog is unconscious and has clonic movements, running movements and a widely opened mouth with some chewing movements. The duration of the ictus is 45 seconds.

Video 2.2.



Generalized epileptic seizure in a French Bulldog with idiopathic epilepsy (IE). The epileptic seizure starts with tonic extension of all limbs with some superimposed clonus while the dog is still in a sternal position. Then consciousness appears to be progressively impaired, the dog starts to salivate, falls to the side and has convulsions of the whole body and the head. This dog was anesthetized for >2 days for treatment of status epilepticus and recovered uneventfully. This dog had a Tier 2 level of IE diagnosis.

Video 2.3.



A milder generalized epileptic seizure in the 4-year-old Border Collie–Australian Shepherd mixed breed dog with idiopathic epilepsy (same dog as in Video 2.2). The dog is in lateral recumbency and shows running automatisms of all limbs and appears to go in and out of the epileptic seizure with some attempts to get up. Note how the dog rapidly regains consciousness when the epileptic seizure stops. The onset of the epileptic seizure is not shown in this video.

Video 2.4.



Nonconvulsive generalized epileptic seizures are less commonly described and include myoclonic epileptic seizures, atonic epileptic seizures, and absence seizures:

- **Myoclonic epileptic seizures** are characterized by bilateral single or repetitive twitches or myoclonic jerks, sometimes resembling electric shocks, usually affecting both sides of the body. Myoclonic epileptic seizures can also occur as reflex epileptic seizures that are elicited by light (Videos 2.5 to 2.7) or sound stimuli.
- **Atonic epileptic seizures** present as a sudden loss of muscle tone that causes drop attacks or sudden occurrence of collapse. Atonic epileptic seizures need to be differentiated from syncope and cataplectic attacks (see Chapter 1, Video 1.2).
- **Absence seizures** present as short episodes of freezing or staring, in which the dog does not respond to stimuli. There are no motor signs or only subtle motor signs in the form of mild facial or eyelid myoclonus (Video 2.8).

Differentiating nonconvulsive epileptic seizures from nonepileptic paroxysmal events is often challenging. Ambulatory video-EEG in the awake dog can help to confirm the epileptic origin of nonconvulsive epileptic seizures (see Chapter 7 for further details on EEG). Occurrence of convulsive epileptic seizures in dogs with concurrent suspected nonconvulsive epileptic seizures can also help support the suspicion of an epileptic origin for the latter. Myoclonic epileptic seizures and absence seizures have been documented in Rhodesian Ridgebacks with a form of genetic idiopathic myoclonic epilepsy, with an onset in young dogs and compared with juvenile myoclonic epilepsy in humans[10] (Videos 2.5 and 2.8).

Epileptic and nonepileptic myoclonus is also a frequent feature of progressive myoclonic epilepsies such as Lafora disease (Video 2.9) and neuronal ceroid lipofuscinoses, but these are classified as epileptic encephalopathies and structural epilepsies (see Chapter 4 for further details).

Focal epileptic seizures

Focal epileptic seizures result from epileptic activity in a localized area of the brain, such as a group of neurons or a network in one cerebral hemisphere. Clinically, focal epileptic seizures can present with motor signs or nonmotor signs, e.g., autonomic signs or behavioral signs, and reflect the region of the brain where the epileptiform activity arises (epileptogenic zone). The motor and nonmotor signs can occur alone or in combination with each other. Classification is often based on the predominant clinical signs and a consistent onset of the focal epileptic seizures. Consciousness is no longer used as a differentiating sign for focal epileptic seizures.

Myoclonic epileptic seizures appear as the first sign of genetic idiopathic epilepsy in young Rhodesian Ridgebacks. In this patient, myoclonic jerks occurred predominantly during rest with a variable intensity. With permission from: Wielander et al., 2017 (see credits).

Video 2.5.



Photosensitvity. Repetitive myoclonic twitches and jerks provoked by light flashes in a Rhodesian Ridgeback with genetic idiopathic epilepsy (juvenile myoclonic epilepsy). With permission from: Wielander et al., 2017 (see credits).

Video 2.6.



Video-EEG with intermittent light stimulation showing generalized epileptiform discharges in association with some muscle artifact in a Rhodesian Ridgeback with genetic idiopathic epilepsy (juvenile myoclonic epilepsy). With permission from: Wielander et al., 2017 (see credits).

Video 2.7.



Video-EEG of absence seizures in a Rhodesian Ridgeback with genetic idiopathic epilepsy (juvenile myoclonic epilepsy). The dog showed multiple short episodes of decreased awareness during the day. Video-EEG confirmed that these were nonconvulsive epileptic seizures. The dog was homozygous for the DIRAS1 gene variant associated with juvenile myoclonic epilepsy (JME). Another dog from the same litter was also affected. With permission from: Wielander et al., 2018 (see credits).

Video 2.8.



Repetitive myoclonus in a 10-year-old female Beagle with Lafora disease. Lafora disease was confirmed by genetic testing in this dog. Myoclonus presented as sudden electric shock-like movements of the neck and body. The video shows repetitive myoclonus being elicited by sudden movements, i.e., when the dog was shaking, but myoclonus was also elicited by bright light stimuli in this dog. Generalized tonic–clonic epileptic seizures and progressive behavioral changes occur in the later stages of Lafora disease in dogs.

Video 2.9.



Focal sensory/behavioral epileptic seizures. According to the IVETF consensus, short episodes of anxiousness, restlessness, unexplainable episodes of fear or abnormal attention seeking can be the expression of a focal sensory/behavioral epileptic seizure. Impaired awareness and decreased responsiveness can also be a feature, but evaluation of consciousness is challenging to perform accurately, particularly when based on review of video footage or the pet owner's description.

Focal autonomic epileptic seizures can manifest as dilated pupils, hypersalivation (Video 2.10) or unexplained vomiting.

Focal motor epileptic seizures can manifest as episodic motor signs that express some rhythmicity and are either restricted to the head or one limb. These include facial muscle twitches, rhythmic blinking of the eyelids, repeated jerking of the head, and rhythmic jerking of one limb (Video 2.11).

In clinical practice, differentiation between nonepileptic paroxysmal dyskinesia (Video 2.12) and focal motor epileptic seizures is a frequent challenge. A short duration of episodes (<5 minutes), signs that are restricted to one region of the body or the head, lateralization of clinical signs (e.g., unilateral facial twitches) and autonomic signs (mydriatic pupils, hypersalivation, urination) are more suggestive of a focal motor epileptic seizure than of a nonepileptic paroxysmal event.

Episodes characterized by head tremors that can be interrupted, with no other signs suggestive of epilepsy (e.g., hypersalivation, facial muscle twitches, progression to bilateral convulsions) and maintained responsiveness are characteristic of **idiopathic head tremor** (Video 2.13).[11,12] Therefore, idiopathic head tremor is often considered a movement disorder related to dystonia. However, isolated head tremor has also been described and observed in dogs with IE and either focal, focal evolving to generalized, or generalized epileptic seizures, and thus it appears that idiopathic head tremor can also be the manifestation of an epileptic seizure

in these dogs. Ictal EEG recordings supported epileptic seizures in some dogs.[13,14]

The recent introduction of long-term ambulatory video-EEG recordings, which provides simultaneous recording of the clinical manifestations and the EEG activity in awake dogs, has shown promise for the diagnosis of nonmotor and nonconvulsive epileptic seizures (Video 2.14).[13,15]

Prominent hypersalivation in a French Bulldog during the final stages of an epileptic seizure. Hypersalivation is a frequent feature of generalized and focal epileptic seizures.

Video 2.10.



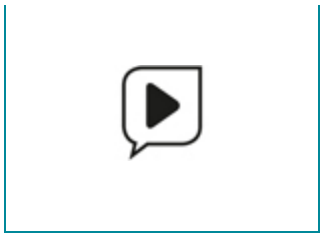
Focal epileptic seizures characterized by facial twitches in an Australian shepherd with idiopathic epilepsy. Electroencephalography confirmed that the facial twitches were focal epileptic seizures. This dog also experienced frequent generalized tonic-clonic epileptic seizures.

Video 2.11.



Suspected paroxysmal dyskinesia. Paroxysmal dyskinesia was suspected in this dog, which presented with long episodes of tonic contractions with no loss of consciousness. No autonomic signs (hypersalivation, urination) occurred in association with the episodes. Diagnostic tests (hematology, serum biochemistry, brain magnetic resonance imaging, cerebrospinal fluid analysis) were unremarkable. The differentiation between paroxysmal dyskinesia and tonic epileptic seizures can be challenging and relies on a longer duration of episodes, preserved consciousness and absence of autonomic signs in dogs with paroxysmal dyskinesia. Unlike the dog shown here, many dogs with dyskinesia maintain a standing position during at least part of the episode.

Video 2.12.



Episodic head tremor in a 3-year-old male French Bulldog. Idiopathic head tremor was suspected. The dog did not lose consciousness during the episodes, there were no autonomic signs and the owners were able to interrupt the head tremor by offering food to the dog. The blood tests and neurological examination were unremarkable.

Video 2.13.



Head nodding episodes in a Rhodesian Ridgeback with juvenile myoclonic epilepsy. With permission from: Wielander et al., 2017 (see credits).

Video 2.14.



Focal epileptic seizures evolving to become generalized

This type of epileptic seizure starts in a localized region in one cerebral hemisphere, which is often referred to as the epileptogenic zone,[16] and subsequently spreads in preformed subcortical networks to involve both cerebral hemispheres. Clinically, this is reflected by localized motor, autonomic, or behavioral signs, which appear alone or in combination, in the seconds or minutes before progressing to generalized tonic-clonic epileptic seizures. Previously, this type of epileptic seizure was also described as secondary generalized seizure or focal (partial) seizure with secondary generalization. Whatever term is used, these epileptic seizures are primarily focal epileptic seizures, which arise from one hemisphere and

then spread to both hemispheres, and they should not be classified as generalized onset epileptic seizures.

Consequently, dog owners need to be thoroughly questioned about the onset of the epileptic seizure (see Chapter 1, Fig. 1.3). Observation of the onset is necessary to classify a tonic-clonic epileptic seizure as generalized from the beginning or as a focal-onset seizure that has become generalized. Video footages of epileptic seizures are only helpful in this context if the beginning of the epileptic seizure is also captured.[16]

In human medicine, the type of epileptic seizure can be further classified based on the specific clinical signs at epileptic seizure onset. A focal epileptic seizure that becomes generalized can be further classified as a focal behavioral epileptic seizure or even a fear-related focal epileptic seizure evolving to a generalized tonic-clonic seizure if intense fear is experienced in the seconds or minutes prior to the generalized tonic-clonic motor activity. Similarly, the IVETF acknowledges that each type of epileptic seizure can be characterized by a consistent onset. However, it may be difficult to get insights into the psychic and sensory correlates of behavioral changes that are observed in dogs at the onset of an epileptic seizure.

Seizure phases

The three phases associated with a seizure are as follows:

- Preictal phase or prodrome
- Ictus
- Postictal phase

The duration and clinical manifestations of these three phases are described in detail in Chapter 1 and illustrated in Fig. 1.1.

Severity and frequency

Factors that have an impact on the perception of epileptic seizure severity include:

- Epileptic seizure frequency
- Occurrence of cluster seizures and/or status epilepticus
- Duration and clinical manifestations of the ictus
- Duration and clinical manifestations of the postictal phase

The unpredictable occurrence of epileptic seizures is a concern for the dog's caregiver. Yet, occurrence of epileptic seizures appears to follow an endogenous rhythm that is characteristic for the individual dog and expresses individual seizure risk. Data from 6 dogs with focal epilepsy monitored for an average of 65 weeks with intracranial EEG suggested that circadian, 7-day, and monthly periodicities in electroencephalographic seizures occur independent of antiseizure drug (ASD) dosing, and these patterns likely reflect endogenous rhythms of seizure risk.[17] In this study, 5 out of the 6 dogs had statistically significant periodicity of electroencephalographic seizure timing; 3 dogs had circadian periodicity, 1 dog had circaseptan (7-day) periodicity, and 2 dogs had approximately monthly periodicity.[17]

The term epileptic seizure density was recently introduced to characterize and quantify time periods with increased frequency of epileptic seizures. Dogs without previous cluster seizures were 6 times more likely to achieve epileptic seizure remission than dogs with cluster seizures.[18]

Photosensitivity and provocative factors

Reflex epileptic seizures are an expression of specific epileptic networks in the brain. These types of seizures are consistently and very rapidly caused by specific provocative factors, most commonly afferent stimuli such as light or sound. Other triggers including complex or cognitive stimuli are also possible. Reflex epileptic seizures present frequently as single or repetitive myoclonic jerks. Progression to generalized tonic-clonic seizures can occur. The term photosensitivity refers to reflex epileptic seizures that are provoked by light stimuli. Flickering light, flashing light, or special patterns such as walking while the sun is shining through the trees are reported by caregivers as causes of epileptic seizures. Photosensitivity is a frequent feature of juvenile myoclonic epilepsy in Rhodesian Ridgeback dogs with idiopathic generalized photosensitive epilepsy.[15] Myoclonus evoked by light stimuli is also a feature of Lafora disease in dogs. Photosensitivity can be further explored using EEG with intermittent light stimulation, which can assess different grades of the photoparoxysmal response. Whether stress-induced epileptic seizures and epileptic seizures occurring in association with visits to veterinarians are true reflex epileptic seizures or just an expression of increased epileptic seizure susceptibility is a matter of debate.

DIAGNOSTIC APPROACH

The diagnosis of IE is based on a history of recurrent epileptic seizures (i.e., ≥2 epileptic seizures at least 24 hours apart), the age of onset of epilepsy (between 6 months and 6 years) and the exclusion of reactive seizures and structural brain disease. The diagnostic approach to patients with seizures is described in detail in Chapter 1, with key points specific to the diagnosis of IE presented below.

Confirmation of epileptic seizures

It is important to initially establish whether the paroxysmal events experienced by the dog are epileptic seizures or other episodic events that can mimic epileptic seizures. Confirmation that such events are epileptic seizures is commonly based on semiology. Epileptic seizures will rarely occur when the dog is at the veterinary practice. Therefore, the information on how the epileptic seizures manifest is mostly obtained from the description provided by the dog's caregivers, video footage of the episodes, and standardized questionnaires completed by the caregivers (see Chapter 1, Fig. 1.3). Disorders that can mimic epileptic seizures and clinical factors that can be used to discriminate between epileptic and nonepileptic paroxysmal events are described in Chapter 1.

Age of onset

The age of onset of epileptic seizures is an important factor in the diagnosis of canine IE. Dogs with IE usually experience their first epileptic seizure between the ages of 6 months and 6 years.

Determining accurately the age of onset of epileptic seizures can be challenging for several reasons:

- The dog may have not always lived with the same owner (e.g., dog adopted from an animal shelter).
- The first observed generalized epileptic seizure may not be the first epileptic seizure that the dog has experienced if it is not always with a caregiver (e.g., dog living outdoors).[19]
- Other types of epileptic seizures (focal or myoclonic) may have occurred before the first generalized epileptic seizure, which the owner did not

recognize as epileptic seizures.[10]

Epilepsy history

The medical history should confirm that the dog suffers from epilepsy, i.e., it has experienced two or more epileptic seizures at least 24 hours or longer apart. It should also aim to get insights into possible underlying causes for the epilepsy, particularly since IE is a diagnosis of exclusion. History details that are particularly relevant to a diagnosis of IE include the occurrence of IE in family members or ancestors. However, knowledge on frequent occurrence of IE in a breed or reports of an increased prevalence in the breed must not be a substitute for a thorough diagnostic workup in the individual dog in order to exclude a structural brain disease. Further details on how to obtain a medical history are included in Chapter 1.

International Veterinary Epilepsy Task Force consensus on the diagnosis of idiopathic epilepsy

The IVETF has recommended a structured approach for the diagnosis of canine IE (see Chapter 1, Box 1.4). The diagnosis of IE is defined as the result of a step-by-step diagnostic workup, which starts with the confirmation of epileptic seizures and thus of epilepsy, followed by the exclusion of metabolic diseases or structural epilepsy with the highest level of confidence possible.[20]

Tier 1 confidence in the diagnosis of IE

Tier 1 confidence defines the minimum requirements for a diagnosis of IE. These include the occurrence of the first epileptic seizure between 6 months and 6 years of age, two or more epileptic seizures at least 24 hours apart, and unremarkable physical and interictal neurological examinations, blood tests and urinalysis. Blood tests should include hematology, serum biochemistry and a preliminary assessment of liver function with baseline fasting ammonia or bile acid concentrations. A bile acid stimulation test may be performed but is not obligatory at this stage. Optional blood tests and examinations may be chosen based on hints and evidence from the history and physical examination. Whether and to what extent testing for infectious diseases is included in the minimum data base for new-onset epileptic seizures depends on the animal's geographical location and travel

history. Details on the minimum data base blood tests recommended by IVETF and other blood tests and examinations are presented in Chapter 1, Box 1.4.

Special considerations. Prolonged postictal neurological deficits may be present after cluster seizures or status epilepticus, but these should normalize on subsequent examinations following a period of seizure freedom. High serum concentrations of ASDs (particularly bromide, in dogs on potassium bromide [KBr] treatment) may also make the neurological assessment less reliable (see Chapter 1, *Neurological examination abnormalities associated with the postictal period and antiseizure drugs*).

Tier 2 confidence in the diagnosis of IE

Idiopathic epilepsy is diagnosed with more confidence if brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and a complete bile acid stimulation test have been performed (in addition to the parameters required for a Tier 1 diagnosis) and the results are unremarkable. The IVETF recommends brain MRI (and CSF analysis) in any dog younger than 6 months or older than 6 years at the time of the first epileptic seizure, and in any dog with an abnormal interictal neurological examination. Other indications for brain MRI are any information from the history or seizure semiology that may suggest a structural brain disease: a history of head trauma, lateralized deficits on the neurological examination, or the consistent presence of lateralizing signs at the onset of the epileptic seizure (or the offset). Brain MRI and CSF analysis are also recommended in dogs with a presumptive diagnosis of IE at Tier 1 level that responds poorly to treatment with ASDs. These may be dogs with cluster seizures or status epilepticus, and dogs that fail to respond to treatment with at least one ASD at the highest tolerated dosage or serum concentration.

Special considerations. Computed tomography, which may be used in general veterinary practice as a readily available substitute for brain MRI with lower costs, is not sensitive enough to detect small epileptogenic lesions, and MRI is therefore the recommended imaging modality for any dog with epilepsy. Visualization of the hippocampus can be improved with an epilepsy-specific MRI protocol with planes parallel or perpendicular to the long axis of the hippocampus (see Chapters 1 and 6).[20,21] Postictal changes may be apparent on MRI if imaging is performed within a short time of the epileptic seizures. Repeat imaging after a period of seizure

freedom may be necessary to clarify their nature more definitely.[20] Lastly, the relationship between structural lesions and epileptic seizures can remain uncertain or undefined on certain occasions (e.g., there appears to be no relationship between Chiari malformation and epilepsy in Cavalier King Charles Spaniels), or head trauma can give rise to structural epilepsy without any visible lesions on brain MRI (particularly with low-field magnets).

Tier 3 confidence in the diagnosis of IE

This confidence level requires, in addition to the criteria detailed for Tier 1 and 2 diagnosis, identification of paroxysms of epileptiform activity on ictal or interictal EEG recordings (see Chapter 7). This confidence level is not yet considered part of the routine diagnostic approach in canine IE, as application and access to EEG varies between veterinary institutions.

BREED-RELATED CHARACTERISTICS

Studies on the prevalence and clinical characteristics of canine IE provide valuable data on the disease in a particular breed at the time the study was conducted, including the age of onset, epileptic seizure types, sex predisposition, clinical course, treatment response and remission rate. However, the data generated by these studies need to be interpreted and compared carefully, considering the following factors:

- Robustness of IE diagnosis
- Inclusion and exclusion criteria
- Population size and sampling method (breeding line vs. country-specific vs. wider geographical distribution)
- Country specific-breeding strategies
- Data collection method (caregiver questionnaire, investigations at the recruiting centers, review of medical records and epileptic seizure video footage)
- Ability to distinguish focal seizures from generalized seizures
- Definition of treatment response and IE remission
- Duration of follow-up
- Definition of survival

Two review papers on breed-specific canine IE were published in 2013 and 2015, respectively.[22,23] Since then, more data have become available from several resources, and include descriptions of IE in other canine breeds, insights into breeds with IE from cohorts that were collected for genotyping, and additional insights from large epidemiological studies reporting on the prevalence of epilepsy in veterinary practices, veterinary diagnostic laboratories or among insured animals. However, most epidemiological studies only report on epilepsy in popular dog breeds but were not designed to identify an increased prevalence or risk for IE in a particular breed.

The following breed-specific sections (arranged in alphabetical order) summarize the data available in published peer-reviewed literature at the time of writing of this chapter. Box 2.1 provides details of dog breeds in which IE has been reported based on the information published to date.

BOX 2.1. Canine breeds in which idiopathic epilepsy (IE) has been reported.

Breeds in which genetic IE has been documented and an epilepsy gene identified:

- Lagotto Romagnolo (*LGI2* gene)
- Rhodesian Ridgeback (*DIRAS1* gene)

Breeds with presumed genetic IE (based on a breed prevalence >2% and/or pedigree analysis and/or association with risk gene variants):

- Australian Shepherd (*ADAM23* risk haplotype)
- Beagle (*ADAM23* risk haplotype)
- Belgian Shepherd (Groenendael, Tervuren; *ADAM23* risk haplotype)
- Belgian Shepherd (Malinois)
- Bernese Mountain Dog
- Boerboel
- Border Collie
- Cane Corso
- Cavalier King Charles Spaniel
- English Springer Spaniel
- Finnish Spitz (*ADAM23* risk haplotype)
- German Shepherd
- Golden Retriever
- Greater Swiss Mountain Dog
- Irish Wolfhound
- Italian Spinone
- Keeshond
- Kromfohrlaender (*ADAM23* risk haplotype)
- Labrador Retriever (*ADAM23* risk haplotype)
- Petit Basset Griffon Vendéen
- Poodle (standard)
- Rottweiler
- Schipperke (*ADAM23* risk haplotype)

- Shetland Sheepdog
- Vizsla (Hungarian)
- Whippet (*ADAM23* risk haplotype)

Breeds with IE of unknown etiology (description of cohorts):

- Border Terrier
- Collie
- Dogue de Bordeaux
- Dalmatian

Australian Shepherd

Studies conducted in the breed. A cross-sectional observational study investigated the clinical features of IE and treatment response in Australian Shepherds from Germany, Austria and Switzerland in 2009 and 2010.[24] The study identified 50 Australian Shepherds with IE through requests placed on websites and in referral hospitals. Epilepsy was confirmed by an epilepsy-specific questionnaire followed by a structured telephone interview and review of medical records. The criteria to diagnose IE were ≥2 generalized epileptic seizures at least 4 weeks apart, an age of onset ≤5 years, an unremarkable interictal neurological examination, normal laboratory values (hematology, serum biochemistry and bile acid stimulation test), and absence of previous head trauma. Brain MRI was required if the onset of IE had occurred ≤6 months of age. Brain MRI and CSF analysis were performed in 47% of the dogs, neurometabolic screening in 20%, and a histopathological examination of the brain was available for 4% of the dogs.

A seizure-specific questionnaire aimed at recognizing focal epileptic seizures in this breed identified 23 additional Australian Shepherds (not included in the 50 dogs of the main study) with recurrent episodes of altered mentation, bizarre behavior, tremors, facial twitching, hypersalivation or mydriatic pupils, without occurrence of generalized epileptic seizures. Structured telephone interviews corroborated the suspicion that these episodes could be focal epileptic seizures, but no further investigations were pursued by the owners due to the mild nature of the seizure manifestations.[24]

Age of onset. The median age of onset of the epileptic seizures was 2.5 years (0.3–5 years).

Sex. Sixty-four percent of the affected dogs were males and 36% females.

Epileptic seizure type. Only dogs with generalized tonic-clonic epileptic seizures were included. Descriptions of epileptic seizure onset indicated generalized epileptic seizures (36%), focal epileptic seizures evolving to become generalized (26%) and both epileptic seizure types (38%). Approximately half of the dogs also experienced focal epileptic seizures (52%). Focal epileptic seizures and focal seizure onsets were described as focal tremors and lateral head turn in association with autonomic (hypersalivation, dilated pupils) and behavioral signs (e.g., decreased responsiveness, panic attacks, sporadic aggression, pacing, staring). Preictal signs occurred in 74% of dogs and were mainly characterized by restlessness and contact-seeking. Less commonly reported preictal signs were hiding, excessive sniffing, vocalization, lameness, or vomiting. Most epileptic seizures occurred when the dogs were sleeping or resting (84%). A diurnal rhythm was evident in 52% of the 50 dogs with IE. In these dogs, epileptic seizures occurred during the night or early morning. Cluster seizures were reported in 68% of the dogs and status epilepticus in 60%; 48% of the dogs experienced both cluster seizures and status epilepticus.

Suspicion of a genetic basis. A pedigree analysis supported a genetic origin: epilepsy occurred frequently in family members (littermates, half-littermates). A common founder of 29 dogs was identified.[24] Association with an *ADAM23* risk haplotype further supported the suspicion of genetic IE.[25]

Treatment response. Epileptic seizures continued to occur on a monthly basis (≥1 seizure/month) in 56% of dogs with a phenobarbital (PB) serum concentration >20 μg/mL, in 60% of dogs with a PB serum concentration >30 μg/mL, and in 64% of dogs with adequate treatment with ≥2 ASDs. The serum PB concentration did not differ significantly between dogs that continued to experience ≥1 seizure/month and dogs with <1 seizure/month (median 28.5 μg/mL). The median serum concentration of KBr was 1210 μg/mL in dogs with poor seizure control (1100–1380) and 1430 μg/mL in dogs with good seizure control (1331–1970). The remission rate (defined as no seizures for at least 1 year) was 12% (6/50 dogs), with 3 of these 6 dogs experiencing remission with ASD treatment and 3 dogs without ASD treatment. A high initial seizure frequency (≥10 seizures in the first 6 months of IE) was associated with a poor treatment response.

Survival. Overall, 30% of the study cohort (15/45) were deceased at data collection end. Twelve dogs died during the 2-year study period. In addition, the owners of 3 dogs that died before 2009 provided medical records. Three dogs died during status epilepticus and 11 dogs were euthanized due to poorly controlled epilepsy. One death was unrelated to epilepsy. The median age of death was 3.1 years for deceased dogs. Survival time was defined as the time from seizure onset to death or data collection end. A high initial seizure frequency (≥10 seizures in the first 6 months of IE) and an age of onset <2 years were associated with a shorter survival time.

Epilepsy mimics. Exercise-induced collapse in Australian Shepherds has a similar phenomenology as in Border Collies but occurs less frequently in the breed.[26,27] Rarely, structural epilepsy may occur due to neuronal ceroid lipofuscinosis (CLN6, CLN8).[28,29] A high prevalence of the 4bp deletion in the *MDR1* gene, which predisposes to neurotoxicity, has been reported in the breed,[30–33] but this gene variant was rarely identified in Australian Shepherds with IE from Germany and Switzerland.[24]

Beagle

Studies conducted in the breed. Idiopathic epilepsy was originally described in laboratory Beagles in the US in 1971.[33,34] The colony consisted of 293 litters born between 1963 and 1968. The diagnostic criteria for IE were one or more clinically observed convulsive seizures; IE was diagnosed in 29 dogs. More recent data on IE in Beagles originate from the description of cohorts from Finland (16 dogs from a hunting line), Germany and Sweden (41 dogs), which were collected for genetic investigations by means of epilepsy-specific questionnaires between 2003 and 2013.[35] The diagnostic criteria for IE were ≥2 seizures ≥2 months apart, an onset between 6 months and 5 years of age and no other predisposing factors. In 2017, 5 other Beagles with IE (Tier 2) from Germany were studied with structural MRI.[36] A cohort of 24 Beagles with IE (Tier 1) from the US also participated in genetic investigations but no clinical data were reported.[37]

Age of onset. The median age of onset was 2.5 years in the German/Swedish cohort (range, 1–5 years) and 3 years in the Finnish hunting Beagles (range, 0.7–5 years). The age of onset was 11–70 months in the previously reported laboratory Beagles.[34]

Sex. More males than females were affected.[36] In the laboratory Beagles, 69% were males (20/29) and 31% (9/29) females.[34]

Epileptic seizure type. The epileptic seizures were typically focal seizures evolving to become generalized. The seizures were described as stiffening of the neck and limbs, falling, muscle fasciculations, tremor, staring, trying to get close to the owner, in association with urination and drooling and impaired or absent consciousness. Typical preictal signs included seeking contact with the owner, restlessness and nausea in the Finnish cohort. Triggering factors were excitement, stress and waking up in the morning in the Finnish cohort. Cluster seizures occurred in 6% of the Finnish dogs and in 14% of the German/Swedish dogs.[35] In the laboratory Beagles, tonic-clonic convulsions and presumed focal epileptic seizures with mydriasis, rhythmic opening of the mouth, hypersalivation and loss of balance were described.[34]

Suspicion of a genetic basis. Familial clustering was reported in the laboratory Beagles. The offspring of two sires had a higher probability for IE.[34] An association with an *ADAM23* risk haplotype has been identified in the breed.[35]

Treatment response. The median number of seizures was 10 per year (range, 1–24 seizures per year). Fifty-six percent of the Finnish cohort (9 dogs) and 64% of the German/Swedish dogs were treated with an ASD. A positive treatment response was reported in 6 Finnish dogs. Seizure freedom was achieved in 2 of these 6 dogs.[35]

Epilepsy mimics. Lafora disease is a form of structural epilepsy with progressive myoclonic epileptic seizures that should be considered as a differential diagnosis for IE in Beagles. Differentiating features are an onset of epileptic seizures at an older age than in IE and spontaneous and stimulus-sensitive myoclonus. Genetic testing (*EPM2B*) is available (see Chapter 4 for additional details).[38–40]

Belgian Shepherd (Groenendael and Tervueren)

Studies conducted in the breed. Several studies have investigated IE in Belgian Shepherds (mainly Groenendael and Tervueren variants) from Denmark,[7,41,4] Finland and other European countries[35,43] and the US[8,44–46]. A population survey was conducted in 2008 in Denmark and investigated 1248 Belgian Shepherds born between 1995 and 2004 and registered with the Danish Kennel Club. The study returned 516 valid questionnaires

(response rate, 42%) and showed an overall prevalence of IE of 9.5% among the registered Belgian Shepherds. Epileptic seizures were confirmed with an epilepsy-specific questionnaire and follow-up telephone interview, but diagnostic investigations were not performed consistently. Only dogs with ≥2 epileptic seizures were included.[41] The prevalence of IE increased to 33% in one breeding line of Danish Belgian Shepherds.[7] In this study, living dogs were invited to participate in a detailed clinical investigation. Survival in this family was studied further in a longitudinal study.[42]

Another population survey of 997 Belgian Shepherds was conducted in the late 1980s in the US with a questionnaire that investigated the occurrence of seizures, number of seizures and focal and generalized seizure semiology. This study estimated the prevalence of IE to be 17% (165/997); however, it also included 23 dogs that had suffered only one epileptic seizure.[8] A large Finnish-European cohort of 94 Belgian Shepherds comprised dogs from Finland (64%) and other European countries. The diagnosis of IE was based on the information derived from epilepsy-specific questionnaires and the diagnosis of the primary care veterinarian in 78% of cases. Only dogs with at least two epileptic seizures were included. The diagnosis was subsequently confirmed with MRI, CSF analysis and/or EEG in 17 dogs from Finland.[43]

A recent genetic study in the US included 35 Belgian Shepherds with owner- and veterinarian-reported (generalized) epileptic seizures and an age of onset of IE between 1 and 6 years (median, 3 years) in all but 2 older dogs, but it did not provide further information on investigations or epilepsy characteristics.[44] A previous genetic study in the US used a similar approach and included 36 Belgian Sheepdogs (Groenendael) and 38 Tervuerens with generalized epileptic seizures based on reports from dog owners and veterinarians.[46]

A form of focal IE with an overall benign clinical course was identified in a longitudinal study on the survival of Belgian Shepherds.[42]

Age of onset. The mean age of onset was 3.3 years (6 months–8 years; 3 months–9 years).[41,43] The median age of onset was 4 years (0.8–11.2 years) in the Belgian Shepherds included in the Danish longitudinal observational study.[42]

Sex. The percentage of affected females ranged from 52.9% to 63.3% and the percentage of affected males from 36.7% to 47.1%, but no significant gender predisposition was identified.[41–43]

Epileptic seizure type. In the 49 Belgian Shepherds from the Danish prevalence study, focal epileptic seizures were the most common presentation and evident in 77.6% of dogs (38/49).[41] Epileptic seizures were either focal (24.5%)—with one or more of the following signs: ataxia, crawling, swaying, salivation, and fear-associated behavior, attention seeking and disorientation—or focal evolving to become generalized (53.1%). Generalized epileptic seizures (18.4%) and unclassified epileptic seizures (4.1%) were less common. The average seizure duration was between 30 seconds and 2.5 minutes. Seizure triggering factors were identified in 22% (11/49) of dogs. These were mostly situations resulting in anxiety, hyperactivity or stress (e.g., demanding working conditions, or aggressive behavior towards other pets).[41]

In the 94 dogs from the Finnish-European cohort, 7.4% experienced focal epileptic seizures, 37.2% focal epileptic seizures evolving to become generalized, and the remaining had generalized epileptic seizures with a generalized or unknown onset.[43] Restlessness, attention-seeking, drooling and nausea were identified by the owners immediately prior to the convulsions in 42.7% of the dogs. The mean epileptic seizure duration was 2–4 minutes and ranged from 0.5 to 60 minutes and the mean seizure frequency was 5.25 per year. Cluster seizures occurred in 27.6%[43] and 33%[42] of the cohorts. Interictal EEG demonstrated paroxysmal epileptiform activity (spikes, sharp waves, spike- and slow wave complexes) with variable foci, and supported focal epilepsy.[43]

Suspicion of a genetic basis. The breed prevalence of IE was estimated to be 9.4% in the Danish population[41] and 17% in the US[8], which is higher than in the general canine population. Confidence intervals were not provided. Aggregation of epilepsy in families and a risk haplotype for IE in association with the *ADAM23* gene suggested strong genetic influences.[7,43,44]

Treatment response. Overall, 51% of the Finnish-European cohort (48/94) were treated with ASDs. Treatment response was evaluated in 33 dogs treated with PB or KBr. Of these 33 dogs, 54.4% became seizure free, 30.3% had a reduction in epileptic seizure occurrence ≥50%, and 12.1% experienced a <50% decrease in epileptic seizure occurrence.[43] Remission was defined as no seizures ≥3 years. Remission without treatment occurred in 13.7% of dogs in the Danish cohort.[42]

Survival time. The long-term clinical course was evaluated in 51 Belgian Shepherds with IE from a family with a high prevalence of IE.[42] At the time of data collection end, 27 dogs were deceased with 70% of the deaths (19/27) related to the epilepsy: 17 dogs had been euthanized and 2 dogs had died suddenly during or after a seizure. Survival time was defined as the time from the first observed epileptic seizure to death. The median survival time was 4.25 years. The median age at death was 8.2 years in dogs with IE and 9.25 years in unaffected family members. Epilepsy-related deaths occurred earlier (median, 8 years; range, 2.5–11) than non-epilepsy-related deaths (median, 9.9 years; range, 2.3–15.4).

Belgian Shepherd (Malinois)

Studies conducted in the breed. Genotyping studies investigated the association between a dopamine transporter polymorphism and abnormal behavior in 138 Belgian Malinois from Europe and the US in 2013.[47,48] Samples were collected through word-of-mouth, gene banks and from dogs participating in a behavioral study. Phenotyping of behavior and seizures was based on a short survey in which the owners were asked to answer yes or no to various questions. Five dogs with owner-reported seizures and 43 dogs with episodes characterized by eyes glazing over with loss of responsiveness to environmental stimuli were identified. Neither interviews nor epilepsy-specific questionnaires were used and no diagnostic tests were performed to confirm IE. The diagnosis of IE was therefore presumed.[48]

Epileptic seizure type. No descriptions were provided. The authors hypothesized that the episodes of eyes glazing over and loss of responsiveness could be focal behavioral epileptic seizures.

Suspicion of a genetic basis. Genetic studies supported a possible association of behavioral traits including seizures with a PolyA(22) variable number tandem repeat (VNTR) allele of the dopamine transporter gene *SLC6A3*.

Bernese Mountain Dog

Studies conducted in the breed. A cross-sectional population study identified 50 Bernese Mountain Dogs with IE in Switzerland in 1999.[49] The study used data from a screening questionnaire sent to veterinarians, breeders and owners, and population data from 3800 dogs registered with the Swiss Bernese Mountain club. Epilepsy and epileptic seizures were

confirmed with an additional epilepsy-specific questionnaire requesting information on signalment and a detailed medical history including age of onset, frequency and type of seizures. The diagnostic criteria for IE were an unremarkable interictal physical and neurological examination and unremarkable hematology and serum biochemistry values, ammonia and fasting bile acids concentrations, urinalysis and CSF analysis. It is unclear whether dogs that had suffered only one epileptic seizure were included or excluded in this study. The prevalence of IE was 0.9% in female dogs and 1.2% in male dogs.

Age of onset. The mean age of onset was 2.2 years (range, 2–70.5 months), with 62% of dogs between 1–3 years of age, 20% younger than 1 year, and 18% older than 3 years at the first epileptic seizure.

Sex. Males comprised 62% of the cohort and females 48%. Males were significantly more affected when compared with the gender ratio of the entire Bernese Mountain Dog population.

Epileptic seizure type. Generalized epileptic seizures were reported in 98% of the dogs, but it is unclear whether analysis for focal epileptic seizures evolving to become generalized was pursued. The duration of the epileptic seizures ranged from 20 seconds to 5 minutes. Half of the dogs experienced a prodromal phase lasting for several hours and characterized by restlessness.

Suspicion of a genetic basis. The study indicated a strong genetic background and results suggested that the disease is controlled by more than one major gene. A pedigree analysis demonstrated an increased prevalence of IE in certain families and subpopulations. Two common founders were identified. Epilepsy occurred in the offspring of epileptic dogs. The first epileptic seizure occurred at an earlier age in the offspring of epileptic dogs.

Treatment response. Epileptic seizures varied widely in frequency from 3 per week to 1 every year. Half of the dogs experienced more than one epileptic seizure every 2 months.

Boerboel

Studies conducted in the breed. Juvenile onset focal epilepsy with fear-related behavior has been reported in related Boerboel dogs from the Netherlands. Pedigree analysis indicated 10 affected dogs from three related litters.[50] Five affected dogs from one litter were studied in detail and had an

unremarkable physical and neurological examination and unremarkable hematology and serum biochemistry values, blood ammonia and fasting bile acids concentrations, urinalysis, brain MRI (3 dogs, at the ages of 5 months, 1 year, and 3 years, respectively) and neurometabolic screening (2 dogs). Electroencephalography was not performed. Two dogs were necropsied at 3 and 10 years of age. The histopathological examination revealed neurons with a single large empty vacuole in the deeper cortical regions of the cerebrum in both dogs. Therefore, the authors discussed this may be an as yet unidentified genetic metabolic disorder that should be classified as a form of structural epilepsy.

Age of onset. The age of onset was 3 months in all dogs.

Sex. Both male and female dogs were affected (7 males, 3 females).

Epileptic seizure type. The dogs presented with short episodes of focal fear-related behavior. The owners described "panic attacks" with a facial expression resembling that of extreme fear, loud vocalization (crying, howling "like a wolf") and generalized trembling in association with autonomic signs such as hypersalivation, urination or defecation in all dogs. Other signs were cowering, trying to hide, freezing, lateralized jerking of facial muscles, jerking of a limb, dystonia, ataxia and falling over. Most dogs (4/5) did not respond when the owner called their name during the episode. Episodes occurred on waking up in all dogs. Excitement and stress served as triggers in 2 dogs. The mean duration was 1 minute (range, 20 seconds–10 minutes). Two dogs experienced episodes in clusters.

Suspicion of a genetic basis. The dogs originated from three closely related litters, and autosomal recessive inheritance was considered.

Treatment response. Dogs experienced on average one to two episodes per week, but the frequency varied over time. Seizure frequency initially decreased ≥50% in 4 dogs with PB administration, but 3 of 4 dogs subsequently became unresponsive to PB. Additional treatment with KBr controlled the seizures. One dog was euthanized at 3 years of age because of refractory epileptic seizures, and another dog was euthanized at 10 years of age for reasons unrelated to the epilepsy. The outcome of the other dogs was not described.[50]

Border Collie

Studies conducted in the breed. An observational study identified 49 Border Collies with IE in Germany. Border Collies were identified via

requests placed on websites and in referral hospitals.[51] The criteria to diagnose IE were ≥2 generalized epileptic seizures at least 4 weeks apart, an age of onset between 6 months and 5 years, an unremarkable interictal physical and neurological examination and unremarkable hematology and serum biochemistry. A brain MRI and CSF analysis were required for inclusion in the study if the epileptic seizure onset had occurred at ≤6 months or >5 years of age, or if there was a history of head trauma.

The Border Collie was reported to be a breed commonly affected with IE among dogs evaluated in primary care veterinary practices in the UK, based on a study published in 2013 (odds ratio, 1.61),[1] and was among the three most commonly affected breeds in a study published in 2020.[52] In addition, Border Collies comprised 10.5% of dogs with IE in a laboratory database,[53] 9.9% of dogs treated for IE in a referral hospital[18] and 5.4% of dogs with a Tier 2 diagnosis of IE in an MRI study.[6] In a UK study on juvenile epilepsy, the Border Collie was among the most commonly affected breeds with an onset of IE at <1 year of age.[54] The popularity of the breed must be considered when interpreting these prevalence data.

Age of onset. The median age of onset in the German Border Collies was 2.4 years (range, 0.4–8.1 years), with an onset between 1 and 5 years in 74% of dogs, ≤1 year in 18% of dogs and >5 years in 8% of dogs.[51]

Sex. Both sexes were equally affected in the German study.[51]

Epileptic seizure type. In the German cohort, the most common epileptic seizure type was focal evolving to become generalized (78%), and less commonly generalized (8%) or unclassified generalized (14%).[51] The onset was characterized by staring into space for a few seconds and lateral head turn or opisthotonus. Additional focal motor seizures described as episodic head or facial twitching with decreased responsiveness occurred in 45% of dogs.[51] About half of the dogs (57%) experienced preictal signs, mostly restlessness or attention seeking in the 30 minutes before the ictus.[51] Most epileptic seizures occurred during sleep at night or in the early morning. When epileptic seizures occurred during daytime, the dogs were often in a resting state. Cluster seizures occurred in 94% and status epilepticus in 60% of these dogs.[51] Among the Border Collies in the UK with juvenile onset IE, 84% of dogs had cluster seizures.[54]

Suspicion of a genetic basis. A common ancestor was observed in the German cohort.[51]

Treatment response. In the German cohort, 48% of dogs still experienced one epileptic seizure per month with adequate treatment with ≥2 ASDs, usually PB and KBr, and serum concentrations in the therapeutic range. Remission rate was 18%; 4 dogs had no seizures for ≥1 year and 5 dogs ≥2 years. Remission was associated with an older age at onset of IE and lower frequency of epileptic seizures in the first 6 months of the epilepsy.[51] In reports from the UK and Italy, the Border Collie was less likely than other breeds to experience remission or a ≥50% reduction in seizures[18] and had an increased risk for drug-resistant epilepsy.[55] Initial promising results on an *ABCB1*-polymorphism and its potential association with drug resistance were not confirmed in a subsequent investigation in a multibreed cohort of dogs with IE.[55,56]

Survival time. Survival time was 2.1 years for 23 dogs that were euthanized or died because of their epilepsy.[51] Longer survival times (median 3.8 years; 1393 days) were reported in Border Collies with IE under primary veterinary care in the UK. The reported median survival time from the first observed seizure to death was 2.6 years (941 days) for Border Collies with an onset of IE ≤1 year of age.[54]

Epilepsy mimics. Border Collie collapse is a form of exercise-induced collapse that occurs frequently in the breed. Episodes occur with strenuous exercise or heat. Dogs appear less responsive during episodes and show ataxia—which is worse in the pelvic limbs—, truncal sway and falling.[57] Neuronal ceroid lipofuscinosis from a *CLCN5* gene variant has been identified in Border Collies in Australia and Japan and is associated with progressive fatal behavioral changes and visual disturbances. Myoclonic and convulsive seizures may occur in the middle and late stages of the disease, at 2–3 years of age.[58,59]

Border Terrier

Studies conducted in the breed. A prospective observational study of 108 Border Terriers with paroxysmal episodes conducted in the UK between 2014 and 2017, identified 28 dogs (25.9%; 28/108) with presumed IE, 45 (41.7%) with paroxysmal dyskinesia and 35 (32.4%) with other paroxysmal involuntary movements (myoclonus, tremor, sleep disorder, head bobbing, trance-like syndromes, myokymia) that remained unclassified.[60] The diagnostic criteria for IE included characteristic features of generalized epileptic seizures documented by video footage, with autonomic signs and

loss of consciousness, ≥3 epileptic seizures per year and an unremarkable interictal neurological examination. Blood tests and a brain MRI were not necessary for a diagnosis of IE, but it was stated that dogs were otherwise healthy based on the review of medical records.[60] This study supported the view that IE exists as a distinct disorder from paroxysmal gluten-sensitive dyskinesia (PD) in the Border Terrier.

Previously, a cross-sectional population survey conducted in 1999–2000 by a German breed club identified 365 Border Terriers with a seizure disorder, based on the information obtained using an epilepsy-specific questionnaire. Detailed clinical examinations were performed in 5 dogs and metabolic screening in 22 dogs. This study suggested a prevalence of IE of 13.1% in the Border Terrier breed in Germany, but it is possible that some of the dogs classified as having IE actually had paroxysmal dyskinesia because 22 dogs only showed tonic seizures, and only 10 dogs lost consciousness during the seizure.[61]

In the UK, the evaluation of 455,000 primary care practice electronic records from 2011 reported a prevalence of epilepsy of 1.51% and of seizure disorders of 1.81% in Border Terriers, as well as a significantly increased odds ratio of 2.7 for IE occurrence in the breed when compared to crossbred dogs. The clinical diagnostic criteria for IE were a history of ≥2 epileptic seizures for more than a year in the absence of other medical problems (documented by physical examination, hematology and serum biochemistry), but, as described above, potential overlap with paroxysmal dyskinesia is a concern.[1,62]

Age of onset. The median age of onset of presumed IE was 48 months in the UK study (range, 12–85 months).[60]

Sex. Both sexes were equally affected (42.9% females, 57,1% males) in the UK study.[60]

Epileptic seizure type. Video evidence was available for each of the 28 Border Terriers with a presumptive diagnosis of IE and demonstrated a typical generalized tonic-clonic seizure and autonomic signs of salivation (93%), urination (21%) or defecation (14%). All dogs lost consciousness and were unresponsive during the episode. Additional focal epileptic seizures evolving to become generalized occurred in 12/28 dogs. Focal onset was described as facial twitching spreading to one limb or salivation.[60] Anti-gliadin IgG antibodies and transglutaminase-2 IgA antibodies (which have been reported to be increased in Border Terriers

with paroxysmal gluten-sensitive dyskinesia, see epilepsy mimics below) were within the reference range in most dogs with IE, thus supporting the clinical observations of two distinct disorders.[60]

In contrast, the German cohort appeared to include both dogs with IE (various seizure types) and dogs with paroxysmal dyskinesia, which presented as generalized tonic epileptic seizures (46.8%) and preserved consciousness (78.7%), a low frequency of prodromal signs (27%) and autonomic signs (17%). Clusters occurred in 8.5% of the dogs in the whole cohort.[61] Another study showed that episodes of paroxysmal dyskinesia and generalized epileptic seizures may occur in the same dog on rare occasions (9.8%).[63]

Suspicion of a genetic basis. Currently there are no reliable data available because the studies reporting an increased prevalence of IE, epilepsy and seizure disorders in Border Terriers did not clearly differentiate between paroxysmal dyskinesia and IE.

Treatment response. In the UK cohort, the median seizure frequency was every 81 days. Approximately half of the 28 dogs experienced more than 1 epileptic seizure per month, and 67.9% (19/28) were treated with ASDs.[60]

Epilepsy mimics. Paroxysmal dyskinesia in the Border Terrier has been reported to be frequently associated with elevated concentrations of both anti-gliadin IgG and transglutaminase-2 IgA antibodies. Episode remission and normalization of antibodies following a gluten-free diet for 4 or more weeks suggest that gluten sensitivity has a role in the pathogenesis of this condition, hence the terminology paroxysmal gluten-sensitive dyskinesia.[60] However, anti-gliadin IgG and transglutaminase-2 IgA antibodies can also be increased in dogs with dermatological or gastrointestinal signs, and the diagnosis of paroxysmal dyskinesia in the Border Terrier must therefore be based on a combination of factors, including the clinical presentation, a normal neurological examination, laboratory investigations and when indicated, brain MRI and CSF analysis. The episodes of paroxysmal dyskinesia are characterized by abnormal muscle tone, abnormal posture and involuntary movements (i.e., rigid extended limbs, back or neck, incoordination, and falling over), with consciousness preserved. The mean age of onset of paroxysmal dyskinesia is 3 years (range, 6 months–7 years). Episodes can last 1 minute to 1 hour and occur once a month to once a year.

Episodes occur when the dog is awake, and sudden movement and stress can trigger episodes in some dogs.

Cane Corso

Studies conducted in the breed. A cohort of 25 Cane Corso dogs with a presumptive diagnosis of IE was studied in France in 2016. Data were collected using an epilepsy-specific questionnaire presented to Cane Corso owners and breeders. The diagnostic criteria for IE were not described.[64]

Age of onset. 17.5 months (median).

Sex. No sex predisposition reported.

Epileptic seizure type. All dogs had generalized epileptic seizures. Cluster seizures were frequent and occurred in 91% of dogs. No detailed description of seizure phenomenology was provided.

Suspicion of a genetic basis. Familial clustering was frequently reported. Pedigree data indicated an autosomal recessive inheritance.

Treatment response. Seizure frequency did not decrease with ASD treatment in 54% of the dogs.

Survival time. Thirty percent of the dogs were euthanatized or died in status epilepticus before 3 years of age.

Cavalier King Charles Spaniel

Studies conducted in the breed. Preliminary evidence suggests that IE occurs in the Cavalier King Charles Spaniel and is not related to Chiari malformation and syringomyelia (CM/SM). The information is derived from a pedigree analysis in the UK of 40 Cavalier King Charles Spaniels with a presumptive diagnosis of IE made by primary care veterinarians and no clinical signs of CM/SM,[65] and from a retrospective investigation of 27 dogs with seizures and CM/SM in a UK referral hospital.[66] The criteria for inclusion were recurrent epileptic seizures and unremarkable physical and neurological examination, hematology, serum biochemistry, bile acid stimulation and CSF analysis and no lesions on MRI other than CM/SM.[66] Brain MRI was performed on all dogs and EEG on 4 dogs. There was no association between epilepsy and either ventriculomegaly or caudal fossa overcrowding.[66] This was in agreement with previous observations.[67,68]

Epileptic seizure type. Epileptic seizures were described in the 27 dogs as focal (36%), focal evolving to become generalized (25%) or generalized epileptic seizures (39%).[66] In 2 dogs with generalized epileptic seizures,

atonic epileptic seizures or cerebellar drop attacks in association with CM/SM were discussed.[66] The EEG, performed under light sedation with medetomidine, was abnormal in 3 dogs and showed generalized interictal spike-wave activity (2 dogs) or rhythmic ictal sharp waves (1 dog).[66] Idiopathic epilepsy was more common in breeding lines from whole-colored dogs.[65]

Suspicion of a genetic basis. The UK pedigree study supported a genetic predisposition for IE.[65]

Epilepsy mimics. Episodic falling in Cavalier King Charles Spaniels is caused by a *BCAN* gene variant.[69] Fly catching episodes are frequently observed in the breed and may represent focal epileptic seizures or a compulsive disorder.[70]

Collie

Studies conducted in the breed. An association study evaluated the *ABCB1-1Δ* gene variant and response to ASD treatment in 29 Collies (mostly rough-coated) with IE from the US in 2012. The diagnostic criteria for IE were an age of onset between 6 months and 5 years and a presumptive diagnosis of IE by the primary care veterinarian based on examination findings and laboratory investigations. Only dogs with a history of at least 6 months of treatment with an ASD were included.[71]

Age of onset. Not evaluated. The median age of affected dogs was 5.0 years and median duration of the epilepsy was 3.0 years.

Sex. Sixty-nine percent were male and 31% were female.

Treatment response. Fourteen dogs were treated with PB, 5 dogs with KBr, 7 dogs with a combination of PB and KBr, 1 dog with PB/levetiracetam (LEV), 1 dog with PB/zonisamide and 1 dog LEV/zonisamide/felbamate. Good treatment response was defined as an average seizure frequency of ≤1 per month, and poor response was defined as an average seizure frequency of >1 per month or cluster seizures while treated with at least one ASD in the last 6 months. A good response was observed in 62% (19/29) of Collies, which experienced 0.29 (mean) seizures per month. Nine dogs had no seizures in the previous 6 months. Poor response was observed in 38% of dogs, which experienced 3.9 (mean) epileptic seizures per month. There was a trend towards higher PB and KBr serum concentrations in dogs with a poor treatment response (mean PB 25.7 mg/L; KBr 2208 mg/L) than in dogs with good treatment response (mean

PB 17.7 mg/L; KBr 1400 mg/L) but differences were not statistically significant. Cluster seizures occurred in 35% of dogs, and were associated with a poor treatment response. Homozygosity for the *ABCB1(MDR1)* gene variant (nt230 [del4]) was associated with a good treatment response. Dogs with a poor treatment response received more ASDs and experienced more adverse effects of the treatment.

Dalmatian

Studies conducted in the breed. An observational study in the US investigated seizure phenomenology in 11 Dalmatians using an epilepsy-specific questionnaire and structured telephone interview. The diagnosis of IE was based on a long history of recurrent epileptic seizures (mean 4.9 years) and a normal interictal status with no evidence of structural epilepsy.[72] Only 10% of the dogs underwent a complete diagnostic investigation including a physical and neurological examination, hematology, serum biochemistry and bile acid stimulation test.[72]

Age of onset. The median age of onset was 2.9 years (range, 1.3–5.8 years).

Sex. More females (64%) than males (36%) were affected, but numbers were too small for reliable assessment of sex predisposition.

Epileptic seizure type. Focal epileptic seizures with or without secondary generalization were observed in 80% of the dogs and generalized epileptic seizures in 20% of the dogs. Cluster seizures occurred infrequently in 64% of the dogs (one or two clusters per dog).

Treatment response. The mean seizure frequency was 9.7 seizures per year. Most dogs (72.7%) were treated with ASDs.

Dogue de Bordeaux

Studies conducted in the breed. Five Dogues de Bordeaux with IE were reported in a research abstract.[64] The criteria for the diagnosis of IE were not specified. In another study on seizure occurrence in dogs under primary care veterinary care in the UK, Dogues de Bordeaux had a significantly increased risk of epileptic seizures compared to Labrador Retrievers (odds ratio, 2.1).[73]

Age of onset. In 4 of the 5 dogs included in the research abstract,[64] the age at the first epileptic seizure was <4 months.

Epileptic seizure type. All dogs had generalized epileptic seizures and clusters.[64]

English Springer Spaniel

Studies conducted in the breed. A cross-sectional population study in the US identified 45 English Springer Spaniels with IE in 2005.[74] Dogs were recruited in association with a breed club and via open requests to the public and veterinarians, with a short health survey followed by an epilepsy-specific questionnaire, telephone interview and review of medical records. The criteria for the diagnosis of IE included: ≥2 epileptic seizures at least 1 month apart, with normal serum biochemistry results, an unremarkable interictal neurological examination and no evidence of toxin exposure or head trauma. Dogs <6 months and >5 years of age at the first seizure were only included if CSF analysis and brain imaging with CT or MRI were unremarkable, or if they had been followed up for ≥2 years with no interictal abnormalities. The pedigrees of the English Springer Spaniels with IE were collected and analyzed.[74] A subsequent genetic investigation in 2011 included 24 English Springer Spaniels with IE diagnosed based on similar criteria.[37]

Results from epidemiological studies are conflicting. In 2013, a UK Breed Health survey of 4327 English Springer Spaniels reported a prevalence of IE of 0.6%, but epilepsy was reported as the cause of death in 3.2% of all dogs that died between 2008–2013, and many of the epilepsy-related deaths occurred in young dogs.[75] The prevalence of suspected IE was 2.3% in a UK laboratory database study in 2011.[53] Evaluation of a large database of electronic patient records in the UK revealed a lower prevalence of epileptic seizures in English Springer Spaniels than in Labrador Retrievers.[73]

Age of onset. The median age of onset in the US study was 3 years (range, 0.5–7 years). There was a bimodal distribution with peaks at 1–3 years (60%) and 5–6 years (20%).[74]

Sex. More males (16/26; 62.5%) than females (10/26; 37.5%) were reported in the subgroup of 26 dogs that participated in a genetic segregation analysis, but these differences did not reach statistical significance.[74]

Epileptic seizure type. Forty-seven percent of the dogs had generalized epileptic seizures, 33% focal epileptic seizures and 20% focal epileptic

seizures evolving to become generalized. Preictal signs consisted of hiding, pacing or acting clingy. Cluster seizures occurred in 38% of dogs in the US study[74] and in 65–80% of English Springer Spaniels with suspected IE in the UK laboratory database study.[53]

Suspicion of a genetic basis. There was marked clustering of IE in US families, which supports a genetic etiology.[74]

Treatment response. Sixty-seven percent of dogs were treated with ASDs.[74] Among these, treatment response was good in 23%, moderate in 47% and poor in 30% of dogs. The median frequency of epileptic seizures ranged from 12 per month to 1 every 2 years (median, 5 per year).

Epilepsy mimics. Fucosidosis is a fatal inherited storage disorder that presents with signs of progressive motor, behavioral and visual changes at 1–2 years of age, and rarely epileptic seizures in the terminal stages.[76] Phosphofructokinase deficiency can cause exercise-induced hemolytic crisis. Paradoxical pseudomyotonia presents as episodes of exercise-induced muscle stiffness, that can evolve into generalized stiffness and lateral recumbency.[77]

Finnish Spitz

Studies conducted in the breed. A cross-sectional population survey was conducted in Finland in 2003–2004, involving 5960 Finnish Spitz dogs born between 1992 and 2002 and registered with Finnish breed clubs.[19] Questionnaires were completed on 214 dogs. Idiopathic epilepsy was diagnosed in 141 dogs (111 alive, 30 dead), based on epilepsy-specific questionnaires, follow-up calls after 1–2 years and review of medical records. The criteria for diagnosis of IE were ≥2 epileptic seizures and an unremarkable physical and neurological examination. A veterinarian evaluated 51.8% (73/141) of the dogs and 27.8% of them had unremarkable hematology and serum biochemistry values. Detailed studies with brain MRI, EEG or positron emission spectroscopy were performed in 18 dogs.[78–80] One dog showed reversible postictal MRI changes. Results were in line with the frequent occurrences of focal seizures and indicated a focal IE in Finnish Spitz dogs.

Age of onset. The overall median age of onset was 3 years (range, 0.5–10 years) in the 111 Finnish Spitz dogs that were alive at the time of the Finnish study.[19]

Sex. The affected dogs were 60.1% males and 39.9% females. Males had an increased risk for IE when compared to females (odds ratio, 1.7).[19]

Epileptic seizure type. Seizure phenomenology was evaluated in the 141 dogs included in the Finnish study. Of these, 85% had a focal onset of the epileptic seizure (120/141), 31% (44/141) showed predominantly focal epileptic seizures and 54% (76/141) had focal epileptic seizures evolving to become generalized. Other seizure types were generalized epileptic seizures without focal onset (1%), or with unknown onset (7%) or unclassified episodes (7%). More than one type of epileptic seizure was observed in 24 dogs.[19] Cluster seizures occurred in 16% of dogs. Initial clinical signs were behavioral (hiding without reason) in most dogs. Other initial clinical signs were automatisms (licking paws, changing positions), motor signs (weakness or tremors) and rarely vomiting. Ictal signs were tremors, weakness, tonic-clonic, tonic or clonic movements. Stress was a frequent trigger. The median duration of the epileptic seizures, including the initial signs, was 11.75 minutes.[19] Interictal EEG under light sedation with medetomidine showed focal epileptiform discharges (spikes, polyspikes, spike-wave complexes) in 20% (3/11) of dogs.[19,79]

Suspicion of a genetic basis. The one-year period prevalence of IE in the Finnish Spitz population was 5.36% in dogs that were alive at the time of the study, which is higher than in the general dog population (111/2069).[19] An association of IE with an *ADAM23* risk haplotype was identified in the breed.[35]

Treatment response. Antiseizure drugs were prescribed to 30.7% (42/137) of dogs. No information was available for the other dogs. Phenobarbital was the most commonly used ASD. Most treated dogs had a generalized seizure phase. Owners considered treatment to be effective in 78.9% (30/38) of dogs. The median seizure frequency was 2 seizures per year. Epileptic seizures with a generalized convulsive phase occurred in 72.5% of dogs younger than 36 months of age and were more frequently associated with a progressive clinical course.

German Shepherd

Studies conducted in the breed. In 1973 and 1974, the UK Alsatian (i.e., German Shepherd dog) league initiated a population survey of epilepsy in registered dogs, and 68 German shepherds with IE were identified. The criteria for the diagnosis of IE were seizures of unknown etiology with no

further details specified. Some dogs participated in an EEG screening program, but clinical information was limited.[81]

In 2013, an epidemiological investigation identified the German Shepherd dog as one of two breeds with a significantly increased risk for IE. The odds ratio for IE was 1.8 compared to mixed-breed dogs, on analysis of 455,000 electronic records in primary care veterinary practice in the UK in 2011.[1] The German Shepherd was also among the five most common breeds with IE in a referral hospital population and a laboratory database in 2011, but no specific breed risks were evaluated.[18,53]

Sex. More males than females were affected.[81]

Epileptic seizure type. An increased risk of cluster seizures or status epilepticus was reported.[81]

Suspicion of a genetic basis. German Shepherds had a significantly increased risk for IE in primary care veterinary practice in the UK.[1] Previous pedigree analyses supported a genetic predisposition.[81]

Golden Retriever

Studies conducted in the breed. A cohort study described the clinical features and long-term clinical course of IE in Golden Retrievers in Switzerland.[82] An epilepsy-specific questionnaire was mailed to the owners of 48 Golden Retrievers with a known diagnosis of IE. Complete questionnaires were returned for 25 dogs. The diagnosis of IE was based on ≥2 epileptic seizures; an unremarkable interictal physical and neurological examination; and unremarkable hematology and serum biochemistry values, urinalysis and CSF analysis in each dog. The dogs were followed up for at least 36 months (36–96 months). A case-cohort study evaluated interictal EEG under light medetomidine sedation in Golden Retrievers with and without IE.[83] Pedigrees from 336 Golden Retrievers with or without IE from Switzerland and Germany were also analyzed.[84] The Golden Retriever comprised 5.6% of dogs with IE in a UK laboratory database study in 2011.[51] The estimated breed prevalence of IE was 1.15–3.11% (95% confidence interval) in veterinary practices in the UK in 2011.[1]

Age of onset. The mean age of onset in the Swiss cohort was 2.1 years (range, 8–56 months).[82]

Sex. A significantly greater proportion of male dogs (76%; 19/25) was affected by IE than female dogs (24%; 6/25).[82] These observations were confirmed in an extended pedigree analysis.[84]

Epileptic seizure type. The cohort study on clinical features of IE in Golden Retrievers described generalized epileptic seizures in 84% (21/25) and focal epileptic seizures in 16% (4/25) of dogs.[82] Signs of restlessness, fear, clinginess, barking and rarely vomiting were observed in the minutes prior to a generalized epileptic seizure. Dogs were commonly unconscious (86%), urinated (81%) and salivated during generalized epileptic seizures. Screaming or howling during the generalized epileptic seizure was reported in 33% of dogs. Focal epileptic seizures were described as contractions of muscles in the face or in one limb, running in circles, salivation or trembling. The postictal phase frequently lasted longer than 30 minutes. Epileptic seizures occurred most often during the night when the dogs were sleeping or during daytime after a short period of rest.[82]

Suspicion of a genetic basis. The increased prevalence of epileptic seizures in breeding lines, and the repeated occurrence of epileptic seizures in different families with the same sires indicated a genetic basis for IE.[84]

Treatment response. Long-term response to treatment with PB was monitored in 14 Golden Retrievers in the Swiss cohort. Treatment was initiated after the 2nd to 8th epileptic seizure. Serum PB concentrations were monitored and maintained in what the authors considered the therapeutic range (15–40 μg/mL). Epileptic seizures decreased initially in 50% of dogs, but the response was not maintained in 4 dogs and seizure frequency subsequently increased. After 4 years, 43% (6/14) of dogs were euthanized because of increasing seizure frequency and the burden of the disease on the dog owners. Dogs with a good long-term response were treated significantly earlier after the first epileptic seizure and had fewer epileptic seizures before treatment initiation.[82] Seven of the 25 dogs included in this study were not treated with an ASD and experienced an increase in seizures intensity and severity.

Survival time. The mean survival time after the first observed epileptic seizure was 46 months (3.8 years; range, 3–102 months) in the 14 PB-treated dogs.[82]

Epilepsy mimics. Acetazolamide-responsive dyskinesia has been described in a 12-week-old female Golden Retriever. The dog showed recurring episodes of arched back, muscle stiffness and collapse that were induced by excitement.[85] Ceroid lipofuscinosis associated with a *CLN5* gene variant has been described in two related litters of Golden Retrievers. Neurological signs were progressive behavioral changes, ataxia, and gum

smacking and fly-biting seizures with an age of onset between 13 and 15 months.[86]

Greater Swiss Mountain Dog

Studies conducted in the breed. A prevalence study was conducted in Switzerland in which records of the Swiss Kennel Club were searched for reports of IE between 1999–2009. Epilepsy was recorded in 24 of 600 Greater Swiss Mountain Dogs. The mean yearly incidence (newly diagnosed cases) was 2.2%. No specific criteria to validate the diagnosis of IE in the records of the breed club were mentioned. Subsequently, the owners of all Greater Swiss Mountain Dogs living in Switzerland were invited to complete an online epilepsy-specific questionnaire.[87] The target population included 400 Greater Swiss Mountain Dogs, of which 128 owners completed the questionnaire (response rate 31.3%). Twenty Greater Swiss Mountain Dogs with IE were identified. The criteria for the diagnosis of IE was ≥2 epileptic seizures and an age of onset between 6 months and 6 years in 11 dogs, and an unremarkable brain MRI study and CSF analysis in 8 dogs. One dog with an age of onset at 7 years and unremarkable physical, neurological and blood examinations was included.[87] In 2011, a candidate genetic study failed in 24 Greater Swiss Mountain dogs with IE.[37]

Age of onset. The mean age of onset was 3 years (range, 6 months–7 years).[87]

Sex. Males represented 55% of affected dogs and females 45%.[87]

Epileptic seizure type. Epileptic seizure types were described in 12 dogs. All 12 dogs had generalized epileptic seizures: 58% (7/12) had focal epileptic seizures evolving to become generalized, and in the others the onset was not observed by the owners. Focal onsets of epileptic seizures were described as facial twitches and grimacing, head shaking, head turn to one side and chewing movements. Epileptic seizures occurred predominantly in the morning and in resting dogs. In 3 dogs, stressful events or particular behaviors were reported just before an epileptic seizure and included pulling on the leash followed by loss of consciousness, playing excessively or frantic licking episodes in the 24 hours before an epileptic seizure occurred. The frantic licking episodes are characterized by indiscriminate licking (e.g., carpet, floors, walls) and/ or indiscriminate eating (e.g., grass, leaves, dirt, carpet), and the dogs will gulp air and swallow constantly. In the study including 12 Greater Swiss Mountain

Dogs, 3 dogs showed postictal aggression. The postictal phase was generally long and lasted >30 minutes in 9 dogs and >24 hours in another 2 dogs. Cluster seizures occurred in 50% (6/12) and status epilepticus in 41.6% (5/12) of dogs.[87]

Suspicion of a genetic basis. All affected Greater Swiss Mountain Dogs had relatives with epilepsy. The prevalence of epilepsy was 15.8% in an online questionnaire study targeting registered Greater Swiss Mountain Dogs in Switzerland. Low response rates and response bias could have contributed to an increased prevalence in the questionnaire study, yet this prevalence is far higher than the epilepsy prevalence in the general dog population.[87]

Treatment response. Eleven Greater Swiss Mountain Dogs were treated with PB, and 2 were also administered KBr and LEV. Imepitoin was initially used in 3 dogs and was not effective. The mean time from the first epileptic seizure to treatment initiation was 2.8 months (1 day–7 months). Epileptic seizure frequency improved in only 33% of Greater Swiss Mountain dogs and failed to improve in 66%, but the serum concentrations of the ASDs were poorly documented. Long-term remission was observed in 1 dog after 1 year of treatment with PB despite very frequent epileptic seizures in the first 3 months.[87]

Survival time. Twenty-five percent of the Greater Swiss Mountain dogs with IE died or were euthanized due to their condition between 9 months and 3 years after the first seizure.[87]

Irish Wolfhound

Studies conducted in the breed. Information from Irish Wolfhounds with epileptic seizures and their relatives was collected retrospectively in the US.[88] The dogs originated from 120 litters, with a total of 796 dogs. The data from questionnaires and the medical records and laboratory reports of each dog were reviewed, and 146 Irish Wolfhounds with IE were identified. The criteria for the diagnosis of IE were a history of ≥2 epileptic seizures, an unremarkable physical and neurological examination and unremarkable hematology, serum biochemistry, ammonia and/or bile acids concentrations, and urinalysis. A histopathological examination of the brain was available in 14 dogs.[88]

Age of onset. The mean age of onset of IE was 2.3 years (range, 0.5–7 years) in females and 2.8 years (range, 0.5–8.9 years) in males. The first

epileptic seizure occurred before 3 years of age in 73% of all dogs and in 83% of female and 67% of male dogs.

Sex. Males represented 61.6% of affected dogs and females 38.4%. The sex proportion differed significantly from the 1:1.08 ratio for the general Irish Wolfhound population born during the same time period.

Epileptic seizure type. Epileptic seizures were described as generalized epileptic seizures, but no further description of their onset was provided.

Suspicion of a genetic basis. A pedigree analysis suggested a genetic basis for IE in the breed. The prevalence of IE was estimated at 18.3% (146/796). The sampling method suggests that these data reflect the prevalence of IE in an extended pedigree with related families that are affected by IE, and not the prevalence in the general Irish Wolfhound population.

Survival time. Of the 146 affected dogs, 126 (86%) had died by the time data collection ended. The mean age at the time of death was 4.7 years. Death was related to the epilepsy in 63% (79/126) of dogs and cause of death included: death during a seizure (16.1%), euthanasia because of uncontrolled seizures (65.8%), hepatotoxicity related to PB (6.6%), aspiration pneumonia during a seizure (6.6%), and euthanasia because of non-recovery during a seizure (3.9%). The life expectancy was reduced by 2 years compared to the general life expectancy of the breed during the same time period, which was 6.5 years.[88]

Epilepsy mimics. Fatal hyperekplexia or startle disease associated with a *SLC6A5* gene variant of the glycine receptor has been described in Irish Wolfhound puppies.[89] Irish Wolfhounds are prone to portosystemic shunts. Impaired ammonia metabolism has been reported in Irish Wolfhounds (not associated with a portosystemic shunt).[90]

Italian Spinone

Studies conducted in the breed. A population survey study investigated the prevalence and clinical features of IE in Italian Spinoni in the UK.[91] The target population consisted of 3331 Italian Spinoni born between 2000 and 2011 and registered with the UK Kennel Club. The owners of 1192 Italian Spinoni returned the initial questionnaire, 63 of which were diagnosed with IE based on a detailed review of all medical records, an IE-specific questionnaire and follow-up information provided by the dog owners. Thirty seven percent of dogs were seen by a veterinary specialist and 30%

of dogs underwent brain MRI. Idiopathic epilepsy was defined as recurrent seizures (≥2 seizures occurring >24 hour apart) with an onset between 6 months and 6 years of age in dogs with normal interictal physical and neurological examinations and hematology and serum biochemistry values within the normal reference range.

Age of onset. The median age of onset was 2.9 years (range, 11–72 months).

Sex. Sixty-seven percent were male and 33% were female.

Epileptic seizure type. All dogs had generalized tonic-clonic epileptic seizures. Analysis of the beginning of the seizure showed focal epileptic seizures evolving to become generalized in 51% of dogs, generalized epileptic seizures at the onset in 23% and generalized epileptic seizures with unknown onset in 26% of dogs. Most dogs (89%) showed rhythmic running movements of all four limbs (see Chapter 1, Video 1.4). Preictal behavioral signs (e.g., anxiety, restlessness, increased affection, contact-seeking behavior, withdrawal, hiding, aggressiveness, vocalization) were reported in 57% of the dogs and occurred for longer than 30 minutes (68%) or less than 30 minutes (32%) before the epileptic seizures. Cluster seizures occurred in 73% and status epilepticus in 21% of dogs. Behavioral changes, most commonly abnormal perception and anxiety, were reported in 55% of the dogs at the onset of IE and prior to treatment with ASDs.

Suspicion of a genetic basis. The prevalence of IE in Italian Spinoni was estimated as 5.3% (95% CI, 4.03–6.57%), which is higher than in the general canine UK population (0.6%).

Treatment response. Most dogs (90%) were treated with ASDs, with 60% being treated with two or more ASDs. Successful seizure control was not achieved in many instances. Remission (i.e., seizure-freedom with or without treatment for ≥1 year) occurred only in 3 (6%) dogs.

Survival time. At the time of study completion, 44% (28 dogs) had died. Survival time from the first epileptic seizure was 22 ± 17 months for 20 dogs that were euthanized due to poorly controlled epilepsy, and 62 ± 38 months for 8 dogs that died from causes unrelated to the epilepsy. Survival time was significantly shorter in the Italian Spinoni that were euthanized because of poorly controlled IE than in the epileptic Italian Spinoni dogs that died of unrelated disorders. Survival was significantly longer in dogs with no cluster seizures and in dogs in which ASD treatment had been initiated after the second seizure rather than after ≥3 seizures.

Keeshond

Studies conducted in the breed. Only two studies with limited clinical information are available in this breed.[92,93] A UK population study involved 21 litters of Keeshonds that included dogs diagnosed with epilepsy. Dogs were classified as being affected by IE when there was a diagnosis of epilepsy by a veterinarian. The Keeshond was an uncommon breed in the UK in 1993 with only 42 breeders and 87 registrations.[93] Another study evaluated the results of EEG screening for epilepsy in 321 Keeshonds, including 9 dogs with clinical seizures.[92]

Age of onset. The median age of onset in the UK population study was 2 years (range, 8 months–6 years).[93]

Epileptic seizure type. Information on seizure phenomenology was limited. There was no association between presumed interictal epileptiform discharges and clinical seizures in 321 Keeshonds, 312 without and 9 with epileptic seizures.[92]

Suspicion of a genetic basis. A founder effect was evident. Twenty-six matings of carriers produced 91 normal and 26 epileptic dogs. The probability of descendants being a carrier declined with the introduction of a genetic counselling program in 1989. Matings with a carrier probability of >0.26 and a high inbreeding coefficient were avoided.[93]

Labrador Retriever

Studies conducted in the breed. A cross-sectional prospective population survey was conducted in 1999–2000 in Denmark that included 29,602 Labrador Retrievers registered with the breed club in 1989–1999.[94] From this population, 550 Labrador Retrievers, (50 from each year) were randomly sampled and investigated with two telephone interviews and an epilepsy-specific questionnaire. Idiopathic epilepsy was diagnosed based on the occurrence of ≥2 epileptic seizures, an unremarkable physical and neurological examination, and no relevant hematology and serum biochemistry abnormalities. Seventeen Labrador Retrievers with IE were identified.[94]

A retrospective population study was conducted in Switzerland in 1995.[95] Pedigrees spanning 11 generations were collected from 792 Labrador Retrievers with a known health status. The criteria for the diagnosis of IE were ≥2 epileptic seizures in the absence of other medical conditions; an unremarkable physical and neurological examination; normal

hematology and serum biochemistry values and ammonia and fasting bile acids concentrations; and normal urinalysis and CSF analysis. Fifty-five Labrador Retrievers with IE were identified.[95] All dogs were re-evaluated 6 months after PB therapy was initiated, at which time the repeat clinical examination and diagnostic investigations including urine and CSF analysis were unremarkable.[95] A cohort study by the same authors reviewed the medical records of 54 Labrador Retrievers with IE in Switzerland (1985–1999) with similar inclusion criteria to the previous study. Videos of epileptic seizures from their onset were analyzed frame by frame in 15 dogs.[96] The authors did not specify whether the two Swiss cohorts overlapped.

The Labrador Retriever was amongst the three most common breeds with IE in large epidemiological studies in the UK, but the breed is also very popular.[1,52,53] A cohort of 117 Labrador Retrievers diagnosed with IE in primary care was extracted from one of these databases and analyzed separately for association between IE and neutering.[97]

Age of onset. Onset was prior to 4 years in 76% of the Danish cohort (13/17 dogs), and the remaining 4/17 dogs had their first epileptic seizure between 4 and 8 years of age.[94] The mean age of onset was 2.6 years in the Swiss study that involved 55 Labrador Retrievers, which included dogs with an age of onset >5 years.[95] The age of onset was between 5 and 91 months in the Swiss study that included 54 Labrador Retrievers.[96]

Sex. Males and females were nearly equally affected in the Danish study (52.9% males, 47.1% females)[94] and in one Swiss study (56% males, 44% females)[95]. More males (61.2%) than females (38.8%) were affected in the other Swiss study and in Labrador Retrievers with IE under primary care in the UK.[1,96,97]

Epileptic seizure type. Focal epileptic seizures with or without evolution into generalized seizures were reported in 70% of Danish dogs.[94] In the retrospective Swiss study,[95] 85.5% (47/55) of dogs displayed tonic-clonic motor activity with loss of consciousness, 10.9% (6/55) retained consciousness, and 3.6% (2/55) had focal epileptic seizures. The authors described unilateral focal motor activity of the head for no longer than 30 seconds, which progressed to the limbs and then to a generalized epileptic seizure in 66% of dogs. This finding suggests that focal epileptic seizures evolving to become generalized are the predominant epileptic seizure type in Labrador Retrievers.[95] In the Swiss cohort study, epileptic seizures were

described as generalized tonic-clonic seizures with loss of or preserved consciousness in 75.9% (41/54) and 7.4% (4/54) of dogs, respectively; as tonic epileptic seizures with long-lasting tonic muscle contractions in 7.4% of dogs (4/54); and as focal epileptic seizures in 9.3% (5/54) of dogs.[96] Focal epileptic seizures presented with focal facial and masticatory muscle contractions lasting 30 seconds to 2 minutes, or fly-biting seizures. Four dogs showed unilateral facial muscle involvement at the beginning of generalized epileptic seizures.[96] A prodromal phase lasting several hours, and characterized by restlessness and fear, was commonly reported. Stress frequently triggered epileptic seizures.[95,96]

Suspicion of a genetic basis. The reported prevalence of IE in the Danish Labrador Retriever population was 3.1%, which is higher than in the general canine population.[94] The prevalence of IE was 6.9% in Swiss breeding lines with IE.[95] The increased prevalence of IE in subfamilies and different families from the same sire supported a genetic origin in the Swiss cohort. A pedigree analysis suggested a polygenic recessive inheritance. A risk haplotype in the *ADAM23* gene was more frequently seen in Labrador Retrievers with IE.[98]

Treatment response. Long-term follow-up, ranging from 8–102 months (mean, 4.2 years), was available in 46/54 Labrador Retrievers in the Swiss study.[96] Thirty-seven dogs were treated with PB and serum PB concentrations were monitored. Eleven dogs became seizure free, 16 dogs experienced an improvement in seizure frequency and duration, and 10 dogs experienced no change in seizure frequency and duration. Dogs with an older age at IE onset and a low seizure frequency or low total number of seizures before initiation of PB had a better outcome. The frequency and duration of seizures worsened in 6/9 untreated dogs.[96]

Survival time. The median survival time for Labrador Retrievers with IE in the UK was 3.4 years (range, 15–4357 days).[97] Survival time was not evaluated in the Swiss studies.

Epilepsy mimics. Paroxysmal dyskinesia has been reported in Labrador Retrievers and is associated with episodes of abnormal posture (often inability to stand up) and movement (mild head and body tremors) with preserved consciousness, no autonomic signs and no postictal signs. In a cohort of 36 affected Labrador Retrievers, 7 (19%) were females and 29 (81%) were males. The median age at episode onset was 2 years and 3 months (range, 9 months to 10 years and 8 months). The median episode

frequency at presentation was one episode every 3 weeks. Episode duration most commonly ranged between 2–30 minutes (range, <2–120 minutes). Episodes were triggered by a sudden movement or startle (58%) or excitement (25%).[99] The frequency and duration of the episodes (without any treatment) and with a median follow-up of 6 years and 8 months decreased in 25/36 (69%) dogs (with episode-freedom for ≥2 years in 14/36 [39%] of dogs), deteriorated in 5/36 (14%) dogs and remained static in 6/36 (17%) dogs.[99]

Lagotto Romagnolo

Studies conducted in the breed. In 2004 and 2005, 25 puppies and 3 young adult Lagotto Romagnolo dogs from Finland were studied in detail clinically and genetically, and a benign familial juvenile IE was diagnosed.[100] Brain MRI was performed in 75%, CSF in 68%, EEG in 68% and a postmortem examination in 7% of dogs. The criteria for the diagnosis of epileptic seizures were loss of consciousness during more severe seizures and interictal epileptiform discharges on EEG. The criteria for the diagnosis of IE were no relevant hematology, serum biochemistry, brain MRI and CSF analysis findings. Postmortem examinations revealed inclusions in Purkinje cells and mild Purkinje cell loss. These changes may explain the abnormal interictal neurological examination (ataxia, intention tremors, postural reaction deficits) in 10 puppies. Neurological examinations were unremarkable in adult dogs. The authors speculated on a common underlying metabolic defect that influences cortical and cerebellar excitability. The early onset of the epilepsy in puppies, EEG features and remitting course were similar to benign remitting focal epilepsies of childhood in humans with an onset between 2 and 10 years of age (e.g., Rolandic epilepsy, Panayiotopoulos syndrome) with centrotemporal and occipital spikes.[100]

Long-term follow-up and neurobehavioral comorbidities were investigated with online questionnaires and telephone calls in 25 of the previously identified Lagotto Romagnolo dogs with benign familial juvenile IE[100,103] and 160 control Lagotto Romagnolos >4 years of age.[101] A case–control study in 8 Lagotto Romagnolos with benign familial juvenile IE identified altered cerebral glucose metabolism with fluorodeoxyglucose-positron emission tomography (FDP-PET) functional brain imaging.[102] Twenty-two dogs with benign familial juvenile IE were selected for

genome-wide association assays from a large pedigree with 212 dogs that included 34 affected dogs.[103]

Age of onset. The mean age of onset was 6.3 weeks (range, 5–9 weeks) in the puppies and 1.6 and 2.1 years in the 3 adult dogs.[100]

Sex. Sixty percent of the puppies were female (15/25) and 40% male (10/25).[100]

Epileptic seizure type. The epileptic seizures were described in the case–control study as episodes characterized by whole body tremors, ataxia and stiffness. The seizures lasted 10 seconds to a few minutes.[102] Some puppies were reported to sit or lay on their side during the generalized tremors. Consciousness appeared impaired in the more severely affected puppies, but others were able to walk and respond during the episodes. Video footage from 6 puppies showed that one side of the body was more severely affected than the other during the epileptic seizures. The 3 adult dogs developed seizures in the form of episodic horizontal head tremor (2 dogs) or generalized tremors (1 dog). Interictal EEG under light medetomidine sedation was abnormal in 87.5% of the examined puppies (14/16) and revealed focal epileptiform discharges in the form of sharp waves and spikes in 13 and generalized discharges in one puppy. Electroencephalography was abnormal in 2 of the 3 adult dogs. In addition, areas of hypometabolism on FDG-PET were reported.[102]

Suspicion of a genetic basis. The causative gene variant for this type of IE has been identified in the *LGI2* gene and a genetic test is commercially available (see Chapter 4). Most affected dogs are homozygous for the *LGI2* gene variant and heterozygous dogs are rarely affected (7% to 13%).[101,103] A high prevalence of the gene variant (32% heterozygote carriers) has been identified in Finland, Sweden and Switzerland.[103]

Treatment response. Benign familial juvenile IE in Lagotto Romagnolo dogs has a benign and self-remitting clinical course. The initial frequency varied from multiple daily episodes to one episode per week. Seizures resolved by 4 months of age in all puppies (mean 10 weeks; range, 7.5–13 weeks). Only one of 25 Lagotto Romagnolo dogs with benign familial juvenile IE experienced an epileptic seizure at the age of 8 months. Thus, the remission rate without treatment was 96% at 4 months. When these puppies became adult dogs, they presented with behavioral changes characterized by inattention and hyperexcitability which resembled attention deficit hyperactivity disorder in people.[101]

Survival time. Eighty-eight percent (22/25) of dogs with benign familial juvenile IE were still alive at a mean age of 7.4 years (range, 4.6–10.7).[101]

Petit Basset Griffon Vendéen

Studies conducted in the breed. A population study was conducted in Denmark involving 820 Petit Basset Griffon Vendéen dogs registered with the Danish breed club from 1999 to 2008.[104] The study used screening surveys followed by telephone interviews and epilepsy-specific questionnaires. The response rate was 57.4% and the study population was 471 dogs representing 175 different litters. Idiopathic epilepsy was diagnosed in 42 Petit Basset Griffon Vendéen dogs; of these, 31 dogs were alive at the time of the study and were invited for clinical investigations. Twenty-three other dogs were validated as epilepsy-negative because of signs typically originating from other diseases and 6 other dogs were not included because they had suffered only one epileptic seizure. The criteria for the diagnosis of IE were ≥2 epileptic seizures at least 24 hours apart with typical semiology, and 42.9% (25/42) of the dogs were seen by a veterinarian. The investigations performed included physical, neurological and cardiological examinations, hematology, serum biochemistry, urinalysis and thyroid testing in 45.2% of dogs (18/42), a bile acid stimulation test in 21.2% (9/42) and brain MRI in 7.1% (3/42). No relevant abnormalities were present.

Age of onset: The median age of onset was 2.0 years (range, 2–78 months).

Sex: Sixty-two percent of the dogs were male (26/42) and 38% female (16/42), but no male predisposition was identified when compared to the general Petit Basset Griffon Vendéen population.

Epileptic seizure type. Most dogs (92.9%; 39/42) experienced focal epileptic seizures with (52.4%; 22/42) or without evolving to become generalized (40.5%; 17/42). Signs of focal epileptic seizures included ataxia, contractions of single muscle groups, vomiting, hypersalivation, and behavioral paroxysms such as excessive attention seeking or standing with a blank stare and not responding to external stimuli. Typical epileptic seizure duration was 1–3 minutes.

Suspicion of a genetic basis. The prevalence of IE among the respondents was 8.9% (95% confidence interval 6.3–11.5%), which was higher than the prevalence of IE in the general canine population. A strong

litter effect was evident: 19 of the 42 dogs with IE originated from 7 different litters and 3 of these litters shared a common sire.

Survival time. Epilepsy was the most common cause of death in the breed and accounted for 13.3% of all deaths. The median survival time was 3 years for dogs that had IE as the cause of euthanasia. For the dogs that were still alive at the time of the study, the median duration of epilepsy was 3.9 years (range 10–113 months) at the time of their examination.

Poodle (standard)

Studies conducted in the breed. A family and cohort study investigated the pedigrees and epilepsy phenotype of 126 standard Poodles in the US and followed a cohort of standard Poodles with probable IE for 2 years.[105] These dogs originated from several large families with multiple dogs with IE. The affected dogs and related litters were identified via requests in newspapers and websites in association with the breed club. The epilepsy phenotype was assessed with screening questionnaires and telephone interviews in 90 dogs: 29% (26/90) had a history of ≥2 epileptic seizures, 4% (4/90) had a history of one epileptic seizure and 67% (60/90) were classified as unaffected at ≥6 years of age. Altogether, 30 dogs fulfilled the criteria for probable IE, which in this study was defined as: ≥1 epileptic seizure, an age of onset between 6 months and 7.5 years, and no evidence of an underlying cause. These dogs were contacted a second time after 2 years for follow-up information.[105]

An observational study was also conducted in standard Poodles from different regions of the US and Canada in 2002.[72] Screening with requests on websites and newspapers between 1996 and 2001 identified 183 standard Poodles with seizures; of these 50 were invited and 41 completed written questionnaires and a structured telephone interview. The criteria for the diagnosis of probable IE were ≥1 epileptic seizure, an unremarkable interictal neurological status and no evidence for structural epilepsy or reactive seizures in the medical records. Only 10% of the dogs had a complete evaluation with a physical and neurological examination, hematology, serum biochemistry and a bile acid stimulation test.[72]

Sex. In the first cohort, 56.7% (17/30) were male and 43.3% (13/30) female,[105] whereas 51% were males in the cohort of 41 standard Poodles.[72]

Age of onset. The median age of onset was 3.7 years (range, 0.5–7 years) in one study[105] and 2.4 years (range 0.5–6.4 years) in the other

study.[72]

Epileptic seizure types. Most dogs had focal epileptic seizures (60%; 18/30), while 30% (9/30) had focal epileptic seizures evolving to become generalized epileptic seizures. Other seizure types were described in 3 (10%) dogs: generalized epileptic seizure from the onset, generalized epileptic seizure with unknown onset, and unclassified seizures.[105] Focal epileptic seizures were described as focal motor (shaking, jerking, shivering, staggering, inability to stand, stiffness, rigidity, head tilt, awkward limb lifting) or sensory/behavioral epileptic seizures (anxiety, aimless wandering, staring) with or without autonomic signs, and automatisms (licking, lip smacking, swallowing, circling) in some instances.[105] Cluster seizures, which were always convulsions, occurred infrequently in 34% (14/41) of dogs.[72]

Suspicion of a genetic basis. One study identified familial clustering and considered an autosomal recessive inheritance.[105]

Treatment response. Only 13% of dogs (4/30) were treated with PB or KBr in the first cohort,[105] while 46% of dogs (19/41) were treated with PB and/or KBr in the other cohort.[72] Treatment response was evaluated in 15 dogs: 7 became seizure free (46.7%) and 5 had a reduction in seizure frequency (33.3%). The median epileptic seizure frequency was 2.8 per year.

Epilepsy mimics. Standard Poodles with fatal neonatal encephalopathy due to an *ATF2* gene variant develop epileptic seizures by 4–6 weeks of age.[106] Polymicrogyria was associated with a focal epileptic seizure presenting as circling and lip smacking in 1 of 5 standard Poodles with polymicrogyria.[107]

Rhodesian Ridgeback

Studies conducted in the breed. Twenty-five Rhodesian Ridgebacks from Central Europe and their pedigrees were studied in detail clinically and genetically.[10,15] Magnetic resonance imaging and EEG were performed in 46% and 65% of the affected Rhodesian Ridgebacks, respectively, and histopathological examination of the brain was available for 4% (1 dog). A genetic IE in juvenile dogs characterized by an onset with photosensitive myoclonic epileptic seizures was diagnosed.[10] This type of IE has parallels with juvenile myoclonic epilepsy (JME) in people.

Age of onset. The onset of the epilepsy was in juvenile and adolescent dogs (median, 3.5 months; mean, 6 months; range 6 weeks–18 months), with frequent myoclonic jerks/twitches.[10,15]

Sex. Males represented 60% of the dogs (15/25) while 40% (10/25) were female.[10,15]

Epileptic seizure type. Only generalized epileptic seizures were identified, and included myoclonic, generalized tonic-clonic and absence epileptic seizures. This classified the epilepsy as a true generalized idiopathic genetic epilepsy. Myoclonic epileptic seizures presented as repetitive myoclonic twitches or violent myoclonic jerks that resembled electric shocks (see Video 2.5). They occurred mostly when the dogs were resting or drowsy in the first stages of sleep, with the eyes either open or closed. Myoclonic jerks also occurred when the dogs were sitting, standing, or walking, but less frequently than in the resting position. Myoclonic twitches and jerks varied in intensity. Some presented as violent electric shock–like jerks of the trunk, neck and upper thoracic limbs that sometimes resulted in backward jerking and falling. Other myoclonic seizures were rather subtle or occurred as repetitive twitches and jerks of the upper thoracic limbs, face and head (chewing movements, eyelid and muzzle twitches or head nodding). Their duration was rather short (<1 second). Myoclonic twitches and jerks occurred on a daily or almost daily basis and their frequency could be as high as 150 per day. Video-EEG confirmed the presence of generalized paroxysmal epileptiform activity, seen as a generalized rhythmic change in background activity preceding the myoclonic activity, and short episodes with spike-and-wave-complexes in association with the myoclonic jerks. In addition, video-EEG provided more objective assessment of the occurrence and frequency of myoclonic epileptic seizures than the observations of the dog owners (underreporting phenomenon). Up to 50 jerks per hour or even 200 jerks per hour were recorded in some dogs.[10,15]

In 38% of the dogs, generalized tonic-clonic epileptic seizures occurred later in life. In some of these dogs, generalized tonic-clonic epileptic seizures started with a series of repetitive myoclonic twitches that progressed to a generalized tonic-clonic seizure. The median time interval between the onset of the myoclonic epileptic seizures and the onset of the generalized tonic-clonic epileptic seizures was 6 months, but there was a wide variation ranging from 1.5 to 18 months, and precise identification of

their dog's first myoclonic epileptic seizure was challenging for some owners.

A characteristic feature of the epilepsy was photosensitivity, but not all Rhodesian Ridgeback dogs were photosensitive. Overall, 35% of the dog owners reported myoclonic epileptic seizures that were provoked by visual stimuli, thus representing reflex epileptic seizures. More precisely, the owners reported that sudden changes in light and distinct changing light patterns caused myoclonic epileptic seizures. Situations such as light flashes from cameras, the sudden appearance of light when opening the shutters in the morning, or sunlight interrupted by trees when walking through a forest were reported to elicit myoclonic jerks. Six dogs with photosensitive epileptic seizures underwent EEG with intermittent light stimulation and 4 dogs (66%) demonstrated generalized paroxysmal epileptiform activity and myoclonic epileptic seizures time-locked to the onset of the intermittent light stimulation (see Video 2.7). Electroencephalography with intermittent light stimulation was unremarkable in clinically healthy Rhodesian Ridgebacks with a wildtype or heterozygous genotype. Another characteristic feature was the association with the sleep–wake cycle. In affected dogs, myoclonic twitches and jerks frequently occurred when the dogs were resting or drowsy.

Absence seizures were documented in an 8-month-old female Rhodesian Ridgeback that was homozygous for the c.564_567delAGAC *DIRAS1* gene mutation. This dog presented with frequent myoclonic seizures and additional multiple episodes of staring blankly into space without any visible purposeful movement since the age of 8 weeks. Video-EEG showed generalized paroxysms of 4 Hz spike-wave complexes in association with the staring episodes and thus provided unequivocal evidence for generalized epileptic activity.[15]

Myoclonic twitches and jerks may interfere with the ability of the affected dogs to rest quietly or sleep. This needs to be differentiated from benign movements of paws during rapid eye movement sleep.

Suspicion of a genetic basis. Pedigree and genetic analyses were consistent with autosomal recessive inheritance of a 4bp deletion in the *DIRAS1* gene (c.564_567delAGAC), resulting in a frameshift and a premature stop codon. Only the homozygous mutant dogs showed the myoclonic epilepsy phenotype. Carriers and controls with a wild-type

phenotype remained healthy. Genotyping of 498 Rhodesian Ridgebacks revealed a carrier prevalence of 15% in Europe.[10]

Treatment response. Twenty-one dogs were treated with a variety of ASDs. Myoclonic epileptic seizures appeared to respond best to LEV or KBr.[10] Follow-up EEG confirmed the positive response to LEV in one dog.[15]

Survival time. At the time the study was conducted 30% of the dogs had died or had been euthanized, 3 because of poor control of epileptic seizures (at 9 months and 2 and 5 years of age), 3 for causes unrelated to the epilepsy and 1 dog for unknown reasons. The other dogs were still alive.[10]

Rottweiler

Studies conducted in the breed. A cross-sectional survey was conducted in Sweden and Norway from 2008 to 2013 in collaboration with the Swedish Rottweiler Club.[108] Requests for participation were announced in journals and on websites. Thirty-seven Rottweilers with IE were identified with an epilepsy-specific questionnaire. The criteria for the diagnosis of IE in this study were ≥2 epileptic seizures on different days, an age of onset between 6 months and 7 years, and no history of serious head trauma or poisoning. A veterinarian examined 94.6% of the dogs. Diagnostic testing included hematology and serum biochemistry (86.5% of dogs), brain CT (2.7%), CSF analysis (2.7%) and brain MRI (5.4%).

Rottweilers were also reported as a breed commonly affected by epilepsy in a Swedish insurance database.[2]

Age of onset. The median age of onset was 36 months and varied widely (range, 8–84 months) with peaks at 18 and 36 months.[108]

Sex. Of the 37 dogs in the study, 62.2% were female and 37.8% were male. Neutering after onset of epilepsy did not influence seizure frequency.[108]

Epileptic seizure type. Most dogs had generalized tonic-clonic epileptic seizures. Eighty-two percent of the dogs always fell to the side, while 6% seldom did and 12% never did. Some owners described turning the head to one side, fear, apnea, nystagmus and tail chasing in their dogs in association with the seizures. Most epileptic seizures occurred when the dogs were sleeping or resting, and only 3 dogs had epileptic seizures while walking. Half of the dogs experienced cluster seizures. A considerable proportion of

owners reported the presence of nystagmus in association with the epileptic seizures. Aggression in the postictal phase occurred in 16% of the dogs.[108]

Suspicion of a genetic basis. All dogs had close relatives affected by epilepsy and 59.5% shared a common ancestor that had been extensively used for breeding.[108]

Treatment response. Wide variation in epileptic seizure frequency from several per week to one per year was observed. Twenty-three dogs were treated with PB. Epileptic seizure frequency decreased in 71% and increased in 29% of treated dogs. Epileptic seizures did not decrease in severity or duration. Reduced ability to work was reported as an adverse effect of ASD treatment in 38% of dogs.[108]

Schipperke

Studies conducted in the breed. A genetic case–control study evaluated 68 Schipperke dogs in Finland.[35] Clinical information was obtained with an epilepsy-specific questionnaire; 56 valid questionnaires were available for evaluation. The clinical criteria for the diagnosis of IE were ≥2 epileptic seizures at least 2 months apart, an age of onset between 6 months and 5 years, and no other known conditions that could predispose to seizures. Diagnostic investigations were performed in 11 dogs and included a neurological examination (11/11), blood tests (10/11), CSF analysis (8/11), brain MRI (10/11), and EEG (11/11). Dogs with an age of onset <6 months and >5 years required a neurological examination, blood tests and a brain MRI to support the diagnosis of IE.

Age of onset. The median age of onset was 1.3 years (mean 2.9 years; range, 0.3–5 years).

Sex. Fifty-seven percent were males (32/56) and 43% were female (24/56).

Epileptic seizure type. Epileptic seizure type was described as focal evolving to become generalized epileptic seizures. The typical signs were stiffening of the limbs and neck, tremor, muscle fasciculations, and staring. Most dogs showed abnormal mentation (79%). The most common autonomic signs were salivation, urination and dilated pupils. The median seizure frequency was four seizures per year. Cluster seizures occurred in 25% (14/56) of dogs.

Suspicion of a genetic basis. A large proportion of the Schipperke dogs with IE were closely related. An *ADAM23* risk haplotype was more

frequently seen in Schipperkes with IE.

Treatment response. Thirty-two percent (18/56) of dogs were treated for their epilepsy and response was evaluated in 13 dogs. Epileptic seizures disappeared in 2 dogs, were reduced in 8 dogs, and remained unchanged in 3 dogs.

Shetland Sheepdog

Studies conducted in the breed. A single family of Shetland Sheepdogs from a single female ancestor comprising 17 litters over five generations and 24 dogs with IE was described in Japan in 2002.[109] The criteria for the diagnosis of IE were recurrent epileptic seizures, epileptiform discharges on EEG and unremarkable findings on pathological examination of the brain other than acute neuronal changes secondary to long-lasting seizure activity.[109] Twelve dogs underwent detailed examinations including hematology and serum biochemistry (100%, 12/12), repeated EEG examinations (83.3%; 10/12), CSF neurotransmitter analysis (53.3%; 7/12), and a postmortem examination of the brain (66.7%; 8/12).[109] A postmortem examination and immunohistochemistry analysis using glutamate, a glutamate transporter and glutamate synthetase antibodies were carried out on the brain of 4 Shetland Sheepdogs from Japan with familial IE that died of status epilepticus.[110] A postmortem examination of the brain was also carried out on 2 other Shetland Sheepdogs with IE from Japan that died in status epilepticus.[111,112] Acute neuronal necrosis, astrocytosis and vascular endothelial swelling were most pronounced in the cingulate cortex and internal area of the frontal lobe, and to a much lesser extent in the hippocampus, central grey matter, and occipital and parietal cortex.[109–112] Glutamate granules and decreased staining for glutamate transporters supported glutamate-mediated excitotoxicity.[110] Electroencephalography findings indicated an epileptic focus in the frontal lobe. Therefore, a familial frontal lobe IE was considered in Shetland Sheepdogs.[109]

Age of onset. The age of onset was after 10 months of age, and usually between 1 and 1.5 years of age.[109]

Sex. Out of the 24 dogs in the study, 79.2% (19) were female and 20.8% (5) were male.[109]

Epileptic seizure type. Epileptic seizures were described as generalized tonic-clonic convulsions with repetitive jaw movements and loss of consciousness. Tonic convulsions with preserved consciousness were

reported in 1 dog. Epileptic seizures occurred predominantly at night or when the dogs were drowsy during the day. Eight puppies were acquired before the onset of IE and monitored continuously: 75% of these dogs showed a prodromal phase with restlessness or obtundation and some of the dogs always exhibited seizures when leaving their cage. In 6 puppies, an interictal EEG was recorded under sedation with xylazine every 1–2 months until the first generalized convulsive epileptic seizure occurred. The authors reported localized paroxysmal epileptiform discharges in frontal electrodes (F4) in dogs before the onset of the IE, which increased during hyperventilation, and an interictal generalized spike-and-wave pattern with a predominance in frontal leads 4 to 10 months after the onset of the epilepsy.[109,110] In another Shetland Sheepdog with intractable IE, parietal spikes and hippocampal sclerosis were additionally demonstrated, but these were considered secondary to the changes in the cruciate sulcus and cingulate gyrus.[111]

Suspicion of a genetic basis. Supported by pronounced familial clustering.

Treatment response. No details on ASDs were described. Seizures were intractable in several dogs. Epileptic seizure frequency was variable in drug-naïve dogs and could be as low as one seizure every 6 months or as high as one seizure every week.

Survival time. Not evaluated. Several dogs (70.8%; 17/24) died in status epilepticus but did not receive treatment.[109]

Epilepsy mimics. Familial hypertonic paroxysmal dyskinesia has been described in 4 related female Shetland Sheepdogs and is caused by a mitochondrial *PCK2* gene variant. The clinical signs included episodes of hypermetric ataxia that lasted from minutes to hours in duration and an inability to stand up and walk during severe episodes. There were no autonomic signs but mentation appeared mildly reduced during the episodes.[113]

Vizsla (Hungarian)

Studies conducted in the breed. A population survey was conducted in 1997–2001 in the US in collaboration with the breed club, and pedigrees of Hungarian Vizslas with IE were collected.[114] The target population were 2900–3000 Vizslas registered per year. Individual dogs with IE were recruited with calls placed in newsletters and from veterinarians and a short

health survey, and further characterized with an epilepsy-specific questionnaire and review of medical records. Twenty-nine Hungarian Vizslas with IE were identified. The criteria to diagnose IE were ≥2 epileptic seizures at least 1 month apart, no history of head trauma or toxin exposure, a normal interictal neurological status and normal serum biochemistry values. In addition, brain CT or MRI was required for dogs <6 months or >5 years of age at the first epileptic seizure. Five dogs underwent CSF analysis and 3 dogs had brain CT or MRI performed.[114] A multibreed genetic study undertaken in the US in 2011 included 31 Hungarian Vizslas with IE, and it is unclear whether some of these dogs were the same as in the previous study conducted in the US.[37] Hungarian Vizslas comprised 0.6% of dogs with IE in a UK laboratory database study.[51]

Sex. In the first US study, 59% (17/29) were male and 12/29 (41%) were female. The difference in sex prevalence was not significant.[114]

Age of onset. The median age of onset was 3 years (range 0.5–5.25 years).[114]

Epileptic seizure type. Focal epileptic seizures or focal evolving to become generalized epileptic seizures were seen in 79.3% (23/29) of dogs and generalized epileptic seizures in 20.7% (6/29) of dogs. Focal epileptic seizures were a combination of isolated limb tremors, isolated head tremors, and isolated facial twitching in association with staring and pupillary dilation in some dogs, and rarely lip smacking and vomiting. Two dogs exhibited fly-biting episodes that responded to ASDs. Some owners of dogs with convulsive epileptic seizures had difficulty recognizing the focal epileptic seizures.[114]

Suspicion of a genetic basis. Autosomal recessive inheritance or polygenic inheritance was suspected on review of pedigrees. A common founder for all affected dogs was reported.[37,114]

Treatment response. The median seizure frequency was 9 seizures per year; 48% of the 29 epileptic dogs received ASD treatment, and 21% of those were not well controlled. Epileptic seizure control appeared more challenging in dogs with focal epileptic seizures evolving to bilateral convulsions.[114]

Other dog breeds and mixed-breed dogs

The current epidemiological data suggest that mixed-breed dogs present by far the largest proportion of dogs with IE. Crossbred dogs represented

20.1% (95% confidence interval, 19.8–20.4%) of dogs with IE in primary care veterinary practice and 20.5% of a laboratory database in the UK in 2011.[1,51] The criteria for the diagnosis of IE were recurrent epileptic seizures for at least 1 year in the absence of other medical problems confirmed by an unremarkable physical examination and normal hematology and serum biochemistry values for dogs in primary care veterinary practices.[1] Clinical research on IE in mixed-breed dogs is lacking. There is also evidence that other purebred dogs such as the Siberian Husky, Staffordshire Bull Terrier, Boxer,[115,116] Kromfohrlaender, Finnish Lapphund, Irish Setter, miniature Pinscher, Pyrenean Shepherd, Whippet,[98] French Bulldog[117] and several Dutch breeds[23] may be affected by IE, but there is either a lack of detailed descriptions of the breed-specific epilepsy phenotype or no consistent criteria for the diagnosis of IE have been applied, or the information is poorly accessible. Lastly, cohorts that were collected for other than breed-specific investigations, e.g., genetic investigations, treatment or imaging studies, suggest that mixed breeds and many more canine breeds can be affected by IE. Some cohorts were composed of dogs from more than 40 breeds.

Insights from cohorts collected for genetic investigations

A pharmacogenomic study in 2019 investigated 102 dogs with IE from 32 dog breeds in Italy. The most frequent dog breeds in this study were the mixed breed (36.3%; 37/102) and Labrador Retriever (6.9%; 7/102) followed by the German Shepherd, Poodle, Beagle and French Bulldog (4.9%; 5/102).[55] All dogs had a Tier 1 diagnosis of IE, 43% had an unremarkable brain MRI and the others were followed up for at least 6 months. The authors did not address the differentiation of epileptic seizures from nonepileptic paroxysmal events (including paroxysmal dyskinesia).[55]

Eight dog breeds were included in a 2017 study investigating the *ADAM23* gene variant in dogs with IE in Finland, including Australian shepherds (61 dogs), Finnish Lapphunds (53 dogs), Irish Setters (22 dogs), Kromfohrlaenders (29 dogs), Labrador Retrievers (26 dogs), miniature Pinschers (25 dogs), Pyrenean Shepherds (20 dogs) and Whippets (24 dogs).[98] This study demonstrated an association with the *ADAM23* risk haplotype with a low penetrance, similar to what is seen in Belgian Shepherds, in the following breeds: Australian Shepherd, Kromfohrlaender, Labrador Retriever, and Whippet. The clinical data were collected with an

epilepsy-specific questionnaire. Additional clinical investigations were performed in subsets of Kromfohrlaenders, Finnish Lapphunds and Pyrenean Shepherds to exclude other causes for the epileptic seizures, but no details were provided. No clinical investigations were performed in the other canine breeds. Therefore, these breeds were not included in the breed-specific section of this chapter. Still, the case summaries provided insights into the clinical characteristics of the presumptive IE in these dog breeds. All dogs had a history of at least two epileptic seizures (mean, 10–38) and a mean age of onset of IE between 2–4.5 years. The median age of IE onset was 2.9 years (range, 4–6 years) for Finnish Lapphunds, 3.2 years (range, 1–6.4 years) for Irish Setters, 2.8 years (range, 0.6–5.4 years) for Kromfohrlaenders, 2 years (range, 0.7–3.6 years) for Labrador Retrievers, 2.5 years (range, 0.8–5.5 years) for miniature Pinschers, 3 years (range, 0.9–5.3 years) for Whippets and a higher median age of 4.6 years (range 1.2–8 years) for Pyrenean Shepherds. The authors provided no specific information on whether brain MRI was performed to substantiate the suspicion of IE in dogs that were older than 6 years at their first epileptic seizure. Both generalized and focal epileptic seizures were reported but no details on any focal onset of generalized epileptic seizures were available. Cluster seizures were most frequently reported in the Irish Setter (77%) and were less common in the other breeds (24–37%). The miniature Pinscher and Irish Setter had the highest epileptic seizure frequency with 15 and 11 epileptic seizures per year, respectively. The mean number of epileptic seizures per year ranged from 4 to 7 in the other dog breeds. The owners were able to predict the seizures in 25% to 39% of the dogs. The typical preictal signs were restlessness, seeking out the owner and vomiting. The remission rate was lowest in the Irish Setter (25%). Higher remission rates from 33–50% were reported in the other dog breeds.[98]

Another genetic study investigated presumptive IE in cohorts of Belgian Shepherds (93 dogs, fine mapping in 127 dogs), Finnish Spitz dogs (61 dogs), Schipperkes (68 dogs) and Beagles (29 dogs) from Northern Europe and Germany in 2015.[35] This study showed an association with an *ADAM23* risk haplotype and supported a possible genetic origin of IE in all four breeds. The authors state that the clinical investigations (which included a physical and neurological examination, hematology, serum biochemistry, CSF analysis, brain MRI and EEG) were performed in the Belgian Shepherd, Finnish Spitz and Schipperke dogs to increase the level of

confidence for IE diagnosis. Clinical studies and a description of the phenotype of IE in Belgian Shepherds and Finnish Spitz dogs had previously been published.[19,43] More detailed information on IE in Beagles, Belgian Shepherds and Finnish Spitz and Schipperke dogs is presented in the breed-specific section in this chapter. The diagnosis of IE was based on two or more epileptic seizures at least 2 months apart. An unremarkable brain MRI was required for dogs younger than 6 months or older than 5 years at the onset of the epilepsy.[35]

In 2011, possible gene variants or markers of IE were investigated in the US in four breeds: the Beagle (24 dogs), the Greater Swiss Mountain Dog (24 dogs), the Vizsla (31 dogs) and the English Springer Spaniel (24 dogs).[37] This study applied stringent inclusion criteria and stated that all medical records were reviewed. Dogs younger than 1 or older than 5 years at the onset of epilepsy were included if CSF analysis or brain CT or MRI were unremarkable. The diagnosis of suspected genetic IE in Vizslas was further substantiated by observation of pedigrees with clustering of IE in litters and related dogs. No other clinical information was provided.

A US pharmacogenomic study in 2009 included 152 dogs from 43 dog breeds with a presumptive diagnosis of IE based on treatment with PB for at least 1 year.[118] The ten most common breeds were the mixed breed (19.7%; 30 dogs), Labrador Retriever (8.6%; 13 dogs), Border Collie (5.9%; 9 dogs), Dalmatian, German Shepherd, Golden Retriever (3.9%; 6 dogs each), followed by the Beagle, Boxer, American Staffordshire Terrier and miscellaneous hounds (3.3%; 5 dogs each). The study did not specify whether the dogs had a history of two or more seizures on different days, whether the presence of epileptic seizures was specifically confirmed and dyskinesia excluded and how many dogs underwent brain imaging.[118]

Insights from large epidemiological studies

Recent epidemiological studies explored large databases reflecting hospital or country populations and stated the use of IVETF criteria for the diagnosis of IE.[6,52,119] These studies showed that popular dog breeds were affected by IE.

Overall, the fact that occurrence of IE has been published in some canine breeds but not in others may just be a reflection of the breed popularity. More detailed information on the differences in the manifestations of epilepsy between different dog breeds and suspicion of a

genetic basis come from descriptions of cohorts of epileptic dogs of a single breed, true breed prevalence studies and pedigree data suggesting clustering of IE in family members. There is a need for future studies comparing epilepsy phenotypes across breeds.

COMORBIDITIES AND LIFESPAN IN CANINE IDIOPATHIC EPILEPSY

Behavioral comorbidities

Veterinary studies have shown that dogs with IE can develop changes in behavior.[120–123] Behavioral comorbidities are a well-known feature of epilepsy in humans: neurobehavioral and psychiatric disorders and epilepsy frequently coexist. People with epilepsy have an increased risk of cognitive decline, depression or suicidal attempts. The relationship between epilepsy and behavioral and psychiatric disorders, when they coexist in the same patient, has been explained by a network hypothesis for the origin of epilepsy. Epilepsy is now defined as a network disorder of the brain. It is proposed that the same neuronal networks and pathophysiological pathways that give rise to epilepsy are also involved in the generation of coexistent behavioral and psychiatric disorders. Further support for this shared network hypothesis comes from the fact that people with a primary diagnosis of a mood disorder also show an increased risk of suffering from epilepsy. Furthermore, it has been shown that in a proportion of epileptic people, the onset of epilepsy coincides with or is preceded by a recent onset of behavioral changes. Similar observations have been made in dogs with IE. There is also an association between seizures and cognitive decline, especially in temporal lobe epilepsy in humans.[124–126]

The association between the onset of epilepsy and the onset of behavioral changes was first described by Shihab et al. in dogs with IE in the UK.[120] Behavioral changes were compared retrospectively before and after the onset of IE. This was a single center study involving a cohort of 80 dogs with IE. The criteria for the diagnosis of IE were recurrent epileptic seizures with no identifiable cause on diagnostic investigations that included brain MRI. The study used a previously validated behavioral questionnaire that scored 10 different behavioral factors: fear/anxiety,

defensive aggression, controlling aggression, abnormal perception, territorial behavior, demanding behavior, abnormal reactivity, attachment disorder, demented behavior, and apathetic behavior.[127,128] The results showed that 71% of the dogs with IE had a higher score in at least one behavioral factors at the onset of epilepsy. Most importantly, the authors identified increases in scores for fear/anxiety and abnormal perception. These behavioral changes occurred independently of treatment with an ASD, suggesting that fear/anxiety and abnormal perception could be a comorbidity of IE. Additional significant changes were encountered for defensive aggression in untreated dogs, and for abnormal reactivity, attachment disorder, demented behavior and apathetic behavior in dogs treated with ASDs. There was no association with epileptic seizure type. Behavioral changes were more frequently seen in male dogs. A strength of this study was that untreated and treated dogs with IE were compared with each other, but there were also limitations, mainly the lack of other control groups and the retrospective study design which is sensitive to recall bias. Owners were asked to recall behavioral factors before the onset of epilepsy (when the mean age of the dogs was 37 months) and 2 years later at the time of questionnaire completion (when the mean age of the dogs was 63 months). Nevertheless, this study provided important information on the appearance of fear/anxiety and abnormal perception in association with IE and unrelated to treatment. Abnormal perception manifested in these dogs as barking without apparent cause, chasing shadows or light spots, aimless pacing, and staring into space. Abnormal perception and demented behavior were associated with increased seizure frequency and developed more frequently in drug-resistant dogs in this cohort.

A recent online cross-sectional questionnaire study across the UK investigated 96 dogs with IE and 292 healthy controls. The 96 dogs with IE were from eight breeds (Golden Retriever, Labrador Retriever, Cocker Spaniel, Border Terrier, German Shepherd dog, Parson Jack Russel Terrier, Boxer, Border Collie).[121] The criteria for the diagnosis of IE were not described in detail. Behavior before and after the onset of epilepsy was assessed using the Canine Behavioral and Assessment Research Questionnaire (CBARQ) and attention deficit hyperactivity disorder (ADHD) rating scales. The authors reported lower trainability scores and more inattention, dog-directed fear or aggression, nonsocial fear, attachment

and attention deficit after the onset of IE. Trainability was lower in epileptic dogs and ASD-resistant dogs when these were compared with controls.[121]

A multibreed cohort of 37 dogs with IE that involved stringent inclusion criteria was analyzed and compared with two nonepileptic control groups in the US (published in 2019). Dogs with IE were more fearful when approached by a stranger than healthy controls but did not react differently from dogs with a history of intervertebral disk disease. In this study, anxiety and fear when being groomed or left alone were more evident in dogs being treated with several ASDs than in those on ASD monotherapy.[122]

Similar observations were made in studies of breed-specific IE. Specifically, in a population survey study including 63 Italian Spinoni with IE in the UK, 55% of dogs developed behavioral changes, mostly anxiety and abnormal perception at the onset of the IE. It is of interest that behavioral abnormalities developed before treatment with ASDs was initiated.[91] In contrast, in the Lagotto Romagnolo dogs with benign familial juvenile epilepsy, which is a genetic idiopathic focal epilepsy, the epilepsy usually remitted after puppyhood and no more seizures occurred. Yet these dogs expressed behavioral changes as adult dogs. Dogs had increased scores for hyperactivity and inattention 4 years after the epileptic seizures had stopped when compared with a large control group of the same breed without epileptic seizures. The behavioral changes were reminiscent of attention deficit hyperactivity disorder in humans. The authors considered the direct influence of altered LGI2 protein expression or a negative effect of early onset seizures on the developing brain.[101]

Cognitive impairment was investigated in a cross-sectional study in the UK in 2016 using an online survey platform.[123] The authors used the Canine Cognitive Dysfunction Rating scale (CCDR) in 286 dogs with IE and a control group of 3765 dogs.[123] The criteria for the diagnosis of IE were ≥2 epileptic seizures, an age of onset between 6 months and 6 years, and unremarkable blood and urine tests. The assessment was based on the answers of the dogs' owners to screening questions. The CCDR scale is validated for assessment of dementia/demented behavior.[129] It provides scores for memory (lack of recognition of owners, house-soiling), orientation (staring blankly, getting lost in the home), apathy (reduced time spent active, avoiding contact with owners), impaired olfaction (difficulty finding food) and locomotion. It also has a section that assesses progression over 6 months.[129] The presence or absence of cognitive dysfunction is

evaluated by a cutoff score of 50. Comparison of the prevalence of cognitive dysfunction between age groups showed a higher prevalence of cognitive impairment at a younger age in dogs with IE when compared to age-matched controls. Dogs with IE showed mostly impairment in memory functions but not in social interaction. Thus, cognitive dysfunction in dogs with IE differs from the classical canine cognitive dysfunction disorder (CCD).[123,130] Subsequent on-site behavioral tests showed that dogs with IE scored worse on performance of a cognitive spatial working memory task and were more often unable to learn a spatial discrimination task than controls.[131,132] The authors concluded that there is a need for longitudinal studies of individual dogs with IE and for repeated assessments over time.

Anxiety and fear appear to be associated with IE in multiple ways, either as a behavioral comorbidity,[120,133,134] or as a change in normal behavior in the minutes, hours or days before an epileptic seizure.[135] In addition, short and isolated episodes of anxiety and fear can represent the clinical manifestations of sensory/behavioral epileptic seizures.[24,50] Fear-related behavior was the main expression of focal epilepsy in Boerboel dogs and also considered in Malinois dogs.[48,50] The simultaneous occurrence of autonomic signs or focal motor signs such as salivation or tremors were hints pointing towards the epileptic origin of these short episodes of fear and anxiety. Previously, it was reported that paroxysms of sudden, stereotypical behavior, which are often interpreted by owners as fear or anxiety, occurred in many dogs and canine breeds with IE in the time period preceding epileptic seizures.[105,136] These behavioral paroxysms may or may not evolve into tonic-clonic convulsive seizures. Fear and anxiety in the time period preceding epileptic seizures is also a feature of many breed-specific IEs.[91,135,137] These transient behavioral changes may represent the prodrome, focal onset of an epileptic seizure or seizure-provoking factors.[41] More recently, EEG has contributed to clarify the epileptic nature of multiple short episodes of staring, freezing and not responding to commands.[15,138]

Attention-deficit. Increased excitability, chasing behavior and decreased trainability are behavioral phenotypes that resemble to some degree ADHD in people, which is characterized by a lack of concentration and increased impulsivity. Twenty-six dogs with IE were evaluated with the CBARQ questionnaire, which assesses 10 behavioral phenotypes with 68 questions and assigns a 5-point score from 0 to 4 for each question. These

dogs achieved the highest scores for the behavioral phenotypes excitability (mean, 1.910; 42.9–52.4% of the dogs had a score of 4) and chasing (mean, 1.8124) and the lowest scores for trainability (mean, 0.437).[139,140] Excitability was assessed by asking whether the dog becomes extremely excited when a member of the household returns after a short absence, when playing with a member of the household or before going for a walk (score 4 in 52.4% of dogs), when visitors arrive at home (score of 4 in 42.9% of dogs), when taken on a car trip or when the doorbell rings (score 4 in 33% of dogs). Increased chasing behavior was assessed by asking whether the dog would chase squirrels or other small mammals (score 4 in 52.4% of dogs), chase cats (score 4 in 47.4% of dogs), chase birds or act aggressively to other animals entering the garden (score 4 in 33.3% of dogs). In contrast, trainability was rather low: about two thirds of the owners reported that their dog was always easily distracted by sights, sounds or smell (score 4 in 66.8% of dogs), while only a quarter stated that their dog always obeyed a sit command immediately (score 4 in 23.8% of dogs) and even fewer that they always obeyed a stay command immediately (score 4 in 9.5% of dogs). Interestingly, scores on chasing behavior and stranger-directed fear decreased significantly when the dogs were fed the medium chain triglyceride (MCT)-enriched diet.[139] ADHD-like behavior was also present in Lagotto Romagnolo dogs with juvenile benign remitting epilepsy.[101]

Trainability. Trainability was explored with a cross-sectional online survey in 286 dogs with a Tier 1 diagnosis of IE and a large control group of 4051 dogs.[141] Trainability was assessed with the trainability section of the CBARQ. This section includes eight questions to assess whether the dog returns immediately when called, obeys sit or stay commands immediately, will fetch sticks or balls, will listen to the owner, is slow to respond to commands, is slow to learn new tricks, or is easily distracted. Results showed significantly reduced trainability in dogs with IE and in dogs treated with KBr, zonisamide or multiple ASDs.[141] Recently, reduced scores for trainability were also observed in 21 dogs at the onset of IE.[121]

Treatment with ASDs. The IVETF proposed that changes in behavior should also be included as an important outcome parameter in treatment studies in IE.[142] Many ASD treatment regimens anticipate negative aspects of ASD on behavior. However, it may be worthwhile to consider that ASDs may also lead to improvement in behavior either because epileptic seizures

are adequately controlled or because of their anxiolytic effects.[133,143] Positive behavioral effects of an MCT-enriched diet or MCT supplement were observed in dogs with and without IE.[139,144,145] Treatment with multiple ASDs at high dosages in difficult-to-treat IE can be associated with pronounced behavioral adverse effects and negatively impair trainability and cognitive functions. Ataxia and excessive sedation is a particular concern with high dosages and serum concentrations of KBr and PB.[146] Treatment with KBr, zonisamide or more than one ASD was associated with decreased trainability.[141] Behavioral changes were also reported with LEV therapy.[143]

Other comorbid conditions. A recent focus has also been on other comorbid conditions that can influence behavior and coexist with epilepsy, e.g., atopy.[148] Another important aspect that has been reported but is currently underrepresented in the veterinary literature is the appearance of aggression in the postictal phase. Descriptions of IE in specific dog breeds reported postictal aggression in Border Collies (5/49; 10.2%), Australian Shepherds (6/50; 12%), Rottweilers (4/25; 16%), Golden Retrievers, Labrador Retrievers, and Greater Swiss Mountain Dogs (3/11; 27.2%).[24,51,82,87,96,108] Postictal aggression can have serious consequences and needs to be clearly discussed with the dog owners. It may be of interest that LEV has been associated with an increased risk of irritability and aggression in people and this may also rarely occur in dogs.[143] Lastly, all described behavioral changes can affect trainability and cognitive performance of dogs, and this has become an additional focus of research in the behavioral aspects of IE.

The effects of IE and its behavioral comorbidities on quality of life are discussed further in Chapter 3.

Effect on survival time and life span

In many dogs, IE is a lifelong disorder that requires lifelong treatment with an ASD. The survival time and life span after the first epileptic seizure are influenced by two factors, the owner's decision for euthanasia (which is the most common cause of end of life) and death during or soon after an epileptic seizure, e.g., during status epilepticus, secondary to aspiration pneumonia, due to suffocation if epileptic seizures occur during swimming or eating/drinking, or sudden unexpected death in epilepsy (SUDEP) (Fig. 2.2). Comparison of survival time and life span between the different

studies on canine IE is challenging due to the various factors that can affect these parameters. Indeed, life span and survival time after the first epileptic seizure were not suggested as a relevant outcome parameter by the IVETF.[142]

The decision whether to continue to care for or euthanize a dog with IE is influenced by many factors. There is a high level of evidence that dogs with cluster epileptic seizures have shorter survival times and are euthanized more frequently than dogs without cluster seizures. In one study on risk factors and outcome in dogs with IE and cluster seizures, two thirds of all deaths of dogs with cluster seizures were related to euthanasia.[149] Yet this study reported median survival times of 95 months in dogs with cluster seizures. The life span was also significantly shorter for dogs with status epilepticus (8.3 vs. 11.3 years).[150]

Other factors that influence an owner's decision to care for a dog with IE are financial aspects, frustration level and social influences, interictal behavioral changes and adverse effects of treatment with ASDs, such as pancreatitis or hepatotoxicity. The breed and purpose of the dog, e.g., smaller versus larger breed dog[119] or whether a dog is kept for working purposes or for companionship,[2] may also influence the willingness to care for a dog with a chronic disease like IE. These factors appear to differ depending on the geographic region.[2,119] In summary, the successful management of IE, i.e., whether long-term epileptic seizure control can be achieved without relevant adverse effects and whether cluster seizures and status epilepticus can be avoided, will influence both the owners' decision to euthanize their dog and the risk of other epilepsy-related deaths besides SUDEP.[149,150]

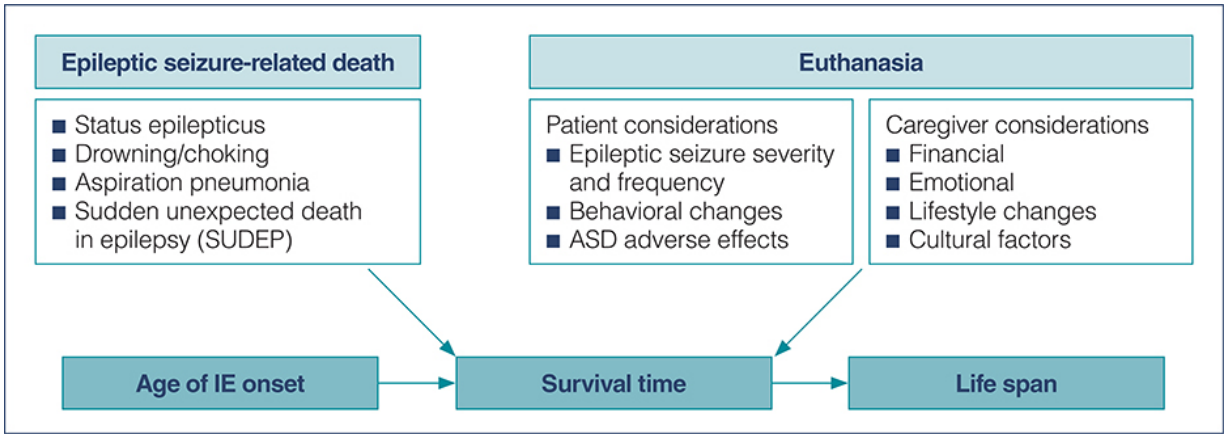


FIGURE 2.2. Factors influencing survival and lifespan in canine idiopathic epilepsy.

The underlying cause of epilepsy has a major impact on the life span of dogs. Dogs with IE have a longer life span than dogs with structural epilepsy. Data from a Danish hospital population showed that dogs with IE had a longer life span (median, 9.2 years) and lived much longer after the first epileptic seizure (median, 5 years) than dogs with structural epilepsy, which lived only 8 months (median) after the first seizure.[151] The authors concluded that dogs with IE can in many aspects have a life span close to what is reported as normal for dogs (median, 10 years in Denmark, 12 years in the UK).[151] Still, more than half of the dogs of this cohort experienced cluster seizures and/or status epilepticus and more than half of the deaths were epilepsy-related, which shows the potential for an even longer life span if better control of the epilepsy could be achieved. The impact of the epilepsy diagnosis on the animal's life span was also demonstrated in a cohort of dogs with an onset of epilepsy prior to one year of age.[54] Dogs with IE (102 dogs) had longer survival times (median, 10.6 years; 3854 days) after the first epileptic seizure than 25 dogs with structural or probable structural epilepsy (median, 3.4 years; 1249 days).[54] The strength of this study was that almost all dogs underwent diagnostic investigations including brain MRI. The life span of Danish Belgian Shepherds with focal IE was in the same range as that in Belgian Shepherds without IE. The median age of death was 8.2 years in Belgian Shepherds with IE, compared to 9.3 years in dogs from the same family without IE.[42] Similar findings but even longer life spans and survival times after the first epileptic seizure were reported in small breed dogs with IE from Japan.[119] The authors discussed an impact of the dog breed as well as the attitude of dog owners in Japan, where, unlike to what occurs in Europe, euthanasia is almost never considered as an option.

Life span results from the additive effects of age of onset of IE and survival time after the first epileptic seizures. Therefore, IE has a greater impact on the life span of dogs with an earlier onset of epilepsy and a more severe course of the disease. Shorter life spans were evident in Border Collies and Australian Shepherds from Germany if the dogs were younger than 2 years at their first epileptic seizure, and if IE had a severe clinical course with frequent cluster seizures and status epilepticus.[24,51] Again, euthanasia was the most common cause of death. Nevertheless, there were

wide variations and remission even occurred after 6 years of ongoing epileptic seizures in some severely affected dogs.[24,51] Shorter life spans with a high proportion of dogs euthanized before 3 years of age were also reported in the Cane Corso.[64] The mean survival time after the first epileptic seizure was 22 months in the Italian Spinone.[91] Life span was reduced by 2 years in Irish Wolfhounds when compared to the general canine population.[88] In contrast, life span appeared unaffected in most Rhodesian Ridgebacks with juvenile myoclonic epilepsy and in Lagotto Romagnolo dogs with benign familial juvenile epilepsy.[10,101]

The owners of dogs with IE should be informed of the clinical course and the chances of remission from IE. Remission has been defined as seizure-freedom for prolonged time periods (longer than 1, 2 or 3 years). Published remission rates for IE are frequently in the range of 14–24% across many canine breeds, up to 30% in Labrador Retrievers,[18,23,24,96] and close to 100% in Lagotto Romagnolo dogs. On rare occasions remission has occurred with a severe clinical course with frequent cluster seizures.[24,51] This view has recently been expanded by observations from the Danish epilepsy research group, who documented fluctuating epileptic seizure patterns, including long periods of remission in new onset and untreated IE.[152]

Association with sex hormones

Sex predisposition. An evaluation of electronic patient records in the UK in 2011 revealed males were 1.5 times more likely to have IE.[1] Another evaluation of an insurance database in Sweden also showed an increased risk in males.[2] In a cohort of 174 Labradors and Border Collies from the UK with IE, 69% (120/174) were male and 31% (54/174) were female.[97] Male dogs were frequently overrepresented in cohorts with IE from specific dog breeds including: Beagle, Bernese Mountain Dog, Collie, German Shepherd, English Springer Spaniel, Irish Wolfhound, Italian Spinone, Labrador Retriever, Petit Basset Griffon Vendéen, Rhodesian Ridgeback, and Schipperke.

Estrus. In a study including 45 female dogs with IE, 38% (17/45) had their first epileptic seizure during heat and 13% (6/45) 1–3 months after heat. In 9 dogs (20%), seizures reoccurred in relation to their estrus cycle.[15] These findings suggest that catamenial epilepsy exists in dogs. Proposed underlying pathophysiological mechanisms include proconvulsive effects of

estrogens leading to increased excitability of NMDA-glutamate receptors and decreased epileptic seizure threshold, and seizure inhibition by progesterone.[153]

Neutering. Neutering does not appear to have a protective effect for IE in either male or female dogs. Intact male and female dogs had longer survival times than neutered ones.[18,97,151] Of 13 Australian Shepherds with IE that were neutered after the onset of the disease, epileptic seizures decreased in 1, increased in 2, and remained unchanged in the other dogs.[24] Similar observations were made in Border Collies. Of 15 Border Collies neutered after the onset of IE, only one owner noted an improvement in seizure control and one owner reported increased seizure frequency. Seizures remained unchanged in the other 13 dogs.[51]

Treatment response. Female dogs were twice as likely to go into remission than male dogs with IE. No effects of the neutering status were found. Therefore, four factors—being female, being intact, having no previous history of cluster seizures and an older age at IE onset—were associated with a higher chance of achieving remission or ≥50% decrease in epileptic seizure occurrence.[18]

TAKE-HOME MESSAGES

- ✔ Idiopathic epilepsy is the most common chronic neurological disease of dogs.
- ✔ The clinical diagnosis of IE relies on the occurrence of two or more unprovoked epileptic seizures at least 24 hours apart, an onset between 6 months and 6 years of age, and no evidence of structural brain disease.
- ✔ Idiopathic epilepsy is further classified as genetic IE, suspected genetic IE or IE of unknown etiology.
- ✔ Genetic IE and causal epilepsy genes were identified in Rhodesian Ridgebacks (juvenile myoclonic epilepsy) and in Lagotto Romagnolo dogs (benign familial juvenile epilepsy).
- ✔ Genetic IE is suspected in dog breeds with a high prevalence of IE or if there is clustering of IE in families and related dogs.

- ✔ A breed prevalence ≥2% and/or association with epilepsy risk gene variants supports a genetic etiology of the IE in the breed.
- ✔ A summary of the published information on IE in different dog breeds is provided in this chapter.
- ✔ Idiopathic epilepsy is not restricted to these breeds and occurs in many other dog breeds and mixed-breed dogs.
- ✔ Interictal behavioral comorbidities and cognitive impairment can occur in dogs with IE.
- ✔ Survival times and life span are influenced by the severity of IE in the individual dog and the owner's decision to care for a dog with IE.

REFERENCES

1. KEARSLEY-FLEET L, NEILL DGO, VOLK HA et al. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. *Vet Rec*. 2013; 172(13):338.
2. HESKE L, NØDTVEDT A, JÄDERLUND KH et al. A cohort study of epilepsy among 665,000 insured dogs: Incidence, mortality and survival after diagnosis. *Vet J*. 2014; 202(3):471–6.
3. OBERBAUER AM, BELANGER JM, BELLUMORI T et al. Ten inherited disorders in purebred dogs by functional breed groupings. *Canine Genet Epidemiol*. 2015; 2(1):9.
4. SCHWARTZ-PORSCHE D. Seizures. In: BRAUND K (ed.). *Clinical Syndromes In Veterinary Neurology*. *2nd ed*. St. Louis: Mosby, Inc.; 1994. pp. 234–251.
5. JAGGY A, BERNARDINI M. Idiopathic epilepsy in 125 dogs: A long-term study. Clinical and electroencephalographic findings. *J Small Anim Pract*. 1998; 39(1):23–29.
6. HALL R, LABRUYERE J, VOLK H, CARDY TJ. Estimation of the prevalence of idiopathic epilepsy and structural epilepsy in a general population of 900 dogs undergoing MRI for epileptic seizures. *Vet Rec*. 2020; 187(10):E89.
7. BERENDT M, GULLØV CH, FREDHOLM M. Focal epilepsy in the Belgian shepherd: evidence for simple Mendelian inheritance. *J Small Anim Pract*. 2009; 50(12):655–661.
8. FAMULA TR, OBERBAUER AM. Reducing the incidence of epileptic seizures in the Belgian Tervuren through selection. *Prev Vet Med*. 1998; 33(1–4):251–259.
9. BERENDT M, FARQUHAR RG, MANDIGERS PJJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11:182.
10. WIELAENDER F, SARVIAHO R, JAMES F, et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci*. 2017; 114:2669–2674.

11. Wolf M, Bruehschwein A, Sauter-Louis C et al. An inherited episodic head tremor syndrome in Doberman pinscher dogs. *Mov Disord*. 2011 Nov; 26(13):2381–2386.
12. Guevar J, De Decker S, Van Ham LML, Fischer A. Idiopathic Head Tremor in English Bulldogs. *Mov Disord*. 2014; 29(2):191–194.
13. James FMK, Cortez MA, Monteith G et al. Diagnostic Utility of Wireless Video-Electroencephalography in Unsedated Dogs. *J Vet Intern Med*. 2017; 31:1469–1476.
14. James FMK, Dugas S, Cortez MA et al. Epileptogenic electroencephalographic findings in canine episodic head tremor syndrome. *J Vet Intern Med*. 2016; 1:444.
15. Wielaender F, James FMK, Cortez MA et al. Absence seizures as a feature of juvenile myoclonic epilepsy in Rhodesian Ridgeback dogs. *J Vet Intern Med*. 2018; 32(1):428–32.
16. Hasegawa D. Diagnostic techniques to detect the epileptogenic zone: Pathophysiological and presurgical analysis of epilepsy in dogs and cats. *Vet J*. 2016; 215:64–75.
17. Gregg N, Nasseri M, Kremen V et al. Circadian and multiday seizure periodicities, and seizure clusters in canine epilepsy. *Brain Commun*. 2020; 2(1):fcaa008.
18. Packer R, Shihab N, Torres B, Volk H. Clinical risk factors associated wit anti-epileptic drug responsiveness in canine epilepsy. *PLoS One*. 2014; 9(8):e106026.
19. Viitmaa R, Cizinauskas S, Orro T et al. Phenotype, inheritance characteristics, and risk factors for idiopathic epilepsy in Finnish Spitz dogs. *J Am Vet Med Assoc*. 2013; 243(7):1001–9.
20. De Risio L, Bhatti S, Muñana K et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015; 11:148.
21. Rusbridge C, Long S, Jovanovik J et al. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol. *BMC Vet Res*. 2015 Aug 28; 11:194.
22. Ekenstedt KJ, Patterson EE, Mickelson JR. Canine epilepsy genetics. *Mamm Genome*. 2012; 23(1–2):28–39.
23. Hülsmeyer VI, Fischer A, Mandigers PJJ et al. International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. *BMC Vet Res*. 2015; 11(1):175.
24. Weissl J, Hülsmeyer V, Brauer C et al. Disease progression and treatment response of idiopathic epilepsy in Australian shepherd dogs. *J Vet Intern Med*. 2012; 26(1):116–125.
25. Lowrie M. Exercise-induced collapse in the dog. *Companion Anim*. 2017; 22:724–728.
26. Minor KM, Patterson EE, Keating MK et al. Presence and impact of the exercise-induced collapse associated DNM1 mutation in Labrador retrievers and other breeds. *Vet J*. 2011 Aug; 189(2):214–219.
27. Katz ML, Farias FH, Sanders DN et al. A missense mutation in canine CLN6 in an Australian shepherd with neuronal ceroid lipofuscinosis. *J Biomed Biotechnol*. 2011; 2011:198042.
28. Guo J, Johnson GS, Brown HA et al. A CLN8 nonsense mutation in the whole genome sequence of a mixed breed dog with neuronal ceroid lipofuscinosis and Australian shepherd ancestry. *Mol Genet Metab*. 2014; 112(4):302–309.
29. Firdova Z, Turnova E, Bielikova M et al. The prevalence of ABCB1: c.227_230delATAG mutation in affected dog breeds from European countries. *Res Vet Sci*. 2016; 106:89–92.
30. Gaens D, Leithäuser C, Hamann M, Geyer J. Adverse drug reactions after administration of emodepside/praziquantel (Profender®) in an MDR1-mutant Australian Shepherd dog: case report. *Front Vet Sci*. 2019; 6:296.

31. Gramer I, Leidolf R, Döring B et al. Breed distribution of the nt230(del4) MDR1 mutation in dogs. *Vet J*. 2011; 189(1):67–71.
32. Geyer J, Döring B, Godoy JR et al. Frequency of the nt230 (del4) MDR1 mutation in Collies and related dog breeds in Germany. *J Vet Pharmacol Ther*. 2005; 28(6):545–551.
33. Edmonds HL, Bellin SI, Chen FC, Hegreberg GA. Anticonvulsant properties of ropizine in epileptic and nonepileptic beagle dogs. *Epilepsia*. 1978 Apr; 19(2):139–146.
34. Bielfelt S, Redman H, McClellan R. Sire- and sex-related differences in rates of epileptiform seizures in a purebred Beagle dog colony. *Am J Vet Res*. 1971; 32(12):2039–2048.
35. Koskinen LLE, Seppälä EH, Belanger JM, et al. Identification of a common risk haplotype for canine idiopathic epilepsy in the ADAM23 gene. *BMC Genomics*. 2015; 16(1):1–10.
36. Frank L, Lüpke M, Kostic D et al. Grey matter volume in healthy and epileptic beagles using voxel-based morphometry - a pilot study. *BMC Vet Res*. 2018; 14(1):50.
37. Ekenstedt KJ, Patterson EE, Minor KM, Mickelson JR. Candidate genes for idiopathic epilepsy in four dog breeds. *BMC Genet*. 2011; 12(1):38.
38. Gredal H, Berendt M, Leifsson PS. Progressive myoclonus epilepsy in a beagle. *J Small Anim Pract*. 2003; 44(11):511–514.
39. Demeny H, Florea B, Tabaran F et al. EEG patterns orienting to Lafora disease diagnosis: a case report in two Beagles. *Front Vet Sci*. 2020; 7(November):1–9.
40. Hajek I, Kettner F, Simerdova V et al. NHLRC1 repeat expansion in two beagles with Lafora disease. *J Small Anim Pract*. 2016; 57(11):650–652.
41. Berendt M, Gulløv CH, Christensen SLK et al. Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995-2004. *Acta Vet Scand*. 2008; 50(1):1–7.
42. Gulløv CH, Toft N, Berendt M. A Longitudinal study of survival in Belgian Shepherds with genetic epilepsy. *J Vet Intern Med*. 2012; 26:12–15.
43. Seppälä E, Koskinen LLE, Gulløv CH et al. Identification of a novel idiopathic epilepsy locus in Belgian Shepherd dogs. *PLoS One*. 2012 Mar 23; 7(3):e33549.
44. Belanger JM, Famula TR, Gershony LC et al. Genome-wide association analysis of idiopathic epilepsy in the Belgian shepherd. *Canine Med Genet*. 2020; 7(1):1–11.
45. Famula TR, Oberbauer AM, Brown KN. Heritability of epileptic seizures in the Belgian tervueren. *J Small Anim Pract*. 1997; 38(8):349–352.
46. Oberbauer AM, Belanger JM, Grossman DI et al. Genome-wide linkage scan for loci associated with epilepsy in Belgian shepherd dogs. *BMC Genet*. 2010; 11:35.
47. Lit L, Belanger JM, Boehm D et al. Characterization of a dopamine transporter polymorphism and behavior in Belgian Malinois. *BMC Genet*. 2013; 14:45.
48. Lit L, Belanger JM, Boehm D et al. Differences in behavior and activity associated with a Poly(A) expansion in the dopamine transporter in Belgian Malinois. *PLoS One*. 2013; 8(12):6–12.
49. Kathmann I, Jaggy A, Busato A et al. Clinical and genetic investigations of idiopathic epilepsy in the Bernese mountain dog. *J Small Anim Pr*. 1999; 40:319–325.
50. Stassen QEM, Grinwis GCM, van Rhijn NC et al. Focal epilepsy with fear-related behavior as primary presentation in Boerboel dogs. *J Vet Intern Med*. 2019; 33(2):694–700.
51. Hülsmeyer V, Zimmermann R, Brauer C et al. Epilepsy in Border Collies: Clinical manifestations, outcome and mode of inheritance. *J Vet Intern Med*. 2010; 24:171–178.

52. Erlen A, Potschka H, Volk HA et al. Seizures in dogs under primary veterinary care in the United Kingdom: Etiology, diagnostic testing, and clinical management. *J Vet Intern Med*. 2020; 34(6):2525–2535.
53. Short AD, Dunne A, Lohi H et al. Characteristics of epileptic episodes in UK dog breeds: an epidemiological approach. *Vet Rec*. 2011; 169(2):48.
54. Arrol L, Penderis J, Garosi L et al. Aetiology and long-term outcome of juvenile epilepsy in 136 dogs. *Vet Rec*. 2012; 170:335.
55. Gagliardo T, Gandini G, Gallucci A et al. ABCB1 c.-6-180T > G polymorphism and clinical risk factors in a multi-breed cohort of dogs with refractory idiopathic epilepsy. *Vet J*. 2019; 253:e105378.
56. Alves L, Hülsmeyer V, Jaggy A et al. Polymorphisms in the ABCB1 gene in phenobarbital-resistant and responsive idiopathic epileptic Border Collies. *J Vet Intern Med*. 2011; 25:484–489.
57. Taylor S, Minor K, Shmon CL et al. Border collie collapse: Owner survey results and veterinary description of videotaped episodes. *J Am Anim Hosp Assoc*. 2016; 52(6):364–370.
58. Melville S a, Wilson CL, Chiang CS et al. A mutation in canine CLN5 causes neuronal ceroid lipofuscinosis in Border collie dogs. *Genomics*. 2005; 86(3):287–94.
59. Mizukami K, Kawamichi T Koie H et al. Neuronal ceroid lipofuscinosis in Border Collie dogs in Japan: clinical and molecular epidemiological study (2000-2011). *Sci World J*. 2012; 2012:383174.
60. Lowrie M, Garden OA, Hadjivassiliou M et al. characterization of paroxysmal gluten-sensitive dyskinesia in Border Terriers using serological markers. *J Vet Intern Med*. 2018; 32(2):775–781.
61. Kloene J, Sewell AC, Hamann H et al. Clinical investigations of seizures in Border Terriers. *Kleintierpraxis*. 2008; 53(1):5–12.
62. O'Neill DG, Darwent EC, Church DB, Brodbelt DC. Border Terriers under primary veterinary care in England: demography and disorders. *Canine Genet Epidemiol*. 2017; 4(1):1–12.
63. Marioni-Henry K, Rusbridge C, Volk HA. Clinical features in Border Terrier dogs with paroxysmal involuntary movements. *Mov Disord Clin Pract*. 2016; 3(1):73–9.
64. Escriou C, Quignon P, Menzer E et al. Genetic epilepsy in Cane Corso and Dogue de Bordeaux. *J Vet Intern Med*. 2016; 30:464.
65. Rusbridge C, Knowler SP. Inheritance of occipital bone hypoplasia (Chiari type I malformation) in Cavalier King Charles spaniels. *J Vet Intern Med*. 2004; 18(5):673–678.
66. Driver CJ, Chandler K, Walmsley G et al. The association between Chiari-like malformation, ventriculomegaly and seizures in cavalier King Charles spaniels. *Vet J*. 2013; 195(2):235–237.
67. Lu D, Lamb CR, Pfeiffer DU, Targett MP. Neurological signs and results of magnetic resonance imaging in 40 cavalier King Charles spaniels with Chiari type 1-like malformations. *Vet Rec*. 2003; 153(9):260–263.
68. Plessas IN, Rusbridge C, Driver CJ et al. Long-term outcome of Cavalier King Charles spaniel dogs with clinical signs associated with Chiari-like malformation and syringomyelia. *Vet Rec*. 2012; 171(20):501.
69. Gill JL, Tsai KL, Krey C et al. A canine BCAN microdeletion associated with episodic falling syndrome. *Neurobiol Dis*. 2012; 45(1):130–136.

70. Wrzosek M, Płonek M, Nicpon J et al. Retrospective multicenter evaluation of the "fly-catching syndrome" in 24 dogs: EEG, BAER, MRI, CSF findings and response to antiepileptic and antidepressant treatment. *Epilepsy Behav*. 2015; 53:184–189.
71. Muñana KR, Nettifee-Osborne JA, Bergman RL, Mealey KL. Association between ABCB1 genotype and seizure outcome in Collies with epilepsy. *J Vet Intern Med*. 2012; 26(6):1358–1364.
72. Licht BG, Licht MH, Harper KM et al. Clinical presentations of naturally occurring canine seizures: similarities to human seizures. *Epilepsy Behav*. 2002 Oct; 3(5):460–470.
73. Erlen A, Potschka H, Volk HA et al. Seizure occurrence in dogs under primary veterinary care in the UK: prevalence and risk factors. *J Vet Intern Med*. 2018; 32(5):1665–1676.
74. Patterson EE, Armstrong PJ, O'Brien DP et al. Clinical description and mode of inheritance of idiopathic epilepsy in English springer spaniels. *J Am Vet Med Assoc*. 2005; 226(1):54–58.
75. Clubs UESSB. 2013 ESS UK Health Survey Report [Internet]. [cited 2021 Jun 2]. Available from: www.englishspringerhealth.org.uk
76. Lowrie M. Seizures in the juvenile patient. *In Pract*. 2014; 36(September):30–36.
77. Stee K, Van Poucke M, Peelman L, Lowrie M. Paradoxical pseudomyotonia in English Springer and Cocker Spaniels. *J Vet Intern Med*. 2020; 34(1):253–257.
78. Viitmaa R, Cizinauskas S, Bergamasco L et al. Magnetic resonance imaging findings in Finnish Spitz dogs with focal epilepsy. *J Vet Intern Med*. 2006; 20(2):305–310.
79. Jeserevics J, Viitmaa R, Cizinauskas S et al. Electroencephalography findings in healthy and Finnish Spitz dogs with epilepsy: visual and background quantitative analysis. *J Vet Intern Med*. 2007; 21(6): 1299–1306.
80. Viiitma D, Haaparanta-Solin M, Snellmann M et al. Cerebral glucose utilization measured with high resolution positron emission tomography in epileptic Finnish Spitz. *Vet Radiol Ultrasound*. 2014; 55(4):453–461.
81. Falco M, Barker J, Wallace M. The genetics of epilepsy in the British Alsatian. *J Small Anim Pr*. 1974; 15:685–492.
82. Lengweiler C, Jaggy A. Clinical, epidemiological and treatment aspects of idiopathic epilepsy in 25 Golden Retrievers: results of a long-term study. *Schweiz Arch Tierheilkd*. 1999; 141(5):231–238.
83. Srenk P, Jaggy A. Interictal electroencephalographic findings in a family of golden retrievers with idiopathic epilepsy. *J Small Anim Pract*. 1996; 37(7):317–321.
84. Srenk P, Jaggy A, Gaillard C et al. Genetic basis of idiopathic epilepsy in the golden retriever. *Tierärztliche Prax*. 1994; 22(6):574–578.
85. Royaux E, Bhatti S, Harvey R et al. Acetazolamide-responsive paroxysmal dyskinesia in a 12-week-old female golden retriever dog. *Vet Q*. 2016; 36(1):45–49.
86. Gilliam D, Kolicheski A, Johnson GS et al. Golden Retriever dogs with neuronal ceroid lipofuscinosis have a two-base-pair deletion and frameshift in CLN5. *Mol Genet Metab*. 2015; 115(2–3):101–109.
87. Sauer-Delhées S, Steffen F, Reichler I, Beckmann K. Clinical characteristics of idiopathic epilepsy in Greater Swiss Mountain dogs in Switzerland. *Schweiz Arch Tierheilkd*. 2020; 162(11):697–706.
88. Casal ML, Munuve RM, Janis MA et al. Epilepsy in Irish Wolfhounds. *J Vet Intern Med*. 2006; 20(1):131–135.

89. Gill JL, Capper D, Vanbellinghen J-F et al. Startle disease in Irish wolfhounds associated with a microdeletion in the glycine transporter GlyT2 gene. *Neurobiol Dis*. 2011; 43(1):184–189.

90. Zandvliet MMJM, Rothuizen J. Transient hyperammonemia due to urea cycle enzyme deficiency in Irish wolfhounds. *J Vet Intern Med*. 2007; 21(2):215–218.

91. De Risio L, Newton R, Freeman J, Shea A. Idiopathic epilepsy in the Italian Spinone in the United Kingdom: prevalence, clinical characteristics, and predictors of survival and seizure remission. *J Vet Intern Med*. 2015; 29:917–924.

92. Wallace M. Keeshonds: a genetic study of epilepsy and EEG readings. *J Small Anim Pr*. 1975; 16:1–10.

93. Hall SJG, Wallace ME. Canine epilepsy: A genetic counselling programme for keeshonds. *Vet Rec*. 1996; 138(15):358–360.

94. Berendt M, Gredal H, Pedersen LG et al. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. *J Vet Intern Med*. 2002; 16(3): 262–268.

95. Jaggy A, Faissler D, Gaillard C et al. Genetic aspects of idiopathic epilepsy in Labrador retrievers. *J Small Anim Pract.* 1998; 39(6):275–280.

96. Heynold Y, Faissler D, Steffen F, Jaggy A. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 Labrador Retrievers: a long-term study. *J Small Anim Pr*. 1997; 38:7–14.

97. Van Meervenne S, Volk HA, Verhoeven PS et al. Associations between neutering and idiopathic epilepsy in Labrador retrievers and Border collies under primary veterinary care in the UK. *Vet J*. 2019; 252: 105354.

98. Koskinen LLE, Seppälä EH, Weissl J et al. ADAM23 is a common risk gene for canine idiopathic epilepsy. *BMC Genet*. 2017; 18(1):4–8.

99. Lowrie M, Garosi L. Natural history of canine paroxysmal movement disorders in Labrador retrievers and Jack Russell terriers. *Vet J*. 2016; 213:33–37.

100. Jokinen TS, Metsähonkala L, Bergamasco L et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. *J Vet Intern Med*. 2007; 21(3):464–471.

101. Jokinen TS, Tiira K, Metsähonkala L et al. Behavioral abnormalities in Lagotto Romagnolo dogs with a history of benign familial juvenile epilepsy: A long-term follow-up study. *J Vet Intern Med*. 2015; 29(4):1081–1087.

102. Jokinen T, Haaparanta-Solin M, Viitma R et al. FDG-PET in healthy and epileptic Lagotto Romagnolo dogs and changes in brain glucose uptake with age. *Vet Radiol Ultrasound*. 2014; 55(3):331–341.

103. Seppälä E, Jokinen TS, Fukata M et al. LGI2 truncation causes a remitting focal epilepsy in dogs. *PLoS Genet*. 2011; 7(7):e1002194.

104. Gulløv CH, Toft N, Baadsager MMN, Berendt M. Epilepsy in the Petit Basset Griffon Vendeen: prevalence, semiology, and clinical phenotype. *J Vet Intern Med*. 2011; 25(6):1372–1378.

105. Licht BG, Lin S, Luo Y et al. Clinical characteristics and mode of inheritance of familial focal seizures in Standard Poodles. *J Am Vet Med Assoc*. 2007 Nov; 231(10):1520–1528.

106. Chen X, Johnson GS, Schnabel RD et al. A neonatal encephalopathy with seizures in standard poodle dogs with a missense mutation in the canine ortholog of ATF2. *Neurogenetics*. 2008 Feb; 9(1):41–49.

107. Moffat JJ, Ka M, Jung E-M, Kim W-Y. Genes and brain malformations associated with abnormal neuron positioning. *Mol Brain*. 2015; 8(1):72.
108. Heske L, Körberg IB, Nødtvedt A, Jäderlund KH. Clinical characteristics of epilepsy of unknown origin in the Rottweiler breed. *Acta Vet Scand*. 2015; 57(1):75.
109. Morita T, Shimada A, Takeuchi T et al. Cliniconeuropathologic findings of familial frontal lobe epilepsy in Shetland sheepdogs. *Can J Vet Res*. 2002; 66(1):35–41.
110. Morita T, Takahashi M, Takeuchi T et al. Changes in extracellular neurotransmitters in the cerebrum of familial idiopathic epileptic shetland sheepdogs using an intracerebral microdialysis technique and immunohistochemical study for glutamate metabolism. *J Vet Med Sci*. 2005; 67(11):1119–1126.
111. Hasegawa D, Fujita M, Nakamura S, et al. Electrocorticographic and histological findings in a Shetland sheepdog with intractable epilepsy. *J Vet Med Sci*. 2002; 64(3):277–279.
112. Yamasaki H, Furuoka H, Takechi M, Itakura C. Neuronal Loss and Gliosis in Limbic System in an Epileptic Dog. *Vet Pathol*. 1991; 28(6):540–542.
113. Nessler J, Hug P, Mandigers PJJ et al. Mitochondrial PCK2 missense variant in Shetland Sheepdogs with paroxysmal exercise-induced dyskinesia (PED). *Genes (Basel)*. 2020; 11:774.
114. Patterson EE, Mickelson JR, Da Y et al. Clinical characteristics and inheritance of idiopathic epilepsy in Vizslas. *J Vet Intern Med*. 2003; 17(3):319–325.
115. Nielen A, Knol B, van Hagen M, van der Gaag I. Genetic and epidemiological investigation of a birth cohort of Boxers. *Tijdschr Diergeneeskd*. 2003; 1128(19):586–590.
116. Van Hagen MAE, Janss LLG, van den Broek J, Knol BW. The use of a genetic-counselling program by Dutch breeders for four hereditary health problems in boxer dogs. *Prev Vet Med*. 2004; 63(1–2):39–50.
117. Chan T, Leschnik M, Pakozdy A. Aetiology and outcome in French Bulldogs with epileptic seizures. A retrospective study. *Wien Tierarztl Monatsschr*. 2019; 106(11–12):233–239.
118. Kennerly EM, Idaghdour Y, Olby NJ et al. Pharmacogenetic association study of 30 genes with phenobarbital drug response in epileptic dogs. *Pharmacogenet Genomics*. 2009; 19(12):911–922.
119. Hamamoto Y, Hasegawa D, Mizoguchi S et al. Retrospective epidemiological study of canine epilepsy in Japan using the International Veterinary Epilepsy Task Force classification 2015 (2003–2013): etiological distribution, risk factors, survival time, and lifespan. *BMC Vet Res*. 2016; 12(1):248.
120. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. *Epilepsy Behav*. 2011; 21(2): 160–167.
121. Watson F, Packer RMA, Rusbridge C, Volk HA. Behavioural changes in dogs with idiopathic epilepsy. *Vet Rec*. 2020; 186(3):93.
122. Levitin H, Hague DW, Ballantyne KC, Selmic LE. Behavioral changes in dogs with idiopathic epilepsy compared to other medical populations. *Front Vet Sci*. 2019; 6:396.
123. Packer RMA, McGreevy PD, Salvin HE et al. Cognitive dysfunction in naturally occurring canine idiopathic epilepsy. *PLoS One*. 2018; 13(2):1–20.
124. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: Current concepts and future perspectives. *Lancet Neurol*. 2016; 15(1):106–115.
125. Hesdorffer DC, Ishihara L, Mynepalli L et al. Epilepsy, suicidality, and psychiatric disorders: A bidirectional association. *Ann Neurol*. 2012; 72(2):184–191.

126. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand*. 2004; 110(4):207–220.
127. Hsu YN, Serpell J. Development and validation of a questionnaire for measuring behavior and temperament traits in pet dogs. *J Am Vet Med Assoc*. 2003; 223:1293–1300.
128. Segurson S, Serpell J, Hart B. Evaluation of a behavioral assessment questionnaire for use in the characterization of behavioral problems of dogs relinquished to animal shelters. *J Am Vet Med Assoc*. 2005; 227:1755–1761.
129. Salvin HE, McGreevy PD, Sachdev PS, Valenzuela MJ. The canine cognitive dysfunction rating scale (CCDR): A data-driven and ecologically relevant assessment tool. *Vet J*. 2011; 188(3):331–336.
130. Seisdedos Benzal A, Galán Rodríguez A. Recent developments in canine cognitive dysfunction syndrome. *Pet Behav Sci*. 2016; (1):47.
131. Winter J, Packer RMA, Volk HA. Preliminary assessment of cognitive impairments in canine idiopathic epilepsy. *Vet Rec*. 2018; 182(22):633.
132. Hobbs SL, Law TH, Volk HA et al. Impact of canine epilepsy on judgement and attention biases. *Sci Rep*. 2020; 10(1):17719.
133. Watson F, Rusbridge C, Packer RMA et al. A review of treatment options for behavioural manifestations of clinical anxiety as a comorbidity in dogs with idiopathic epilepsy. *Vet J*. 2018; 238:1–9.
134. Packer RMA, De Risio L, Volk HA. Investigating the potential of the anti-epileptic drug imepitoin as a treatment for co-morbid anxiety in dogs with idiopathic epilepsy. *BMC Vet Res*. 2017; 13(1):90.
135. Finnegan SL, Volk HA, Asher L et al. Investigating the potential for seizure prediction in dogs with idiopathic epilepsy: owner-reported prodromal changes and seizure triggers. *Vet Rec*. 2020; 5:285–299.
136. Berendt M, Gredal H, Alving J. Characteristics and phenomenology of epileptic partial seizures in dogs: Similarities with human seizure semiology. *Epilepsy Res*. 2004; 61(1–3):167–173.
137. Forsgård JA, Metsähonkala L, Kiviranta AM et al. Seizure-precipitating factors in dogs with idiopathic epilepsy. *J Vet Intern Med*. 2019; 33:701–707.
138. Poma R, Ochi A, Cortez MA. Absence seizures with myoclonic features in a juvenile Chihuahua dog. *Epileptic Disord*. 2010; 12(2):138–141. doi: 10.1111/jvim.14892.
139. Packer RMA, Law TH, Davies E et al. Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy. *Epilepsy Behav*. 2016; 55:62–68.
140. Law TH, Davies ESS, Pan Y et al. A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. *Br J Nutr*. 2015; 114(9):1438–1447.
141. Packer RMA, Mcgreevy PD, Pergande A, Volk HA. Negative effects of epilepsy and antiepileptic drugs on the trainability of dogs with naturally occurring idiopathic epilepsy. *Appl Anim Behav Sci*. 2018; 200:106–113.
142. Potschka H, Fischer A, Löscher W et al. International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. *BMC Vet Res*. 2015 Aug 28; 11:177.
143. Erath JR, Nessler JN, Riese F et al. Behavioral changes under levetiracetam treatment in dogs. *Front Vet Sci*. 2020; 7:169.
144. Berk BA, Law TH, Packer RMA et al. A multicenter randomized controlled trial of medium-chain triglyceride dietary supplementation on epilepsy in dogs. *J Vet Intern Med*. 2020;

34(3):1248–1259.

145. Pan Y, Larson B, Araujo JA et al. Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs. *Br J Nutr*. 2010; 103(12):1746–1754.
146. Koch T, Mueller RS, Dobenecker B, Fischer A. Cutaneous adverse drug reactions in dogs treated with antiepileptic drugs. *Front Vet Sci*. 2016; 3(APR):1–10.
147. Baird-Heinz HE, Van Schoick AL, Pelsor FR et al. A systematic review of the safety of potassium bromide in dogs. *J Am Vet Med Assoc*. 2012; 240(6):705–715.
148. Herrmann I, Kradischnig C, Skor O et al. Higher prevalence of seizure activity in a small population of atopic dogs: a retrospective breed- and age-matched study. *Vet Dermatol*. 2021; 32(2):126-e27.
149. Monteiro R, Adams V, Keys D, Platt SR. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. *J Small Anim Pract*. 2012; 53(9):526–530.
150. Saito M, Muñana KR, Sharp NJH, Olby NJ. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects on outcome and survival time: 32 cases (1990-1996). *J Am Vet Med Assoc*. 2001; 219:618–623.
151. Fredso N, Koch BC, Toft N, Berendt M. Risk factors for survival in a university hospital population of dogs with epilepsy. *J Vet Intern Med*. 2014; 28(6):1782–1728.
152. Fredsø N, Toft N, Sabers A, Berendt M. A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs. *BMC Vet Res*. 2016; 13.
153. Van Meervenne SAE, Volk HA, Van Ham LML. Association between estrus and onset of seizures in dogs with idiopathic epilepsy. *J Vet Intern Med*. 2015; 29(1):251–253.
154. Van Meervenne S a E, Volk H a, Matiasek K, Van Ham LML. The influence of sex hormones on seizures in dogs and humans. *Vet J*. 2014; 2014:15–20.

VIDEO CREDITS

Video 2.5
With permission from: Wielaender F, Sarviaho R, James F et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci U S A*. 2017; 114(10):2669–2674. doi: 10.1073/pnas.1614478114. Movie S1. Myoclonic twitches. Myoclonic jerks occurred predominantly during rest with a variable intensity.

Video 2.6
With permission from: Wielaender F, Sarviaho R, James F et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci U S A*.

2017; 114(10):2669–2674. doi: 10.1073/pnas.1614478114. Movie S3. Photosensitivity. In this dog myoclonic twitches were provoked by light flashes.

Video 2.7
With permission from: WIELAENDER F, SARVIAHO R, JAMES F et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci U S A*. 2017; 114(10):2669–2674. doi: 10.1073/pnas.1614478114. Movie S4. Video EEG. Simultaneous video-EEG shows photoconvulsions in association with some muscle artifact during photic stimulation. Blue markers highlight start and stop of intermittent photic stimulation.

Video 2.8.
With permission from: WIELAENDER F, JAMES FMK, CORTEZ MA et al. Absence seizures as a feature of juvenile myoclonic epilepsy in Rhodesian Ridgeback dogs. *J Vet Intern Med*. 2018; 32(1):428–432. doi: 10.1111/jvim.14892. Video S1. Absence seizure with generalized 4 Hz SWC at 14:12:34 hours. The RR is nonresponsive to stimuli, slightly swaying and holds the neck in a flexed position. Referential montage (G2 = Ref). Low pass filter: 70 Hz; high pass filter: 0.53 Hz; gain: 150 μV/cm.

Video 2.14.
With permission from: WIELAENDER F, SARVIAHO R, JAMES F et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci U S A*. 2017; 114(10):2669–2674. doi: 10.1073/pnas.1614478114. Movie S2. Head nodding. Some dogs showed head nodding in a vertical manner. These movements could occur as an isolated sign or progress to more severe myoclonic twitches.

Quality of Life Issues in Canine Epilepsy

03

Rowena MA Packer

Canine caregivers and veterinary professionals alike wish for companion (pet) dogs to have long, happy and healthy lives, free of diseases that shorten their lifespan and affect their well-being. Epilepsy is the most common chronic brain disease in dogs, affecting around 0.6–0.75% of all dogs,[1,2] and threatens both the lifespan and well-being of affected dogs. Dogs with idiopathic epilepsy (IE) are often diagnosed at a young age (between 6 months and 6 years) and the disorder is often lifelong, with remission rarely achieved.[3,4] This chapter will explore the impact of epilepsy on what can be considered the heart of this issue: the quality of life (QoL) of affected dogs and their caregivers. The chapter will primarily focus on QoL in IE rather than in structural epilepsies, as this is the epilepsy type on which the greatest number of QoL studies have been conducted to date. However, in addition to the seizures themselves the underlying disease process is likely to affect QoL in individuals with structural epilepsy and the QoL of these patients is starting to be studied.[5]

The QoL of companion dogs is an area of growing importance in veterinary medicine, with improvements in veterinary care and nutrition resulting in dogs living longer[6] and increasingly being considered family members[7]. From a "one health" perspective, this has also led to an increased awareness of the negative consequences of owning a chronically ill animal upon their human caregivers.[8] As such, understanding the impact of chronic disease diagnoses upon the QoL not only of affected dogs but also of their caregivers is increasingly vital. This chapter will consider some of the challenges the veterinary team face when aiming to maximize the QoL of the dog–caregiver dyad in the context of epilepsy and, taking inspiration

from human epilepsy management (particularly pediatric neurology), it will include recommendations on how communication, education and resources can be used and improved towards this aim.

WHAT IS QUALITY OF LIFE?

Before exploring QoL in the context of canine epilepsy, it is first important to explore what we mean by QoL for both affected dogs and their caregivers. Quality of life is a term commonly used in veterinary conversations (for example, when describing treatment benefits or during euthanasia discussions), but it is a complex concept that is often poorly defined in veterinary medicine.[9] Although discussing the various definitions of QoL is outside of the scope of this chapter, some of the key concepts and challenges when considering canine QoL will be briefly outlined to frame later discussions. In humans, the World Health Organization has defined QoL as "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[10] This multidimensional concept clearly has some aspects (e.g., cultural values) that go beyond the experiential capacities of dogs. Therefore, the definition of QoL from Belshaw and Yeates,[11] which states that QoL "broadly represents the aspects of an animal's life that make that life better or worse for that specific animal", will be adopted in this chapter when referring to canine QoL. Although this chapter will mainly focus on "health-related QoL" (HRQoL), wider impacts of epilepsy on QoL will be considered if relevant information is available.

The human and animal definitions of QoL mentioned previously both point towards the notion that QoL is a highly personal perception, which is a core reason why QoL is such a challenging concept to measure.[12] For example, if you personally reflect on what would constitute a "good" QoL for you, your answer will likely be different from that of other readers of this book and other people you know, even within your own family. Indeed, what "good" QoL means differs across cultures,[13] for people of different ages,[14] and even at different time points within one individual's lifetime.[15] Although dogs may not construct a conscious concept of QoL, if we extend

this exercise to dogs, it is likely that a given individual dog will value certain areas of their life more than other dogs do, with these preferences potentially based on factors including their life experiences, age and health; however, data on these influences are lacking at present. Although companion animal QoL assessment tools are being published in increasing numbers,[9] individual variation is rarely included in these studies. However, some initial studies have made efforts to acknowledge individual differences in their assessment tools, and have asked human caregivers to rate the importance their dog places upon elements such as companionship, exploration, activity, eating, sleeping and playing, before considering the impact of disease upon these areas.[16] Although imperfect, not least because these ratings are derived from caregivers as proxies (who may be biased), this approach acknowledges individual differences in the impact of a specific disease upon a potentially diverse population. Such an approach has yet to be taken with studies of QoL in canine epilepsy; it is worth being mindful when reading this chapter that the impacts of epilepsy on QoL described here are likely to vary between individual dogs (and indeed their caregivers).

IMPACT OF EPILEPSY ON CANINE QUALITY OF LIFE

Epilepsy is a complex brain disease with a broad range of impacts upon canine and caregiver QoL; this chapter will therefore break epilepsy down into individual elements to consider their impacts separately (Fig. 3.1). Where data from veterinary medicine is not available, inferences from data from human epilepsy patients will be considered when relevant.

Epileptic seizures

As the signature clinical sign of epilepsy[17] and the predominant target of epilepsy treatment,[18] the impact of recurrent epileptic seizure activity on the QoL of dogs has been an area of growing interest in veterinary neurology. The impact of recurrent epileptic seizures is particularly important given that more than two-thirds of dogs with IE will, despite treatment, continue

to experience epileptic seizures in the long term,[19–23] and 20–30% will remain poorly controlled (<50% reduction of seizure frequency) despite adequate treatment with antiseizure drugs (ASDs)[24–26]. Epileptic seizure type, duration and severity can be highly variable between individuals (and indeed, within some individuals). In a study of caregiver-perceived QoL in dogs with IE, seizure frequency (i.e., how often epileptic seizures occurred over a unit of time), but not seizure severity (i.e., how intense or long a seizure is) was significantly associated with caregiver perception of their dog's QoL.[27] This is somewhat surprising given that seizure severity in people with epilepsy (as quantified using the Liverpool Seizure Severity Scale[28]) has been independently associated with QoL;[29,30] however, objective measures of epileptic seizure severity have not yet been devised for canine epilepsy. In a US study conducted in 2017, an inverse association was identified between caregiver-reported canine QoL score and both monthly seizure frequency and the presence of cluster seizures, thus corroborating the importance of high epileptic seizure frequency on canine QoL.[31]

So, what is it about epileptic seizures, and particularly there being more of them, that leads caregivers to think they negatively impact their dog's QoL (i.e., per our earlier definition, why do they have the capacity to make life worse for that specific animal)? To answer this question, we must consider how the dog and its caregiver may feel during the three phases associated with an epileptic seizure as well as the interictal period (i.e., between seizures). Each of these four phases has the potential to negatively impact a dog's emotional state (or "feelings") in different ways and to different extents (indeed, some dogs may not experience some states such as the prodrome at all). Each phase will now be considered separately for aspects that are relevant to QoL (see Chapter 1 for details on the clinical features of the three phases associated with an epileptic seizure).

Preictal phase (prodrome)

The preictal (prodrome) phase is commonly characterized by alterations in emotional state. In a recent review of eight studies, 21.9% of human patients reported they experienced a preictal phase (prodrome), with the most frequent symptoms being emotional and cognitive disturbances including confusion (9.0%), anxiety (8.6%), and irritability (7.7%), with the duration of signs typically between 10 minutes and 3 days before an

epileptic seizure.[32] In the first study of its kind in dogs, nearly two-thirds of caregivers reported that they recognized prodromal changes in their dog, including signs such as restlessness (29.2%), clinginess (25.0%) and fearful behavior (12.0%).[33] The behavioral signs of the prodromal phase are in line with this being a negative emotional experience. In people with epilepsy, fear and anxiety may be heightened during the prodromal phase, which is associated with an increase in brain neuronal activity and preictal spikes on the electroencephalogram (EEG).[34] This increase in preseizure spikes has been demonstrated in canine patients with intracranial EEG,[35] but whether concurrent behavioral and emotional changes occur with these spikes has yet to be objectively explored.

- Educate caregivers that some of their dog's "naughty" behavior may be a result of their reduced ability to learn and remember, and that punishing them should be avoided, particularly with harsh methods.
- Consider adding medium-chain triglycerides (MCTs) to the dog's diet to improve cognitive abilities (and potentially seizure control).
- Encourage caregivers to engage in fun training games with their dog.

- Ensure caregivers understand ongoing seizure activity is likely and encourage them to focus on effective seizure management.
- This includes creating a calm and safe environment when prodromes or seizures occur, being confident in administering emergency medications (where applicable) and knowing when to seek veterinary help.

Interictal cognitive comorbidities: Memory and learning impairments, reduced trainability

Preictal (prodrome) phase: Emotional changes, fear and distress

Seizure (ictal) phase: Fear during seizures where consciousness is maintained, physical injuries

Interictal behavioral comorbidities: Fear and anxiety, aggression, light/shadow chasing, ADHD-like behavior

Quality of Life

Postictal phase: Disorientation, blindness, lethargy, distress, muscle pain

Behavioral effects of ASDs: Abnormal reactivity, apathy, hyperattachment, anxiety, dementia-like behavior

Secondary consequences of ASDs: Obesity due to polyphagia and lethargy, lifestyle limitations

ASD adverse effects (physical): Lethargy, ataxia, thirst, hunger

- Consider behavioral history before selecting an ASD for seizure control.
- Encourage caregivers to closely monitor their dog's behavior after their initial diagnosis, and after additions or changes in ASDs.
- If necessary, refer dogs to an accredited veterinary behaviorist to devise a behavioral treatment plan that may include pharmacotherapy and/or behavioral therapy.

- Encourage caregivers to closely monitor any adverse effects that arise following additions or changes to their dog's ASD regimen.
- Balance the positive effects of seizure control on QoL against the harms of ASD adverse effects.
- Counsel caregivers on an appropriate diet for their dog (type and quantity) and weigh dogs at each ASD check to avoid obesity.

FIGURE 3.1. Influences upon the quality of life (QoL) of dogs diagnosed with idiopathic epilepsy, grouped into four areas: seizure-related impacts, antiseizure drug (ASD) adverse effects, behavioral comorbidities and cognitive comorbidities. Suggestions are made for activities practicing veterinarians can do to minimize each of these areas of impact.

In people with epilepsy, prodromal changes may be used as a predictor of upcoming seizure activity,[36] and indeed some caregivers of dogs with epilepsy use these changes to predict epileptic seizures in their dog[33]. Whether dogs can learn to predict the onset of a seizure, and experience negative anticipation during this phase is not known; however, retrograde amnesia may occur after a generalized seizure due to loss of consciousness impairing normal brain processes, disrupting the encoding and storage of information.[37] This would in turn protect dogs from "seizure worry",[38] with epileptic seizures instead occurring "out of the blue". If caregivers recognize prodromal signs in their dog, they should be reassured that providing comfort to their dog if they appear fearful or distressed (e.g., physical affection if it is safe to do so) cannot reinforce this involuntary behavioral response in their dog. During this phase, a caregiver's focus should be upon creating, if possible, a calm and safe environment for their dog while preparing or administering emergency ASDs based on the instructions of their veterinarian (see chapters 1 and 19).

Ictal phase

When considering the impact of epileptic seizures upon a dog's QoL, a key component of this impact will depend on the dog's awareness of the event, and thus whether the epileptic seizure has the capacity to influence their emotional state. Although generalized tonic-clonic epileptic seizures may have the most dramatic visual presentation (see Chapter 1, Video 1.1), dogs frequently lose consciousness during seizures of this type. As such, although potentially very distressing for caregivers to witness, the impact of the ictal stage of generalized tonic-clonic epileptic seizures upon the affected dog's emotional state (i.e., their feelings) is likely to be protected by this lack of consciousness and total amnesia of the event, as reported in people.[39]

In contrast to generalized tonic-clonic epileptic seizures, during focal epileptic seizures, consciousness can be maintained (albeit sometimes in a reduced capacity).[17] For focal epileptic seizures during which some degree of consciousness is maintained, negative impacts on the animal's emotional

state and longer-term QoL are likely. Indeed, in people with epilepsy, rates of emotional disorders are higher in focal epilepsies than in generalized epilepsy.[40] In dogs, focal epileptic seizures with a sensory or "psychic" component often manifest as behavioral changes, including anxious behaviors, restlessness, pacing, and seeking out their caregiver.[41] In humans, this epileptic seizure type has been described as being dominated by unpleasant or frightening sensations, including unexplained feelings of fear and apprehension.[42,43] In humans, ictal fear has been associated with the involvement of the mesial temporal lobe, particularly the amygdala.[44] Breed-specific focal epilepsies involving ictal fear have recently been identified in dogs, including a familial juvenile onset epilepsy in Boerboel dogs, with fear behavior as the main ictal feature.[45] In this population, ictal behaviors included fearful facial expressions, crying vocalizations, generalized trembling, hiding, cowering and freezing. All dogs also showed autonomic or motor signs during the ictus.[45] In addition, a study of English Bull Terriers with paroxysmal behavioral abnormalities and EEG abnormalities documented extreme unexplained fear responses in these dogs.[46] In cases such as these where fear is a core ictal feature, consciousness is suspected to be maintained, and epileptic seizures are recurrent, it is highly likely that QoL will be negatively affected. Although less likely to have a direct emotional effect, focal motor seizures involving localized motor phenomena during which dogs are presumed to be conscious (e.g., rhythmic twitching of an extremity) may cause confusion and distress; however, close behavioral analysis during and after this type of epileptic seizure has not been performed to support this as yet.

As recently highlighted, one of the most common caregiver concerns is whether or not epileptic seizures are painful for their dog.[47] Drawing on evidence from human neurology, it appears unlikely that epileptic seizures are painful, with <3% of patients reporting painful seizures in two large studies.[48,49] Most painful epileptic seizures are associated with seizure activity in the primary somatosensory cortex in the parietal lobe,[50] and in such cases, direct involvement of this sensory area of the brain is suspected to lead to pain, rather than conscious awareness of painful involuntary motor movements during the epileptic seizure.[48] Pain from headaches has also been associated with epileptic seizures as a preictal, ictal or postictal phenomenon in people, but is often neglected due to the dramatic

neurological manifestations of the epileptic seizure.[51] In addition, headache is poorly defined in dogs at present.[52]

In summary, the impact of the ictal phase on canine QoL is likely to differ based on seizure type, and although the dramatic visual manifestation of generalized epileptic seizures may be extremely stressful for caregivers to witness, those seizure types in which consciousness is maintained and negative emotional states are evoked are most likely to impact QoL of affected dogs.

Postictal phase

The postictal phase comprises a variety of sensory, cognitive and motor deficits including unresponsiveness and memory impairments.[53] The relevance of this phase was recently highlighted in human neurology, owing to its value as a differential diagnostic feature, but also because of its personal impact, given that postictal signs often exceed the seizure in duration.[54] The extent and intensity of the postictal phase affects patients' QoL substantially and correlates strongly with their rating of seizure severity.[55] The postictal phase may last from minutes to hours as the brain regains normal function. In people with epilepsy, this phase has been studied in detail, with a recent systematic review of 45 studies identifying its three most common characteristics as postictal headaches (33%), migraines (16%), and psychosis (4%).[56] To date, no published data on the prevalence of postictal changes in dogs has been published. Behavioral changes such as aggression and hyperexcitability, as well as fearful behaviors such as hiding and seeking their caregiver's attention have been reported, which may indicate a state of distress.[57] As in humans,[58] some dogs appear to be blind during this phase, something which, although transient, has the potential to cause confusion and distress. In humans, muscles may be sore after a generalized epileptic seizure due to the accumulation of lactic acid during the seizure;[59] however, signs of postictal musculoskeletal pain in dogs have not been studied. Given the duration of and distress associated with the postictal phase, greater emphasis should be placed on this phase in epilepsy management to avoid it becoming a neglected entity, as previously highlighted in human neurology.[60] As recommended for the preictal phase, caregivers should be encouraged to create a calm and safe environment for their dog during the postictal phase

if possible, while also focusing on their own safety given the potential for injuries related to postictal transient aggression.

Interictal phase

Although focus has historically been placed upon seizure events themselves, epileptic seizures commonly only last seconds to minutes, and as such, most of the lives of dogs with epilepsy happens in the interictal phase. The impact of epileptic seizure management, particularly ASD therapy, is likely to affect QoL during this phase, as well as recently recognized comorbidities of epilepsy occurring during this phase. As such, if we are to fully consider the effects of epilepsy upon the QoL of affected dogs, we must also take the approach of "epilepsy beyond seizures".[57]

Antiseizure drug adverse effects

The aim of ASD treatment in epileptic patients is to maximize seizure control while minimizing the occurrence of adverse effects (AEs). In recent studies, over 80% of dogs administered ASDs experienced AEs including thirst, ataxia, lethargy and increased appetite, associated with commonly administered ASDs including phenobarbital, bromide, zonisamide and levetiracetam (LEV).[31] In many cases, AEs are present at their greatest intensity in the first 2–4 weeks of treatment, and subside after this period once the serum ASD concentration reaches a steady state.[61–63] However, in other dogs, AEs are permanent while the dog is treated.[64] These enduring AEs have the greatest likelihood of impacting QoL given they may be present for much of the interictal period (and thus the dog's life while on treatment). Therefore, it is important to modulate ASD treatment to minimize AEs (see Chapter 9 and ASD-specific chapters).

In people with epilepsy, increases in the AEs of ASDs are negatively associated with self-reported QoL, more so than epileptic seizure frequency.[65] In dogs with epilepsy, caregiver-reported QoL scores were significantly lower in dogs experiencing AEs,[31] and when broken down into specific AEs in a separate study of dogs with IE, lethargy and ataxia were particularly associated with lower caregiver-perceived QoL scores[27]. When thinking in terms of our definition of QoL (considering aspects of an animal's life that can make that life better or worse for a specific animal) lethargy and ataxia have the potential to inhibit a dog's ability to perform moderate-high energy activities that could make their life better, depending

on their individual preferences, for example, playing, exercising, or interacting with both their owners and conspecifics (other dogs).

In addition to the direct AEs of ASDs (e.g., those where suppressed brain excitability leads to seizure suppression but also general activity suppression), secondary consequences may also be experienced that reduce QoL. Dogs affected by polyphagia and sedation as AEs of ASDs may be predisposed to obesity as a result of increased calorie intake combined with reduced activity. Obesity can in turn impede a dog's ability to behave normally and predispose them to obesity-related diseases.[66] Obesity has also been found to have a significant negative impact upon the QoL of dogs with other neurological disorders.[67] To avoid chronic weight gain in their epileptic dog, caregivers should:

- Be made aware of polyphagia as a potential common ASD AE and the negative impact of obesity on their pet's QoL.
- Receive clear and recurrent advice on the ideal diet (type and daily quantity) for their dog, including the importance of avoiding scavenging.
- Be encouraged to attend periodic veterinary checkups for regular weighing as part of ASD treatment monitoring (see Table 9.3 in Chapter 9).

In addition to this suite of well-recognized physical AEs, an increasing number of behavioral AEs are being recognized that may be associated with reduced QoL. In a study of behavioral changes in dogs with epilepsy, those treated with ASDs experienced a greater number of changes compared to drug-naïve dogs, and several of these changes were unique to this group including increases in abnormal reactivity (i.e., anxiety with unpredicted movements or with sudden or loud noises), attachment disorder (i.e., signs of separation anxiety), demented behavior (i.e., dementia-like changes including reduced ability to recognize familiar people), and apathetic behavior (i.e., reduced interest in activities).[68] As dogs in this study were treated with a variety of ASDs both as monotherapy and polytherapy, further studies of individual effects are needed to better appreciate their potential to impact QoL. In a recent single-ASD study including 84 dogs (58 with IE, 24 with structural epilepsy and 2 with reactive seizures), the effects of LEV upon behavior were considered.[69] In dogs with preexisting behavioral abnormalities prior to LEV treatment, 4/44 developed new

negative changes in behavior including anxiety and depression-like behavior, and 14/44 experienced worsening of their preexisting behavioral abnormalities following LEV treatment. In dogs without preexisting behavioral abnormalities prior to LEV treatment, 10/40 reported negative behavioral changes for the first time following treatment, most commonly anxiety and depression-like behavior.[69] Given that these changes were not reversible following cessation of treatment in all dogs, careful ASD selection in light of a dog's behavioral history is vital to maintain QoL.

This scenario of conflicting risks versus rewards of treatment leaves veterinarians and caregivers in a conundrum, where the QoL of dogs with epilepsy can be negatively affected by the clinical signs of their chronic disease (i.e., epileptic seizures), but also by the attempts to reduce them. Despite some caregivers being extremely motivated to stop their dog's epileptic seizures, epileptic seizure freedom cannot be pursued at all costs when QoL is to be maintained. Indeed, acceptable AEs of ASDs have been considered one of the three greatest concerns for caregivers of dogs with IE when assessing seizure management, alongside acceptable seizure frequency (considered as one seizure every 3–6 months).[70] In order to achieve a favorable outcome that acknowledges QoL as an important factor in treatment decision-making, the dose of the drug or drugs of choice must be carefully adjusted to reach the optimal therapeutic effect whilst minimizing possible AEs.[71,72]

As previously alluded to, some dogs with epilepsy are treated with several ASDs in combination ("polytherapy"); however, this practice may add significant risks to the cost–benefit equation of ASD use and its impact on QoL. It has previously been demonstrated that adding in sequential ASDs in an attempt to control seizures is a "law of diminishing returns", with the probability of seizure control diminishing progressively with successive ASD treatments.[23] Indeed, only one-third of dogs (37.5%) that received a third-line ASD after treatment failure with two ASDs achieved a >50% reduction in seizure frequency following the addition of the third drug.[23] This potential benefit should be considered in light of data indicating that AEs are more commonly reported in patients treated with ASD polytherapy,[31,73,74] with dogs receiving third-line ASDs reported by their caregivers to have a significantly lower QoL than those treated with one or two ASDs[27].

Behavioral and cognitive comorbidities of epilepsy

Behavioral AEs of ASDs are now recognized in dogs with epilepsy; however, above and beyond ASDs, there is mounting evidence that IE is not simply a seizure disorder, with behavioral changes reflecting the impact of epilepsy as a more global brain disease. In people with epilepsy, the prevalence of psychiatric disorders is higher than in either the general population or patients with other chronic medical diseases, including disorders such as anxiety and depression.[75–78] Behavioral comorbidities may be a cause of epilepsy, a consequence of epilepsy, or a separate condition that is associated with epilepsy because there is a common cause for the epilepsy and the comorbidity.[79] The impact of comorbid psychiatric disorders on patient QoL may be severe, with interictal anxiety and depression found to have greater adverse effects on the QoL of people with epilepsy than seizure frequency, severity and chronicity.[80]

Comorbid anxiety is increasingly recognized in dogs with IE, with increases in behaviors indicative of fear and anxiety observed in several independent studies including drug-naïve animals and animals treated with ASDs. Comorbid anxiety has been identified in studies including pre- and postepilepsy diagnosis comparisons,[68,81] single-breed studies of behavior before the initiation of ASDs[82] and comparisons between dogs with IE and healthy controls[83]. As such, treatment that does not solely focus upon seizure control may be beneficial to the QoL of patients with epilepsy.[84] As current evidence suggests that existing ASDs may have no beneficial effect[73] or potentially negative effects upon anxiety in dogs with epilepsy,[85] and several anxiolytics are contraindicated for use in dogs with seizures or epilepsy (Table 3.1), further work is required to improve these patients' emotional health. This could include nonpharmacological methods such as clinical behavior interventions, as increasingly seen in people with epilepsy.[86]

In addition to behavioral comorbidities, cognitive comorbidities have recently been recognized in dogs with IE, particularly related to learning and memory. Impaired cognition in people with epilepsy is so prevalent that there are calls for cognitive screening of all children affected by epilepsy, and neuropsychological assessment considered a pivotal investigation in the routine care of people with epilepsy.[87] In a large-scale multibreed study, dogs with IE exhibited reduced "trainability" (a measure including attention and learning speed) compared with healthy controls, with the greatest

reductions seen in dogs treated with multiple ASDs.[88] Indeed, ASDs have a dose-dependent effect on cognitive functioning in people with epilepsy, with maximal impairments seen in patients receiving polytherapy.[89] Further, dogs with epilepsy within the same study population were found to exhibit signs of dementia-like cognitive dysfunction compared with healthy controls.[90] Areas of cognitive compromise largely reflected impaired memory, such as reduced recognition of their caregivers, and spatial memory impairment including staring blankly, getting lost in the home, and having difficulty finding food.[90] Dogs with a history of cluster seizures and high seizure frequency showed greater signs of impairment, which may reflect progressive hippocampal damage from seizure activity.[91] Impairments in spatial working memory have further been demonstrated in dogs with IE in simple food-finding practical tasks in the clinic,[92] and cognitive tasks in which dogs with IE were less likely to acquire a spatial discrimination than age- and breed-matched controls.[93]

TABLE 3.1. Behavioral drugs contraindicated or for which caution is advised in dogs with a history of seizures or treated with ASDs, and reasons for this. Local drug prescribing laws and regulations need to be considered for all medications discussed.

Drug class	Drug	Indication	Reasons for contraindication or caution advised
Tricyclic antidepressant (TCA)	Clomipramine	Separation anxiety, chronic situational fears	Clomipramine is not currently contraindicated for dogs with seizures in the UK,[1] but is contraindicated elsewhere.[2] Evidence from human epilepsy indicates that patients treated with TCAs have a significantly higher risk of seizures than with SSRIs (1.0% for clomipramine vs. 0.1% for SSRIs)[3] and thus SSRIs should be considered first for treating anxiety in epilepsy patients. Care is further warranted in dogs treated with ASDs, as serum concentrations of some ASDs (e.g., phenytoin and carbamazepine) may be increased by clomipramine.
	Amitriptyline	Separation anxiety, chronic situational fears	Contraindicated in dogs with a history of seizures.[1,2] Data from canine epilepsy patients are lacking; however, amitriptyline may lower the seizure threshold in human patients with a history of seizure disorders.
	Imipramine	Panic-related, generalized and separation anxieties, especially when associated with urine elimination	Contraindicated in dogs with a history of seizures in the UK[1]; only caution is noted for its use in animals with seizure disorders elsewhere.[2] Data from epileptic dogs are lacking; however, imipramine may lower the seizure threshold in human patients with a history of seizure disorders.
Selective serotonin reuptake inhibitor (SSRI)	Fluoxetine	Chronic situational fears	Data from canine patients are lacking. However, based on the International League Against Epilepsy (ILAE) guidelines, SSRIs should be the first choice of anxiolytic for treating anxiety in human epilepsy patients, with some evidence of potentially positive effects on seizure frequency.[3] However, fluoxetine use in people with epilepsy receiving ASD treatment is not recommended due to possible cytochrome inhibition, which alters the pharmacokinetics of some drugs, particularly phenobarbital. Fluoxetine use in dogs with a history of seizures is contraindicated in the UK[1]; only caution is advised for its use in dogs with seizure disorders elsewhere.[2] If used in epileptic dogs, close serum ASD concentration monitoring is indicated.
	Paroxetine	Generalized anxiety	Like other SSRIs, paroxetine may antagonize the effects of ASDs, and so is not recommended for use in canine epilepsy patients or in association with other agents that lower seizure threshold, e.g., phenothiazines.[1] However, only caution is advised for its use in epileptic dogs elsewhere.[2]
	Sertraline	Compulsive type behavior including acral lick	Like other SSRIs, sertraline may antagonize the effects of ASDs, and so is not recommended for use in epilepsy patients or in association with other agents that lower seizure threshold, e.g., phenothiazines.[1] However, sertraline is not considered contraindicated in epileptic dogs elsewhere.[2]

References:
1. BSAVA. *Small Animal Formulary*. Ramsey I, editor. Gloucester, UK: BSAVA; 2011.
2. Plumb DC. *Plumb's Veterinary Drug Handbook*, 9th ed. Hoboken: John Wiley & Sons; 2018.
3. Watson F, Rusbridge C, Packer RMA et al. A review of treatment options for behavioural manifestations of clinical anxiety as a comorbidity in dogs with idiopathic epilepsy. *The Veterinary Journal*. 2018; 238:1–9.

Although impaired cognition is unlikely to have the same QoL impacts on dogs as it has on people (e.g., inhibiting education, employment and independence), some impairments may cause confusion and distress, while others have the potential to negatively influence the dog–caregiver relationship. Caregivers may misinterpret their dog's inability to learn and

remember as being "naughty", with caregivers of dogs with epilepsy more likely to use aversive training techniques than caregivers of control dogs.[88] Given that these techniques have been found to induce a negative emotional state in dogs,[94] improving caregiver awareness of potential cognitive challenges their dog may face and encouraging training methods based on the principles of positive reinforcement may avoid these potential QoL compromises. Nonpharmacological therapies such as MCT (medium-chain triglyceride) oil supplementation are being developed to improve cognition as well as epileptic seizure control in this population.[95]

IMPACT OF EPILEPSY ON CAREGIVER QUALITY OF LIFE

Throughout this chapter we have considered the pervasive and potentially severe QoL impacts of epilepsy upon affected dogs; however, it would be remiss to not acknowledge the impact of canine epilepsy on humans. The lives of dogs with epilepsy and their caregivers are often tightly intertwined, with evidence demonstrating that decreases in caregiver-reported QoL of dogs with epilepsy correlated with their perception of their own QoL.[27] Caregivers of dogs with epilepsy have the challenging task of managing their dog's epilepsy chronically (e.g., medicating their dogs with ASDs several times a day at consistent times while managing AEs and comorbidities) and acutely (e.g., managing seizures and administering emergency medications when needed). Epileptic seizures, as the hallmark clinical sign of epilepsy, appear to confer the greatest risk to the emotional state and subsequent QoL of caregivers.

Epileptic seizures are physiologically stressful for caregivers to witness and manage, with caregivers experiencing significant increases in cortisol following their dog having an epileptic seizure compared to time-matched points on nonseizure days.[96] Those caregivers scoring highest for the personality factor neuroticism were found to have the highest cortisol levels throughout the study, emphasizing the importance of caregiver personality and personal factors upon their QoL. The lack of control over and unpredictability of seizures, combined with sleep deprivation and feelings of helplessness are known factors in the development of stress in people.[97,98]

In a recent qualitative study of caregivers of dogs with epilepsy, caregivers described the negative impacts of their dog's seizures upon their sleep and well-being, highlighting the unpredictable nature of seizures as a source of stress, as if they were "living with a ticking time bomb".[99] Furthermore, in a Danish study, caregivers expressed fears regarding their dogs' epilepsy that largely focused on seizure unpredictability and the risk of death associated with them, including their dog having an epileptic seizure when left alone or dying from an epileptic seizure while alone.[21] In an international study of 159 caregivers, around one-third reported that they suffered to some degree from depression or panic attacks as a result of caring for their dog.[27] From this growing body of literature, it is clear that recurring, unpredictable epileptic seizure events have the capacity to negatively impact the emotional state of caregivers and that this population of caregivers requires strong support from veterinary professionals to attempt to maintain their own QoL.

In a recent systematic review of the QoL of parents of children with epilepsy, most studies found that these parents had poorer QoL relative to parents of healthy control children, with poorer parental QoL consistently associated with child QoL.[100] Evidence of the specific impacts of canine epilepsy management on caregiver QoL is growing, with mixed findings, which may reflect the heterogeneity of epilepsy as a disease, alongside differences in caregiver lifestyles and perceptions of their dogs' care. This emphasizes how QoL is a highly individual concept. Some daily caregiving behaviors associated with epilepsy management do not appear to be considered a "burden" by most caregivers of dogs with epilepsy. An early prospective, longitudinal study in the USA of 19 dogs diagnosed with epilepsy found that caregivers considered the work necessary to maintain their dog was not a burden or detriment to their own QoL.[101] Similarly, in a UK survey of 29 caregivers of dogs with epilepsy, most caregivers did not consider administering medications or veterinary examinations for ASD monitoring a nuisance.[70] These findings were corroborated by a US study where a composite dog–caregiver QoL score was not associated with the number of ASDs being administered or the average monthly cost of the medication.[31] These findings may be explained by caregiving behaviors positively contributing to the dog–caregiver relationship; indeed, previous studies have found that high levels of caregiving are associated with high

levels of attachment to dogs. Caregiving activities may actually facilitate attachment development, which then motivates sustained caregiving.[102]

In contrast, the effects of epilepsy on caregivers' wider lives appear more pronounced, including their work life and free time. In a prospective, longitudinal study of 63 epileptic dogs in Denmark, 60% of caregivers reported that having a dog with epilepsy had a negative influence on their daily life, with the management of their dog's epilepsy imposing restrictions to social activities, vacations and activities that could not involve their dog.[21] Similarly, in a UK study, up to two-thirds of caregivers reported that caring for their dog had an impact on their work and day-to-day activities, and around 60% of caregivers reported that the responsibilities had affected their free time.[70] Caregivers struggled to spend time away from their dog due to being unable to find care for them, and being worried about leaving them in case they had a seizure.[70] This may lead to feelings of isolation, reported in around 20% of caregivers in an international study.[27] In a recent qualitative study of caregivers in England, caregivers reported a range of lifestyle changes made to manage their dog's epilepsy, with some changes as dramatic as reducing or ceasing employment to dedicate more time to their dog.[99] Despite these impacts appearing severe and, in many cases, seemingly negative, some caregivers in this study avoided directly describing their QoL as being affected by these changes. These findings can be framed in light of recommendations from pediatric neurology, where caregiving impacts experienced by parents of children with epilepsy are advised to not be inferred as positive or negative, as depending on the views of the parent and the context, many impacts could be deemed as either, or have both positive and negative outcomes.[103]

Caregiver support, communication and resources

The emotional impacts experienced by caregivers of dogs with epilepsy, combined with the chronic and potentially challenging management of affected dogs indicates a need for increased support for caregivers by veterinary professionals. Clear communication with veterinarians is a core part of this, given the complex nature of epilepsy and the potentially long-term relationship between these caregivers and veterinarians. To this end, aiming for a partnership approach to epilepsy management could be beneficial, where both parties work together to achieve effective communication and trust, a deeper appreciation of each other's expertise

and values, development of common goals, and shared accountability and responsibility.[104] In human medicine, this coproductive approach towards healthcare underpins good quality patient- and family-centered care (PFCC).[105] For people with epilepsy, the PFCC approach promotes a more holistic view of the patient that goes beyond merely addressing the individual's diagnosed condition and treatment,[106] respecting the supporting roles played by caregivers coordinating their loved one's care (e.g., accompanying them to clinic visits, providing witness reports of seizure events, and alerting medical professionals towards changes in epilepsy status or AEs of treatment that require prompt response)[107].

Given the striking similarities with the caregiver–dog relationship, working towards a strong caregiver–veterinarian relationship should be a priority in epilepsy treatment. In practical terms, identifying the veterinarian within a practice most comfortable and confident with epilepsy cases, and where possible, promoting continuity of care with this veterinarian is likely to help build foundations of trust and understanding that will enhance caregiver QoL. Indeed, in a long-term, prospective, longitudinal study of canine epilepsy, the large majority of caregivers reported that support from, regular contact with, and easy access to their veterinarian was important in reducing their anxiety associated with their dog's epilepsy.[21]

Although caregivers are likely to build their own expertise regarding their own dog's epilepsy, for example via diary-keeping (e.g., of epileptic seizures, AEs and seizure triggers) and self-directed research,[99] the provision of expert information from veterinarians from the diagnosis through to the death of their dog is core to canine and caregiver QoL. In people with epilepsy, provision of information at the onset of the disorder results in caregivers having greater levels of confidence and competence in managing the disease.[108] These early conversations need to include core "first-aid" seizure information about the nature of seizure events, what to expect during a typical seizure, when a seizure is considered an emergency and what to do in an emergency.[47] Outlining a plan for the acute management of seizures may provide caregivers with a sense of greater control and reduce feelings of helplessness if they are able to be active in the management of the epileptic seizure (even if this is as simple as timing or videoing the event while ensuring the dog is in as safe an environment as possible). Providing emergency medications where appropriate may

enhance these feelings while reducing seizure length and/or severity for some dogs.

Beyond these initial discussions, other important topics to discuss include the potential etiology of seizures, treatment options, goals of treatment, and prognosis[47] (see Box 9.1 in Chapter 9). As highlighted by Pergande et al., potential challenges that caregivers may face along with negative outcomes may not be adequately discussed by veterinarians in an attempt to avoid upsetting or overwhelming caregivers (or in some cases, due to lack of awareness of challenges caregivers may face).[99] However, avoiding the provision of data on negative outcomes in epilepsy may not necessarily benefit caregivers, with data from pediatric neurologists indicating that the vast majority of caregivers want to be informed of potential negative outcomes for children with epilepsy.[109] Therefore, there may be some benefit in veterinarians discussing more severe clinical signs or outcomes in canine IE with some caregivers, where they believe it will benefit their understanding.

Setting caregiver expectations regarding aims of epilepsy treatment at an early stage is key in avoiding caregivers believing they have "failed" if their dog continues to seizure, given the high likelihood of this occurring and there being no "cure" at present. Instead, veterinarians should encourage caregivers to be actively involved in discussions regarding ASD use (and indeed the use of adjunctive treatments such as diet and dietary supplements[110]), and to use information from their own record-keeping (including frequency, severity and duration of seizures, AEs and seizure triggers) to make decisions about their treatment plans and potential modification. This shared role in therapeutic monitoring and treatment decisions may give caregivers a greater sense of control and the capability to manage what they can about their dog's illness.[47] Encouraging caregivers to use dedicated smartphone apps to digitally record and share information with their veterinarian may aid the reliability and efficacy of these discussions.

Where caregivers feel uncertain or concerned regarding recommendations from their veterinarian, they may be more likely to use the internet to perform self-directed research.[111] Although the internet may provide sources of emotional support for those feeling isolated (e.g., in discussion forums with other caregivers of dogs with epilepsy), problems may arise due to exposure to misinformation and negative stories from

other caregivers. In the long-term, the creation of a moderated environment for caregivers to use to communicate online with peers could reduce fear and improve satisfaction, whilst maintaining the accuracy of medical information.[99] While such resources are not available, encouraging conversations with caregivers who use the internet for self-directed research regarding what they have read (including both positive and negative information) may allow honest dialogue without caregivers feeling embarrassed or secretive regarding this behavior, and avoid caregivers making changes to their dogs' management regime without the knowledge of their veterinarian.

TAKE-HOME MESSAGES

- ✔ Recurrent epileptic seizures pose risks to the emotional state and subsequent QoL of affected dogs, while witnessing and managing seizures is physiologically and emotionally stressful for their caregivers. Optimizing and individualizing ASD treatment to control seizures while minimizing AEs is key to optimizing both caregiver and canine QOL.
- ✔ Antiseizure drug AEs have the greatest likelihood of impacting the QoL of ASD-treated dogs with IE given they may be present for much of the interictal period (and thus the dog's life while on treatment). Therefore, it is important to educate caregivers on the occurrence of AEs and modulate ASD treatment over time in order to minimize AEs.
- ✔ Given the low likelihood of seizure freedom for many dogs with IE, the provision of expert information from veterinarians to set caregivers' expectations of epilepsy treatment is key to creating a treatment plan that focuses on QoL, ensuring the potential benefits of seizure control are balanced against the potential harms of AEs.
- ✔ Obesity secondary to polyphagia and inactivity due to sedation and ataxia can have a significant negative impact on QoL in epileptic dogs. Caregivers should be counselled on an ideal diet (type and daily quantity) for their dog and encouraged to attend periodic veterinary checkups for regular weighing as part of ASD treatment monitoring.

- ✔ Behavioral and cognitive comorbidities can occur in dogs with IE and can affect QoL. Caregivers should be made aware of potential behavioral and cognitive challenges their dog may face, and where necessary, referred to an accredited veterinary behaviorist to devise a behavioral treatment plan that may include appropriate drug therapy and/or behavioral therapy with an aim of improving QoL.
- ✔ The impact of epilepsy on caregiver and canine QoL is extremely variable. Promoting continuity of care by assigning one veterinarian to each epilepsy case within a veterinary practice (where possible) will help veterinarians to build strong relationships with caregivers, understand the challenges they face, and maximize the tailoring of advice to their personal circumstances.
- ✔ Greater awareness and empathy from veterinary professionals regarding the range and severity of QoL impacts that affected dogs and their caregivers may face is likely to improve caregiver–veterinarian communication and lead to better outcomes for both parties, preventing caregivers from turning to unreliable sources of advice to aid the management of their dog and feeling embarrassed or ashamed to discuss some topics with their veterinarian.

REFERENCES

1. KEARSLEY-FLEET L, NEILL DG, VOLK HA et al. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. *Vet Rec*. 2013; 172(13): 338.
2. HESKE L, NØDTVEDT A, JÄDERLUND KH et al. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. *Vet J*. 2014; 202(3):471–476.
3. ARMAŞU M, PACKER R, COOK S et al. An exploratory study using a statistical approach as a platform for clinical reasoning in canine epilepsy. *Vet J*. 2014; 202(2):292–296.
4. PACKER RMA, SHIHAB NK, TORRES BBJ, VOLK HA. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. *PLOS ONE*. 2014; 9(8):e106026.
5. WEISKE R, SROUFE M, QUIGLEY M et al. Development and evaluation of a caregiver reported quality of life assessment instrument in dogs with intracranial disease. *Front Vet Sci*. 2020; 7:537.
6. REID S, PETERSON M. Methods of estimating canine longevity. *Vet Rec*. 2000; 147(22):630–631.
7. CHARLES N. Post-Human Families? Dog-human relations in the domestic sphere. *Sociol Res Online*. 2016; 21(3):83–94.

8. Britton K, Galioto R, Tremont G et al. Caregiving for a companion animal compared to a family member: burden and positive experiences in caregivers. *Front Vet Sci*. 2018; 5:325.
9. Belshaw Z, Asher L, Harvey ND, Dean RS. Quality of life assessment in domestic dogs: An evidence-based rapid review. *Vet J*. 2015; 206(2):203–212.
10. World Health Organization (WHO). *WHOQOL-BREF: Introduction, administration, scoring and generic version of the assessment*. 1996. Available from: http://www.who.int/mental_health/media/en/76.pdf [Accessed 21st May 2021].
11. Belshaw Z, Yeates J. Assessment of quality of life and chronic pain in dogs. *Vet J*. 2018; 239:59–64.
12. Gill TM, Feinstein AR. A Critical appraisal of the quality of quality-of-life measurements. *JAMA*. 1994; 272(8):619–626.
13. Kagawa-Singer M, Padilla GV, Ashing-Giwa K. Health-related quality of life and culture. *Semin Oncol Nurs*. 2010; 26(1):59–67.
14. Farquhar M. Elderly people's definitions of quality of life. *Soc Sci Med*. 1995; 41(10):1439–1446.
15. Carr AJ, Gibson B, Robinson PG. Is quality of life determined by expectations or experience? *BMJ*. 2001; 322(7296):1240–1243.
16. Budke CM, Levine JM, Kerwin SC et al. Evaluation of a questionnaire for obtaining owner-perceived, weighted quality-of-life assessments for dogs with spinal cord injuries. *J Am Vet Med Assoc*. 2008; 233(6):925–930.
17. Berendt M, Farquhar RG, Mandigers PJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11(1):182.
18. De Risio L, Bhatti S, Muñana K et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015; 11(1):148.
19. Heynold Y, Faissler D, Steffen F, Jaggy A. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 Labrador Retrievers: A long-term study. *J Small Anim Pract*. 1997; 38(1):7–14.
20. Berendt M, Gredal H, Pedersen LG et al. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. *J Vet Intern Med*. 2002; 16(3):262–268.
21. Berendt M, Gredal H, Ersbøll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. *J Vet Intern Med*. 2007; 21(4):754–759.
22. Arrol L, Penderis J, Garosi L et al. Aetiology and long-term outcome of juvenile epilepsy in 136 dogs. *Vet Rec*. 2012; 170(13):335.
23. Packer RMA, Shihab NK, Torres BBJ, Volk HA. Responses to successive anti-epileptic drugs in canine idiopathic epilepsy. *Vet Rec*. 2015; 176(8):203.
24. Schwartz-Porsche D, Löscher W, Frey HH. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. *J Vet Pharmacol Ther*. 1985; 8(2):113–119.
25. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. *J Vet Intern Med*. 1993; 7(5):318–327.
26. Trepanier L, Van AS, Schwark W, Carrillo J. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992-1996). *J Am Vet Med Assoc*. 1998; 213(10):1449–1453.

27. WESSMANN A, VOLK H, PACKER R et al. Quality-of-life aspects in idiopathic epilepsy in dogs. *Vet Rec*. 2016; 179(9):229.
28. BAKER GA, SMITH DF, JACOBY A et al. Liverpool seizure severity scale revisited. *Seizure*. 1998; 7(3):201–205.
29. BAUTISTA RED, TANNAHILL Glen E. Seizure severity is associated with quality of life independent of seizure frequency. *Epilepsy Behav*. 2009; 16(2):325–329.
30. VITEVA EI. Seizure frequency and severity: How really important are they for the quality of life of patients with refractory epilepsy. *Ann Indian Acad Neurol*. 2014; 17(1):35–42.
31. NETTIFEE JA, MUÑAANA KR, GRIFFITH EH. Evaluation of the impacts of epilepsy in dogs on their caregivers. *J Am Anim Hosp Assoc*. 2017; 53(3):143–149.
32. BESAG FMC, VASEY MJ. Prodrome in epilepsy. *Epilepsy Behav*. 2018; 83:219–233.
33. FINNEGAN SL, VOLK HA, ASHER L et al. Investigating the potential for seizure prediction in dogs with idiopathic epilepsy: owner-reported prodromal changes and seizure triggers. *Vet Rec*. 2020; 187(4):152.
34. GOTMAN J. Relationships between interictal spiking and seizures: human and experimental evidence. *Can J Neurol Sci.* 1991; 18(S4):573–576.
35. BRINKMANN BH, PATTERSON EE, VITE C et al. Forecasting seizures using intracranial EEG measures and SVM in naturally occurring canine epilepsy. *PLOS One*. 2015; 10(8):e0133900.
36. MACKAY M, MAHLABA H, GAVILLET E, WHITTAKER RG. Seizure self-prediction: Myth or missed opportunity? *Seizure*. 2017; 51:180–185.
37. BUTLER CR, ZEMAN AZ. Recent insights into the impairment of memory in epilepsy: transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. *Brain*. 2008; 131(Pt 9):2243–2263.
38. LORING DW, MEADOR KJ, LEE GP. Determinants of quality of life in epilepsy. *Epilepsy Behav*. 2004; 5(6):976–980.
39. GOLDENSOHN E, GLASER G, GOLDBERG M (eds.). *Epilepsy*. Philadelphia: Lea and Febiger; 1984.
40. PERINI GI, TOSIN C, CARRARO C et al. Interictal mood and personality disorders in temporal lobe epilepsy and juvenile myoclonic epilepsy. *J Neurol Neurosurg Psychiatry*. 1996; 61(6):601–605.
41. BERENDT M, GREDAL H, ALVING J. Characteristics and phenomenology of epileptic partial seizures in dogs: similarities with human seizure semiology. *Epilepsy Res*. 2004; 61(1–3):167–373.
42. ALI F, RICKARDS H, CAVANNA AE. The assessment of consciousness during partial seizures. *Epilepsy Behav*. 2012; 23(2):98–102.
43. LENNOX W, LENNOX M. *Epilepsy and related disorders*. Boston, USA: Little Brown; 1960.
44. CENDES F, ANDERMANN F, GLOOR P et al. Relationship between atrophy of the amygdala and ictal fear in temporal lobe epilepsy. *Brain*. 1994; 117(4):739–746.
45. STASSEN QEM, GRINWIS GCM, VAN RHIJN NC et al. Focal epilepsy with fear-related behavior as primary presentation in Boerboel dogs. *J Vet Intern Med*. 2019; 33(2):694–700.
46. DODMAN NH, KNOWLES KE, SHUSTER L et al. Behavioral changes associated with suspected complex partial seizures in bull terriers. *J Am Vet Med Assoc*. 1996; 208(5):688–691.
47. DUCOTÉ JM. Common Neurologic problems: impact on patient welfare, caregiver burden and veterinarian wellbeing. *Vet Clin North Am Small Anim Pract*. 2019; 49(3):463–476.
48. YOUNG BG, BLUME WT. Painful epileptic seizures. *Brain*. 1983; 106 (Pt 3):537–554.

49. Siegel AM, Williamson PD, Roberts DW et al. Localized pain associated with seizures originating in the parietal lobe. *Epilepsia*. 1999; 40(7):845–855.
50. Mauguiere F, Courjon J. Somatosensory epilepsy: a review of 127 cases. *Brain*. 1978; 101:307–332.
51. Dainese F, Mai R, Francione S et al. Ictal headache: Headache as first ictal symptom in focal epilepsy. *Epilepsy Behav*. 2011; 22(4):790–792.
52. Plessas I, Volk H, Kenny P. Migraine-like episodic pain behavior in a dog: Can dogs suffer from migraines? *J Vet Intern Med*. 2013; 27(5):1034–1040.
53. Pottkämper JCM, Hofmeijer J, van Waarde JA, van Putten MJAM. The postictal state — What do we know? *Epilepsia*. 2020; 61(6):1045–1061.
54. Doudoux H, Fournier M, Vercueil L. Postictal syndrome: The forgotten continent. An overview of the clinical, biochemical and imaging features. *Rev Neurol (Paris)*. 2020; 176(1):62–74.
55. Fisher RS, Nune G, Roberts SE, Cramer JA. The Personal impact of epilepsy scale (PIES). *Epilepsy Behav*. 2015; 42:140–146.
56. Subota A, Khan S, Josephson CB et al. Signs and symptoms of the postictal period in epilepsy: a systematic review and meta-analysis. *Epilepsy Behav*. 2019; 94:243–251.
57. Packer RM, Volk HA. Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs. *Vet Rec*. 2015; 177(12):306–315.
58. Sadeh M, Goldhammer Y, Kuritsky A. Postictal blindness in adults. *J Neurol Neurosurg Psychiatry*. 1983; 46(6):566–599.
59. Orringer CE, Eustace JC, Wunsch CD, Gardner LB. Natural History of Lactic Acidosis after Grand-Mal Seizures. *N Engl J Med*. 1977; 297(15):796–799.
60. Fisher RS, Schachter SC. The postictal state: a neglected entity in the management of epilepsy. *Epilepsy Behav*. 2000; 1(1):52–59.
61. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. *J Am Vet Med Assoc*. 2012; 240(9):1073–1083.
62. Schwartz-Porsche D, Löscher W, Frey H. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. *J Vet Pharmacol Ther*. 1985; 8(2):113–119.
63. Podell M. Antiepileptic drug therapy. *Clin Tech Small Anim Pract*. 1998; 13(3): 185–192.
64. Dewey CW. Anticonvulsant therapy in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2006; 36(5):1107–1127.
65. Gilliam F. Optimizing health outcomes in active epilepsy. *Neurology*. 2002; 58:S9–20.
66. German AJ. The growing problem of obesity in dogs and cats. *J Nutr*. 2006; 136(7):1940S–6S.
67. Rutherford L, Wessmann A, Rusbridge C et al. Questionnaire-based behaviour analysis of Cavalier King Charles Spaniels with neuropathic pain due to Chiari-like malformation and syringomyelia. *Vet J*. 2012; 194:294–298.
68. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. *Epilepsy Behav*. 2011; 21(2):160–167.
69. Erath JR, Nessler JN, Riese F et al. Behavioral changes under levetiracetam treatment in Dogs. *Front Vet Sci*. 2020; 7(169).
70. Chang Y, Mellor D, Anderson TJJoSAP. Idiopathic epilepsy in dogs: owners' perspectives on management with phenobarbitone and/or potassium bromide. *J Small Anim Pract*. 22006; 47(10):574–581.

71. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy – a systematic review. *BMC Vet Res*. 2014; 10(1):257.
72. Podell M, Volk HA, Berendt M et al. 2015 ACVIM small animal consensus statement on seizure management in dogs. *J Vet Intern Med*. 2016; 30(2):477–490.
73. Packer RMA, De Risio L, Volk HA. Investigating the potential of the anti-epileptic drug imepitoin as a treatment for co-morbid anxiety in dogs with idiopathic epilepsy. *BMC Vet Res*. 2017; 13(1):90.
74. Neßler J, Rundfeldt C, Löscher W et al. Clinical evaluation of a combination therapy of imepitoin with phenobarbital in dogs with refractory idiopathic epilepsy. *BMC Vet Res*. 2017; 13(1):33.
75. Gaitatzis A, Carroll K, Majeed A, Sander JW. The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia*. 2004; 45(12):1613–1622.
76. Kobau R, Gilliam F, Thurman DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 Healthstyles Survey. *Epilepsia*. 2006; 47(11):1915–1921.
77. Boro A, Haut S. Medical comorbidities in the treatment of epilepsy. *Epilepsy Behav*. 2003;4: 2–12.
78. LaFrance Jr WC, Kanner AM, Hermann B. Psychiatric comorbidities in epilepsy. *Int Rev Neurobiol*. 2008; 83:347–83.
79. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol*. 2016; 15(1):106–115.
80. Johnson EK, Jones JE, Seidenberg M, Hermann BP. The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. *Epilepsia*. 2004; 45(5):544–550.
81. Watson F, Packer RMA, Rusbridge C, Volk HA. Behavioural changes in dogs with idiopathic epilepsy. *Vet Rec*. 2019; 186:93.
82. De Risio L, Newton R, Freeman J, Shea A. Idiopathic Epilepsy in the Italian Spinone in the United Kingdom: Prevalence, Clinical Characteristics, and Predictors of Survival and Seizure Remission. *J Vet Intern Med*. 2015; 29(3):917–924.
83. Levitin H, Hague DW, Ballantyne KC, Selmic LE. Behavioral changes in dogs with idiopathic epilepsy compared to other medical populations. *Front Vet Sci*. 2019; 6:396.
84. Brooks-Kayal AR, Bath KG, Berg AT et al. Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia*. 2013 ;54:44–60.
85. Watson F, Rusbridge C, Packer RMA et al. A review of treatment options for behavioural manifestations of clinical anxiety as a comorbidity in dogs with idiopathic epilepsy. *Vet J*. 2018; 238:1–9.
86. Packer RMA, Hobbs SL, Blackwell EJ. Behavioral interventions as an adjunctive treatment for canine epilepsy: a missing part of the epilepsy management toolkit? *Front Vet Sci*. 2019; 6:3.
87. Wilson SJ, Baxendale S, Barr W et al. Indications and expectations for neuropsychological assessment in routine epilepsy care: Report of the ILAE Neuropsychology Task Force, Diagnostic Methods Commission, 2013-2017. *Epilepsia*. 2015; 56(5):674–681.
88. Packer RM, McGreevy PD, Pergande A, Volk HA. Negative effects of epilepsy and antiepileptic drugs on the trainability of dogs with naturally occurring idiopathic epilepsy. *Appl Anim Behav Sci*. 2018; 200:106–113.

89. Trimble MR. Anticonvulsant drugs and cognitive function: a review of the literature. *Epilepsia*. 1987; 28:S37–S45.
90. Packer RMA, McGreevy PD, Salvin HE et al. Cognitive dysfunction in naturally occurring canine idiopathic epilepsy. *PLOS One*. 2018; 13(2):e0192182.
91. Dodrill CB. Neuropsychological effects of seizures. E*pilepsy Behav*. 2004; 5:21–24.
92. Winter J, Packer RMA, Volk HA. Preliminary assessment of cognitive impairments in canine idiopathic epilepsy. *Vet Rec*. 2018; 182:633.
93. Hobbs SL, Law TH, Volk HA et al. Impact of canine epilepsy on judgement and attention biases. *Sci Rep*. 2020; 10(1):17719.
94. Vieira de Castro AC, Fuchs D, Morello GM et al. Does training method matter? Evidence for the negative impact of aversive-based methods on companion dog welfare. *PLOS One*. 2020; 15(12):e0225023.
95. Berk BA, Packer RMA, Law TH et al. Medium-chain triglycerides dietary supplement improves cognitive abilities in canine epilepsy. *Epilepsy Behav*. 2021; 114(Pt A):107608.
96. Packer RMA, Volk HA, Fowkes RC. Physiological reactivity to spontaneously occurring seizure activity in dogs with epilepsy and their carers. *Physiol Behav*. 2017; 177:27–33.
97. Henn FA, Vollmayr B. Stress models of depression: forming genetically vulnerable strains. *Neurosci Biobehav Rev*. 2005; 29(4-5):799–804.
98. Koolhaas JM, Bartolomucci A, Buwalda B et al. Stress revisited: a critical evaluation of the stress concept. *Neurosci Biobehav Rev.* 2011; 35(5):1291–301.
99. Pergande AE, Belshaw Z, Volk HA, Packer RMA. "We have a ticking time bomb": a qualitative exploration of the impact of canine epilepsy on dog owners living in England. *BMC Vet Res*. 2020; 16(1):443.
100. Puka K, Tavares TP, Anderson KK et al. A systematic review of quality of life in parents of children with epilepsy. *Epilepsy Behav*. 2018; 82:38–45.
101. Lord L, Podell M. Owner perception of the care of long-term phenobarbital-treated epileptic dogs. *J Small Anim Pract*. 1999; 40(1):11–15.
102. Kurdek LA. Pet dogs as attachment figures. *J Soc Pers Relat*. 2008; 25(2):247–266.
103. Jensen MP, Liljenquist KS, Bocell F et al. Life impact of caregiving for severe childhood epilepsy: Results of expert panels and caregiver focus groups. *Epilepsy Behav*. 2017; 74:135–143.
104. Batalden M, Batalden P, Margolis P et al. Coproduction of healthcare service. *BMJ Qual Saf*. 2016; 25(7):509–517.
105. Institute for Patient and Family Centered Care (IPFCC). *What is patient and family-centred health care?* 2020. Available from: https://www.ipfcc.org/about/pfcc.html [Accessed 21st May 2021].
106. Liberati EG, Gorli M, Scaratti G. Invisible walls within multidisciplinary teams: disciplinary boundaries and their effects on integrated care. *Soc Sci Med*. 2016; 150:31–39.
107. Feinberg LF. Moving toward person-and family-centered care. *Public Policy Aging Rep*. 2014; 24(3):97–101.
108. Preedy VR, Watson RR (eds.). *Handbook of Disease Burdens and Quality of Life Measures*. Springer; 2010.
109. Gayatri NA, Morrall MC, Jain V et al. Parental and physician beliefs regarding the provision and content of written sudden unexpected death in epilepsy (SUDEP) information. *Epilepsia*. 2010; 51(5):777–782.

110. Berk BA, Packer RMA, Law TH, Volk HA. Investigating owner use of dietary supplements in dogs with idiopathic epilepsy. *Res Vet Sci*. 2018; 119:276–284.

111. Belshaw Z, Robinson NJ, Dean RS, Brennan ML. Motivators and barriers for dog and cat owners and veterinary surgeons in the United Kingdom to using preventative medicines. *Prev Vet Med*. 2018; 154:95–101.

Genetics of Epilepsy in Dogs and Cats

04

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In regard to the genetics of recurrent epileptic seizures in dogs and cats, the most relevant cause is idiopathic epilepsy (IE). The prevalence of IE in the general canine population has been estimated as 0.67–0.75%.[1,2] Importantly, IE is the most common cause of epileptic seizures in dogs, with it accounting for 57.5% of dogs diagnosed with epilepsy in a prospective longitudinal study in Denmark.[3] The subclassification of IE proposed by the International Veterinary Epilepsy Task Force (IVETF)[4] introduced into the veterinary field the additional terms of "suspected genetic" and "genetic" IE (see Chapter 2, Fig. 2.1). The IVETF proposed three tiers of testing recommendations to achieve a diagnosis of IE[5] (see Chapter 1, Box 1.4). The IVETF classification of structural epilepsy also includes genetic conditions resulting in identifiable cerebral/intracranial pathology as the underlying cause of recurrent epileptic seizures.[4]

More than 700 inherited diseases and traits in dogs and over 300 in cats are recognized,[6] but in many of these, the biochemical or molecular basis is not yet identified. Advances in the past 30 years in genomic technology capabilities, including publication of the sequence of the canine genome in 2005[7] and feline genome in 2007,[8] have allowed the rapid development of genetic tests for companion animals. There are just over 185 published DNA genetic tests for canine and feline diseases.[6]

A regularly updated listing of laboratories worldwide doing companion animal genetic testing is produced on the world wide web by the Orthopedic Foundation for Animals:

https://www.ofa.org/about/educational-resources/links/laboratories.

Some of the currently available genetic tests are for idiopathic (genetic) epilepsy and structural epilepsy in dogs. While these genetic tests are useful for a few very specific conditions in single dog breeds, the vast majority of genetically related recurrent epileptic seizure conditions in dogs and cats do not yet have a genetic test developed. There have been a number of comprehensive reviews of the genetics of canine epilepsy published within the past 10 years.[9,10] No review of feline epilepsy has been published to date, as there is very limited knowledge or published information regarding recurrent epileptic seizures in cats. This chapter will not be another comprehensive review of the genetics of canine or feline epilepsy, as its purpose is to summarize practical clinical considerations regarding the genetics of canine epilepsy, and to indicate the very limited information known about feline IE.

GENETIC OR SUSPECTED GENETIC IDIOPATHIC EPILEPSY IN DOGS

Available published evidence to date indicates that canine IE is thought to have an underlying genetic basis (i.e., genetic or suspected genetic IE). It is very likely that for most cases, even in purebred dogs, the mode of inheritance is polygenic. In polygenic (complex) inheritance there is the combined effect of a number of genes each with a small effect—often with some additional environmental influences. In human epilepsy, primary generalized epilepsies are thought to generally have a genetic basis, and a few relatively rare, generalized epilepsies have been found to have an underlying single gene mutation and thus are termed monogenic. Many of the mutations in these rare single gene epilepsies in people are located in ion channel genes and were discovered in small isolated human populations, such as in isolated cultures in South Pacific islands.[12] Since inbreeding in some dog breeds is similar to that found in some isolated human populations, it was initially thought that it was possible or probable

that many canine, breed-specific, idiopathic epilepsies might be caused by simple single gene mutations and be monogenic. A 2011 investigation of Beagles, English Springer Spaniels, Greater Swiss Mountain Dogs and Vizslas with suspected genetic epilepsy for genetic markers near 50 documented human ion channel epilepsy mutations excluded the vast majority from being associated with epilepsy in the four breeds, with a few inconclusive results and none confirmed as statistically associated with canine IE.[13] From that study and others since, it appears that simple single gene ion channel mutations or similar genetic mutations will be very rarely, if ever, the cause of IE in a dog breed.

The comprehensive reviews of the genetics of canine epilepsy[9,10] and the prevalence and clinical features of IE in purebred dogs[11] as well as breed-specific studies[14] within the last 10 years have indicated or suggested a likely significant genetic contribution to IE in the following breeds: Australian Shepherd, Belgian Shepherd, Beagle, Belgian Tervueren Sheepdog, Bernese Mountain Dog, Border Collie, Border Terrier, Cavalier King Charles Spaniel, Collie, Dalmatian, English Springer Spaniel, Finnish Spitz, German Shepherd, Golden Retriever, Irish Wolfhound, Italian Spinone, Keeshond, Labrador Retriever, Lagotto Romagnolo, Petit Basset Griffon Vendéen, Rhodesian Ridgeback, Schipperke, Shetland Sheepdog, Standard Poodle, and Vizsla. The clinical features of breed-specific IEs are described in Chapter 2. A Purdue Veterinary Medical Database search and analysis found that all dog breeds had a measurable incidence of IE hospital admissions (0.2–2.1% range) based on dogs presenting to veterinary teaching hospitals for IE versus all other admissions for the breed, and importantly that mixed breed dogs had an incidence in the middle of the range for purebred dogs.[15] As IE is common in numerous dog breeds, an understanding of its genetic contributions can be relevant for the clinician, particularly when a genetic test is available to support the diagnosis.

Monogenic idiopathic (genetic) epilepsies

In dogs there are two **monogenic idiopathic (genetic) epilepsies** documented with an identified causative single gene mutation:

- Benign juvenile idiopathic (genetic) epilepsy in Lagotto Romagnolo dogs
- Generalized myoclonic epilepsy with photosensitivity in juvenile Rhodesian Ridgebacks

Benign juvenile idiopathic (genetic) epilepsy in Lagotto Romagnolo dogs

An autosomal recessive mutation in the *LGI2* gene has been detailed as the causative mutation of benign juvenile idiopathic (genetic) epilepsy in Lagotto Romagnolo dogs[16,17] and a genetic test is commercially available. The *LGI1* gene is associated with autosomal dominant lateral temporal lobe epilepsy in people. LGI1, LGI2, LGI3, and LGI4 are all neuronally secreted and act on the ADAM family of neuronal receptors, which play a role in synaptic function. *ADAM23* knockout mice exhibit spontaneous seizures, and mice heterozygous for the *ADAM23* knockout gene have a lower seizure threshold; thus, the *LGI2* gene mutation might contribute to the development of seizures through its effect on *ADAM23*.[18] The clinical characteristics of this form of canine genetic epilepsy are different from those of most presumed genetic IEs in dogs where age of epileptic seizure onset is between 6 months and 6 years, and spontaneous remission rarely occurs. Benign juvenile idiopathic (genetic) epilepsy in Lagotto Romagnolo dogs is characterized by recurrent epileptic seizures with an onset at 5–9 weeks of age and usually spontaneous resolution by 8–13 weeks.[17] The epileptic seizures are characterized by generalized (all body) tremor, ataxia, and stiffness. The amplitude of the tremor seems to increase with exercise in puppies that are able to move during the seizure. Most puppies appear conscious during the seizure. The severity of the clinical signs during a seizure varies between puppies, including between littermates. Epileptic seizures occur anytime during the day, including during sleep or during exercise such as playing with other puppies. The frequency of epileptic seizures varies from multiple episodes per day to one episode per week. Epileptic seizure duration ranges from 10 seconds to a few minutes.

Puppies with severe epileptic seizures also present with interictal neurological signs, such as generalized ataxia and hypermetria. No significant abnormalities have been detected following extensive diagnostic investigations. Phenobarbital (PB) was reported to be efficacious in the only puppy in which it was administered. However, epileptic seizure freedom persisted following PB discontinuation and was achieved in the untreated puppies around 4 months of age.[17]

Generalized myoclonic epilepsy with photosensitivity in juvenile Rhodesian Ridgebacks

In this juvenile-onset, genetic epilepsy, a mutation in the *DIRAS1* gene leads to myoclonic jerks (see Chapter 2, Videos 2.5–2.7) starting about 6 months of age (range, 1.5–18 months), and photosensitivity in which flickering lights can induce seizures in 35% of affected dogs. No autonomic signs occur during the myoclonic epileptic seizures. Myoclonic jerks are often limited to or start at one side of the body; however, a consistent side predilection could not be detected.[14] Progression to generalized tonic-clonic epileptic seizures was reported to occur in 38% of 24 affected dogs within a median of 6 months (range, 1.5–29 months) after myoclonic seizure onset. The generalized tonic-clonic epileptic seizures are frequently preceded by a series of myoclonic twitches. Some dogs appear disoriented, frightened and restless after an epileptic seizure. The myoclonic twitches occur daily or almost daily (e.g., every second to third day) with a frequency of up to 150 twitches per day. The epileptic seizures are typically lifelong. The myoclonic epileptic seizures appear to respond best to levetiracetam or potassium bromide (KBr) based on information obtained from the dog owners. Cognitive function was reported to remain normal by the owners of 3 dogs that were >8 years of age at the time of the final follow-up. Three dogs were euthanized due to the severity of the epilepsy. The *DIRAS1* gene is a novel epilepsy gene with expression pattern in the CNS and it has been shown to be necessary for acetylcholine transmission at neuromuscular junctions in *Caenorhabditis elegans* and neuronal development in zebrafish, consistent with the possibility of contributing to epilepsy, though its function in mammals has not been directly documented yet.[14]

Further clinical details can be found in the sections on Lagotto Romagnolos and Rhodesian Ridgebacks in Chapter 2.

Polygenic idiopathic (genetic) epilepsies

In Belgian Shepherds, six genetic loci (specific chromosomal locations) have been indicated to potentially be involved in a predisposition to idiopathic (suspected genetic) epilepsy in the breed.[19] This has not yet led to a screening genetic test involving all six genetic loci. Ideally, eventually a screening test with an algorithm involving variants in the six loci or any additional loci could lead to a genetic susceptibility test that indicates a specific dog's likelihood of developing IE and this susceptibility

information could be used to guide breeding decisions. The six or more loci in the Belgian Shepherd indicate a polygenic (complex) genetic predisposition, and it is likely that a similarly complex predisposition is underlying suspected genetic IE in most dog breeds. The mean age of IE onset in Belgian Shepherds has been reported as 3.3 years and epileptic seizures are often focal, with or without secondary generalization. Dogs are normal during the interictal period and many dogs respond favorably to antiseizure drugs (ASDs) (such as PB and KBr). Further clinical details can be found in the section on Belgian Shepherds in Chapter 2.

A common risk haplotype (chromosomal location) including the *ADAM23* gene on canine chromosome 37 (CFA37) was documented as one of the IE susceptibility loci (chromosomal locations) in Belgian Shepherds, and also as a contributing loci in the Australian Shepherd, Beagle, Finnish Spitz, Kromfohrlaender, Labrador Retriever, Pyrenean Shepherd, and Schipperke breeds.[20,21] This shared risk chromosomal area suggests a number of breeds share a common or similar contributing low penetrance genetic mutation in the coding sequence or nearby genetic regulatory areas of *ADAM23* for polygenic IE. In addition, the *LGI2* gene, which is the cause of benign juvenile IE in the Lagotto Romagnolo, as previously indicated in the section on this disease, has been shown to act on *ADAM* family members. ADAM23 and LGI1 affect voltage-gated potassium channel function,[22] which is consequently consistent with them being related to IE susceptibility. Additionally, *ADAM23* knockout rodent models have seizure phenotypes. Taken together it appears that *ADAM23* may play a key role in many IEs of dogs. It is likely, however, that all variants contributing to IE between any two breeds are not shared, and that *ADAM23* may not always contribute to IE in all breeds. Each breed is likely to have a unique combination of risk alleles contributing to the susceptibility for developing IE.

STRUCTURAL EPILEPSIES IN DOGS

A number of breed-specific autosomal recessive genetic mutations have been identified for structural epilepsies in dogs for which there is identifiable cerebral pathology as the underlying cause of the recurrent

epileptic seizures and progressive interictal neurological signs, and genetic tests are available.

Lafora disease in dogs

Lafora disease is an autosomal recessive, late-onset, progressive myoclonic epilepsy caused by mutations in the *EPM2A* gene encoding the glycogen phosphatase laforin, or the *EPM2B* (*NHLRC1*) gene encoding the ubiquitin E3 ligase malin.[23–25] It has been reported most commonly in miniature Wirehaired Dachshunds, but also in a small number of Basset Hounds and Beagles, and single cases have been reported in the miniature and standard Poodle, Pointer, and Corgi.[23–25] The mutations in the *EPM2A* and *EPM2B* (*NHLRC1*) genes have been reported only in the miniature Wirehaired Dachshund, Basset Hound and Beagle.

The underlying pathology in Lafora disease is transformation of spherical and soluble glycogen to a more linear and insoluble glucan called polyglucosan. Gradual precipitation, aggregation, and accumulation of polyglucosans results in neurotoxic intracellular inclusions (referred to as Lafora bodies).[24]

Clinically, the condition is characterized by spontaneous and reflex myoclonic seizures, i.e., sudden and brief involuntary single or multiple contraction(s) of muscle(s) or muscle groups in response to light, sound and/or movement in the visual field. Consciousness is not impaired and there are no autonomic signs (see Chapter 2, Video 2.9).

In a survey study including 27 miniature Wirehaired Dachshunds with Lafora disease (diagnosed with *EPM2B* mutation genetic testing in 16 dogs), the mean age at disease onset was 6.9 years (range, 3.5–12 years) and the most common initial clinical sign was reflex and spontaneous myoclonus (77.8%).[24] Hypnic myoclonus (i.e., myoclonus while falling asleep) and generalized tonic-clonic seizures occurred in 51.9% and 40.7% of dogs, respectively. Focal epileptic seizures occurred in 25.9% of dogs. Anecdotally, there was an initial response to levetiracetam. The severity, frequency and refractoriness of the myoclonic seizures increased over time. In the later stages of the disease the dogs developed cognitive decline (51.9%), blindness (48.1%), aggression toward people (25.9%) and dogs (33.3%), deafness (29.6%) and fecal (29.6%) and urinary (37.0%) incontinence as a result of loss of house training.[24]

Complete blood count, serum biochemistry, urinalysis and cerebrospinal fluid analysis are unremarkable.[24–25] Electroencephalography (EEG) can reveal bilateral synchronous polyspikewave paroxysms and erratic myoclonus. Magnetic resonance imaging can reveal generalized cortical cerebral atrophy with ventriculomegaly. Electromyography can detect abnormal spontaneous activity (i.e., positive sharp waves and fibrillation potentials) of the epaxial, appendicular and head muscles.[24]

In the 2 Beagles with Lafora disease reported to date, myoclonic seizures were first observed at the age of 6.5 and 7.8 years, respectively. The clinical manifestations were similar to the myoclonic seizures described in the miniature Wirehaired Dachshunds.[25] Generalized tonic-clonic epileptic seizures developed 6 months after the onset of the myoclonic seizures in the older Beagle. Disease progression seems more benign than in the miniature Wirehaired Dachshund, but information is limited.

Neonatal encephalopathy with seizures in standard Poodles

Neonatal encephalopathy with seizures (NEWS) is an autosomal recessive disease of standard Poodle puppies caused by a mutation in the *ATF2* gene. The *ATF2* gene encodes for activating transcription factor 2, which regulates the transcription of various genes associated with antiapoptosis, cell growth, and the DNA damage response. This gene has an important role in neuronal development and migration.[26,27] Affected puppies are small and weak at birth, with many dying in the initial weeks of life. Those surviving past 1 week develop ataxia, generalized tremor, and, by 4–6 weeks of age, severe generalized clonic-tonic epileptic seizures. Puppies reported with this condition die or are humanely euthanized by 2 months of age.[26,27]

Magnetic resonance imaging (3 Tesla) of a 64-day-old Poodle with NEWS revealed reduced whole-brain size, enlarged ventricles, and cerebral white matter and cerebellar abnormalities. Histopathology detected irregular neuronal migration in the subventricular zone of the lateral ventricles in the frontal lobe, white matter rarefaction especially at the level of the occipital lobe in the cerebrum, and cerebellar cortical dysplasia.[27]

L-2-hydroxyglutaric aciduria

L-2-hydroxyglutaric aciduria (L2HGA) is a metabolic disorder characterized by accumulation of L-2-hydroxyglutaric (L2HG) acid within

various tissues resulting in structural brain pathology. Increased levels of L2HG in the brain are associated with oxidative stress through impaired antioxidant defenses and increased reactive oxygen species generation, resulting in reactive astrogliosis and a decreased neuronal population.[28] In Staffordshire Bull Terriers, L2HGA is an autosomal-recessive, metabolic-structural epilepsy caused by mutations of the gene encoding L2HG dehydrogenase (L2HGDH). A questionnaire study targeting owners of Staffordshire Bull Terriers diagnosed as homozygous for the *L2HGDH* mutations in the UK described the clinical characteristics and course of the disease in 27 dogs.[28] All dogs had neurological signs with a mean age at onset of 12 months (median, 8; range, 2.5–60 months). Posture and gait abnormalities were the most common (26/27 dogs) and earliest recognized clinical signs. Behavioral changes and cognitive dysfunction (24/27) frequently occurred. Eighteen dogs (67%) demonstrated paroxysmal episodes suggestive of epileptic seizures or dyskinetic episodes. In 9 dogs, a full description of these episodes was available from the owner: 6/9 dogs were unresponsive, 8/9 dogs had autonomic signs (e.g., urination, defecation, and/or hypersalivation). In 2 of the 9 dogs, the episode description was consistent with generalized tonic-clonic epileptic seizures. In 7 of 9 dogs, the paroxysmal episodes were triggered by stress or excitement and avoidance of these triggers decreased episode frequency. Ten of the 18 dogs with paroxysmal episodes were treated with ASDs (most commonly PB). Tremors unrelated to seizure activity were reported in 19/26 dogs. After the onset of neurological signs, 19/27 (70%) dogs were alive at a median of 69 months (range, 12–170 months). Six (22%) of the 27 dogs included in this study where euthanized due to progression of the neurological signs, including epileptic seizures.[28] A genetic test is commercially available to diagnose L2HGA in dogs with clinical signs and inform breeding decisions (see the *Genetic counseling for breeding dogs with epilepsy* section of this chapter). Diagnostic investigations in affected dogs have shown increased levels of L2HG acid and lysine in urine, plasma and cerebrospinal fluid. Magnetic resonance imaging revealed bilaterally symmetrical, diffuse areas of gray matter (mostly in the thalamus, hypothalamus, dentate nucleus, basal ganglia, dorsal brainstem, cerebellar nuclei and cerebellar gyri), which appeared hyperintense on T2-weighted images, hypointense on T1-weighted images, did not contrast enhance and

did not exhibit a mass effect. Cerebrospinal fluid cell count, cytology and protein concentration were unremarkable.

L2HGDH mutations resulting in L2HGA have also been reported in 3 Yorkshire Terriers (2 of which had generalized tonic-clonic epileptic seizures) and 1 West Highland White Terrier.[29,30,31]

Neuronal ceroid lipofuscinosis in dogs

There are over ten documented genetic forms of neuronal ceroid lipofuscinosis (NCL) in dogs, with different autosomal recessive mutations in different genes for each breed in American Bulldogs, American Staffordshire Terriers, Australian Shepherds and Border Collies, and two mutations in two different genes in Dachshunds, English Setters, Tibetan Terriers[9] and Chihuahuas[32]. In general, the clinical characteristics of NCL in dogs include progressive epileptic seizures, progressive neurological deficits, vision loss and premature death. Neuronal ceroid lipiofuscinosis has also been reported in Cocker Spaniels, Dalmatians, Labrador Retrievers, Polish Owczarek Nizinnys, Salukis, and Yugoslavian Shepherds[32], with the molecular basis as yet unknown in these breeds and therefore no available genetic test for these additional breeds.

Table 4.1 summarizes the currently available genetic tests for idiopathic or structural epilepsy in dogs. Details of diagnostic laboratories that conduct these genetic tests can be found at https://www.ofa.org/about/educational-resources/links/laboratories.

TABLE 4.1. Monogenic epilepsies in dogs with available genetic tests.

Disease	Dog breed(s)	Epilepsy category	Inheritance	Gene(s)	Age at epileptic seizure onset	Epileptic seizure phenomenology	Interictal neurological signs	Disease course
Benign familial juvenile epilepsy	Lagotto Romagnolo	Idiopathic genetic	Autosomal recessive	*LGI2*	5–9 weeks of age	Generalized tremors, ataxia and stiffness	Ataxia and hypermetria in some puppies	Spontaneous resolution of epilepsy at 8–13 weeks of age, but behavioral abnormalities can persist into adulthood
Juvenile myoclonic epilepsy (JME)	Rhodesian Ridgeback	Idiopathic genetic	Autosomal recessive	*DIRAS1*	1.5–18 months (median, 3.5 months; mean, 6 months)	Myoclonic jerks nearly every day, with photosensitivity reported in approximately 1/3 of dogs	None	Progression to generalized tonic-clonic seizures reported in approximately 1/3 of dogs within 1.5–29 months after onset of myoclonic seizures. Poor seizure control can lead to euthanasia in some dogs
Lafora disease	Miniature Wirehaired Dachshund (MWHD), Beagle, Basset Hound	Structural	Autosomal recessive	*EPM2B (NHLRC1), EPM2A*	3.5–12 years (mean age, 6.9 years in MWHDs and 7 years in Beagles)	Progressive spontaneous and reflex myoclonic seizures. Concurrent generalized tonic-clonic epileptic seizures in some dogs. Focal seizures can also occur	Initially, dogs can be normal interictally. Later in the disease course, MWHD can develop blindness, deafness, dementia, aggression, and urinary incontinence	Progressive severity and frequency of myoclonic and generalized tonic-clonic epileptic seizures. Humane euthanasia is often performed within a few years of diagnosis
Neonatal encephalopathy with seizures (NEWS)	Standard Poodle	Structural	Autosomal recessive	*ATF2*	2–6 weeks	Generalized tonic-clonic seizures	Ataxia, generalized tremor, generalized weakness, inability to suckle	Death by 7 weeks of age
L-2-hydroxyglutaric aciduria	Staffordshire Bull Terrier, Yorkshire Terrier, West Highland White Terrier	Structural	Autosomal recessive	*L2HGDH*	2.5 months–5 years (median, 8 months; mean, 12 months)	Generalized tonic-clonic seizures	Cerebellar ataxia, head tremors, behavioral changes and cognitive dysfunction	Progressive neurological disease that can be managed successfully in some Staffordshire Bull Terriers. Disease progression and epileptic seizures can result in euthanasia
Neuronal ceroid lipofuscinosis (NCL)	1. American Bulldog 2. American Staffordshire Terrier 3. Australian Shepherd 4. Border Collie 5. Chihuahua 6. Dachshund 7. English Setter 8. Tibetan Terrier	Structural	Autosomal recessive	1. *CLCN10* 2. *ARSG* 3. *CLN6* 4. *CLN5* 5. *MFSD8* 6a. *CLN1* 6b. *CLN2* 7. *CLN8* 8. *APT13A2*	6 months–8 years with causative gene/breed variability	Epileptic seizures not always readily apparent. Can be focal or generalized	Aggression, personality changes, hyperactivity, anxiety, tremors, cerebellar ataxia, vision loss	Progressive epileptic seizures, neurological deficits with decline over time, and premature death

PHARMACOGENETICS IN EPILEPTIC DOGS

For people with epilepsy, there have been a large number of studies on the pharmacogenetics of the metabolism of ASDs and any corresponding potential therapeutic consequences.[33] In these human epilepsy studies, there is some strong evidence and some less strong evidence for genetic variants in specific cytochrome (CYP) genes affecting serum concentrations of some ASDs. There is also some, but not clear-cut, documentation for genes encoding enzymes involved in glucuronidation and acetylation in people. There is unclear evidence regarding drug transporter genes for people, such as P-glycoprotein (*P-gp*) genes and specifically *ABCB1*,[33] also known as the *MDR* (multidrug resistance) gene, for which there is good evidence related to chemotherapy and other drugs metabolism in people and dogs.

In dogs there have been a very limited number of pharmacogenetic studies for response to ASDs. A study of pooled samples from many dog breeds evaluated 30 genes related to drug metabolism, transport, targeting etc., and five genes suggestive of an association with drug response were identified.[34] A number of these genes encode for ion channels. To the author's knowledge, to date, no pharmacogenomic genetic test has been developed for any of these five genes/chromosomal locations. The eventual development of specific pharmacogenomic tests for dogs would help guide therapy in potentially predicting which dogs are likely and not likely to respond to specific ASDs, as well as which dogs are likely to be ASD-responders and ASD-resistant to two or more drugs prior to starting therapy.

A coding mutation in the *ABCB1* gene (c.296_299del) of Border Collies and related breeds has been well documented to cause ivermectin toxicosis and other drug sensitivities.[35] An epilepsy pharmacogenetic study in 236 Border Collies from Switzerland and Germany examined the *ABCB1* gene sequence, and found a DNA variant (c.-6-180T>G) in an intron of the gene that was associated with PB responsiveness/nonresponsiveness, defined as a 50% or more reduction in seizures while on PB for at least 3 months, with serum concentrations within the established reference range.[36] There was no association with drug responsiveness or with the development of IE identified for the (c.296_299del) drug sensitivity mutation in this population. This new (c.-6-180T>G) variant was further assessed in a study 2 years later in 472 Border Collies in Japan and the authors indicated "It is necessary to further study the association between P-gp and c.-6-180T>G

and the interaction between these mutations in the canine *MDR1/ABCB1* gene before the pharmacogenetic information related to c.-6-180T>G can be applied to clinical practice."[37]

GENETIC COUNSELING FOR BREEDING DOGS WITH EPILEPSY

With the likelihood that IE in the vast majority of dog breeds is likely to be inherited in a polygenic manner, breeding recommendations are similar to those for other polygenic diseases such as hip dysplasia.

For likely polygenic canine idiopathic epilepsies:

- Do not breed affected dogs.
- Do not breed unaffected dogs if their parents or grandparents are affected.
- Do not breed unaffected dogs if more than 25% of their littermates are affected.[38]

For the limited number of documented monogenic IE and structural epilepsy genetic conditions in dogs:

- Screen with the genetic test prior to breeding if it is a common disease in the breed, or has been identified in close relatives.
- Do not breed affected dogs.
- Do not breed two carrier individuals.
- A carrier individual could be bred to a clear individual only if the carrier is a quality individual for other traits (the clear and carrier status should be based on genetic testing of both individuals). This is the breed and replace strategy.
- Overall, aim to have a lower percentage of carrier individuals in each progressive generation.[38]

Most simply, do not breed dogs affected with idiopathic or structural epilepsy if it is likely to be polygenic or is proven to be a monogenic form, and breed carrier individuals or unaffected dogs with affected dogs for the polygenic forms with caution and as indicated above.

FELINE EPILEPSY GENETICS

For recurrent epileptic seizures in cats, it is thought that less than 30% of cats have feline IE[39] in which no underlying cause can be identified despite extensive diagnostic investigations (see chapters 1 and 5). It is possible that these feline IE cases are a form of suspected genetic epilepsy, although to this author's knowledge, only one study to date has identified a feline breed disposition or shown a potential mode of inheritance. The one documented feline IE is a spontaneous occurring IE documented in just two generations from a research cat colony.[40] The inheritance pattern is consistent with autosomal recessive inheritance, and the seizures are focal seizures (head turning, unilateral facial twitching, salivation and circling) with secondary generalization and no interictal signs or other abnormalities noted to date.

Given that such a low percentage of feline epilepsy cases have no detectable known cause compared to the high percentage of dogs with IE, it is also possible that IE in cats is different than IE in dogs and is truly of unknown cause in the vast majority of cases, although it does generally have a good long-term prognosis[41] compared to the other common causes of recurrent seizures in cats.

Epileptic seizures can be part of the phenotype in GM1 gangliosidosis, a rare genetic lysosomal storage disease documented in cats,[42] for which a genetic mutation has been identified. Epileptic seizures are not always a feature, especially early in the course of the disease. Generally, any of the feline lysosomal storage diseases that sometimes have recurrent epileptic seizures as part of the phenotype are rare, unlikely to be encountered in clinical veterinary practice, and other signs such as head and pelvic limb tremors, generalized dysmetria and impaired vision are often readily apparent before epileptic seizures.

TAKE-HOME MESSAGES

- ✔ Idiopathic epilepsy (suspected genetic and genetic) is common in dogs.
- ✔ In a vast majority of dogs, IE is very likely to have polygenic (complex) inheritance in which a number of genes in combination each exert a small effect on the predisposition to epilepsy.

- ✔ There are two, uncommon, single-gene (monogenic) epilepsies in dogs with an identified mutation: one in the Lagotto Romagnolo and the other in the Rhodesian Ridgeback. These two epilepsies differ in the age of onset and progression from most (presumed genetic) idiopathic epilepsies, in which the typical age of onset is 6 months to 6 years of age and the epileptic seizures are lifelong.
- ✔ In dogs, single-gene defects have been identified for four breed-specific, progressive structural or metabolic-structural epilepsies: Lafora disease, NEWS, L2HGA and over 10 genetic forms of NCL. In these structural epilepsies, the epileptic seizures and interictal neurological signs all progressively worsen, often leading to premature death.
- ✔ Feline IE is less common than in dogs; to date there have not yet been any identified breed or familial dispositions of increased incidence in client-owned cats.
- ✔ Research into the pharmacogenomics of ASD metabolism, transport and binding in dogs has some interesting results, though it has not yet resulted in any clearly helpful genetic test for individual epileptic dogs.

REFERENCES

1. KEARSLEY-FLEET L, NEILL DG, VOLK HA et al. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. *Vet Rec*. 2013; 172(13):338.
2. HESKE L, NØDTVEDT A, JÄDERLUND KH et al. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. *Vet J*. 2014; 202(3):471–476.
3. FREDSØ N, TOFT N, SABERS A, BERENDT M. A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs. *BMC Vet Res*. 2017 Feb 16; 13(1):54.
4. BERENDT M, FARQUHAR RG, MANDIGERS PJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015 Aug 28; 11:182.
5. DE RISIO L, BHATTI S, MUÑANA K et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015 Aug 28; 11:148.
6. PATTERSON EE. Methods and availability of tests for hereditary disorders of dogs. In: BONAGURA J., TWEDT D (eds.). *Current Vet Therapy XV*. Louis MO: Saunders Elsevier; 2014. pp. 221–225.

7. Lindblad-Toh K, Wade CM, Mikkelsen TS et al. Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature*. 2005 Dec 8; 438(7069):803–819.
8. Pontius JU, Mullikin JC, Smith DR et al. Initial sequence and comparative analysis of the cat genome. *Genome Res*. 2007 Nov; 17(11):1675–1689.
9. Ekenstedt KJ, Patterson EE, Mickelson JR. Canine epilepsy genetics. *Mamm Genome*. 2012 Feb; 23(1-2):28–39.
10. Ekenstedt KJ, Oberbauer AM. Inherited epilepsy in dogs. *Top Companion Anim Med*. 2013 May; 28(2):51–58.
11. Hülsmeyer VI, Fischer A, Mandigers PJ et al. International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. *BMC Vet Res*. 2015 Aug 28; 11:175.
12. Andrade DM, Minassian BA. Genetics of epilepsies. *Expert Rev Neurother*. 2007 Jun; 7(6):727–734.
13. Ekenstedt KJ, Patterson EE, Minor KM, Mickelson JR. Candidate genes for idiopathic epilepsy in four dog breeds. *BMC Genet*. 2011 Apr 25; 12:38.
14. Wielaender F, Sarviaho R, James F et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci U S A*. 2017 Mar 7; 114(10):2669–2674.
15. Patterson EE. *Developing a canine model of idiopathic epilepsy*. PhD dissertation. Minneapolis, MN: University of Minnesota Graduate School. ©Edward Earl Patterson; 2004.
16. Seppälä EH, Jokinen TS, Fukata M et al. LGI2 truncation causes a remitting focal epilepsy in dogs. *PLoS Genet*. 2011 Jul;7(7).
17. Jokinen TS, Metsahonkala L, Bergamasco L et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. *J Vet Intern Med*. 2007; 21(3):464–471.
18. Pakozdy A, Patzl M, Zimmermann L et al. LGI Proteins and Epilepsy in Human and Animals. *J Vet Intern Med*. 2015 Jul-Aug; 29(4):997–1005.
19. Oberbauer AM, Belanger JM, Grossman DI et al. Genome-wide linkage scan for loci associated with epilepsy in Belgian shepherd dogs. *BMC Genet*. 2010 May 4; 11:35. doi: 10.1186/1471-2156-11-35.
20. Koskinen LL, Seppälä EH, Belanger JM et al. Identification of a common risk haplotype for canine idiopathic epilepsy in the ADAM23 gene. *BMC Genomics*. 2015 Jun 18; 16(1):465.
21. Koskinen LL, Seppälä EH, Weissl J et al. ADAM23 is a common risk gene for canine idiopathic epilepsy. *BMC Genet*. 2017 Jan 31; 18(1):8.
22. Hivert B, Marien L, Agbam KN, Faivre-Sarrailh C. ADAM22 and ADAM23 modulate the targeting of the Kv1 channel-associated protein LGI1 to the axon initial segment. *J Cell Sci*. 2019 Jan 16; 132(2): jcs219774. doi: 10.1242/jcs.219774.
23. Lohi H, Young EJ, Fitzmaurice SN et al. Expanded repeat in canine epilepsy. *Science*. 2005 Jan 7; 307(5706):81.
24. Swain L, Key G, Tauro A et al. Lafora disease in miniature Wirehaired Dachshunds. *PLoS One*. 2017 Aug 2; 12(8):e0182024. doi: 10.1371/journal.pone.0182024.
25. Hajek I, Kettner F, Simerdova V et al. NHLRC1 repeat expansion in two beagles with Lafora disease. *J Small Anim Pract*. 2016 Nov; 57(11):650–652
26. Chen X, Johnson GS, Schnabel RD et al. A neonatal encephalopathy with seizures in standard poodle dogs with a missense mutation in the canine ortholog of ATF2. *Neurogenetics*. 2008 Feb; 9(1): 41–49.

27. Yu Y, Hasegawa D, Chambers JK et al. Magnetic Resonance Imaging and Histopathologic Findings From a Standard Poodle With Neonatal Encephalopathy With Seizures. *Front Vet Sci*. 2020 Nov 10; 7:578936. doi: 10.3389/fvets.2020.578936. PMID: 33244473; PMCID: PMC7683776.
28. Shea A, De Risio L, Carruthers H et al. Clinical features and disease progression of L-2-hydroxyglutaric aciduria in 27 Staffordshire bull terriers. *Vet Rec*. 2016; 179(21):545.
29. Sanchez-Masian DF, Artuch R, Mascort J et al. L-2-hydroxyglutaric aciduria in two female Yorkshire terriers. *J Am Anim Hosp Assoc*. 2012 Sep–Oct; 48(5):366–371. doi: 10.5326/JAAHA-MS-5967. Epub 2012 Jul 27. PMID: 22843824.
30. Farias FH, Zeng R, Johnson GS et al. A L2HGDH initiator methionine codon mutation in a Yorkshire terrier with L-2-hydroxyglutaric aciduria. *BMC Vet Res*. 2012 Jul 26; 8:124. doi: 10.1186/1746-6148-8-124. PMID: 22834903; PMCID: PMC3461439.
31. Garosi LS, Penderis J, McConnell JF, Jakobs C. L-2-hydroxyglutaric aciduria in a West Highland white terrier. *Vet Rec*. 2005 Jan 29; 156(5):145–147. doi: 10.1136/vr.156.5.145. PMID: 15715007.
32. Ashwini A, D'Angelo A, Yamato O et al. Neuronal ceroid lipofuscinosis associated with an MFSD8 mutation in Chihuahuas. *Mol Genet Metab*. 2016 Aug; 118(4):326–332.
33. Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. *Neurosci Lett*. 2018 Feb 22; 667:27–39.
34. Kennerly EM, Idaghdour Y, Olby NJ et al. Pharmacogenetic association study of 30 genes with phenobarbital drug response in epileptic dogs. *Pharmacogenet Genomics*. 2009 Dec; 19(12):911–922.
35. Mealey KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr1 gene. *Pharmacogenetics*. 2001 Nov; 11(8):727–733
36. Alves L, Hülsmeyer V, Jaggy A et al. Polymorphisms in the ABCB1 gene in phenobarbital responsive and resistant idiopathic epileptic Border Collies. *J Vet Intern Med*. 2011 May–Jun; 25(3):484–489.
37. Mizukami K, Yabuki A, Chang HS et al. High frequency of a single nucleotide substitution (c.-6-180T>G) of the canine MDR1/ABCB1 gene associated with phenobarbital-resistant idiopathic epilepsy in Border Collie dogs. *Dis Markers*. 2013; 35(6):669–672.
38. Bell JS. Researcher responsibilities and genetic counseling for pure-bred dog populations. *Vet J*. 2011 Aug; 189(2):234–245.
39. Hazenfratz M, Taylor SM. Recurrent seizures in cats: Diagnostic approach - when is it idiopathic epilepsy? *J Feline Med Surg*. 2018 Sep; 20(9):811–823.
40. Kuwabara T, Hasegawa D, Ogawa F et al. A familial spontaneous epileptic feline strain: a novel model of idiopathic/genetic epilepsy. *Epilepsy Res*. 2010; 92:85–88.
41. Wahle AM, Brühschwein A, Matiasek K et al. Clinical characterization of epilepsy of unknown cause in cats. *J Vet Intern Med*. 2014 Jan-Feb; 28(1):182–188. doi: 10.1111/jvim.12250.
42. Ueno H, Yamato O, Sugiura T et al. GM1 gangliosidosis in a Japanese domestic cat: a new variant identified in Hokkaido, Japan. *J Vet Med Sci*. 2016 Jan; 78(1):91–95.

Feline Epilepsy

05

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The literature on feline seizure disorders is limited compared with the number of studies available on canine epilepsy. Therefore, there is often the tendency to extrapolate information from dogs to cats, similarly to what is done in other fields of veterinary medicine. Although this may be acceptable for some aspects of epilepsy, feline seizure disorders have several peculiar characteristics, which will be covered in this chapter.

PREVALENCE OF SEIZURE DISORDERS IN CATS

In a recent epidemiological study of recurrent seizure disorders in cats presented to primary care veterinary practices in the United Kingdom, the 1-year period prevalence was 0.16% (458/285,547). Cats with reactive seizures were not included, and recurrent seizure disorders were defined as at least two seizure events separated by at least 24 hours, an epilepsy diagnosis, or antiseizure drug (ASD) treatment recorded in the medical record. The prevalence of recurrent seizure disorders did not differ between crossbred cats and purebred cats.[1] In previous studies, the prevalence of seizures in referral populations of cats was reported to be 2.1% in Germany[2] and 3.5% in Austria.[3] Data on seizure prevalence in cats need to be interpreted considering that recognition of seizures in cats may be challenging due to the heterogenous semiology of the condition in this species and the fact that seizures may not be witnessed in cats that spend a considerable proportion of their time outdoors.

TERMINOLOGY

The consensus on epilepsy definition, classification and terminology published by the International Veterinary Epilepsy Task Force[4] is applicable to both cats and dogs (see *Terminology* section in Chapter 1).

Etiological classification of seizure disorders in cats

The etiological classification of seizure disorders in cats is very similar to that used for dogs (see Chapter 1, Fig. 1.5). Etiologies of seizure disorders in cats are listed in Table 5.1 in this chapter, and included in Boxes 1.2 and 1.3 in Chapter 1. There has been controversy on whether idiopathic epilepsy (IE) occurs in cats, and while IE—defined as a disease in its own right—does occur in cats, a genetic predisposition has not been confirmed in this species, other than in a feline research colony (see Chapter 4). In previously published studies on feline epilepsy, the term IE has been used interchangeably with epilepsy of unknown origin (EUO) or epilepsy of unknown cause (EUC) to indicate recurrent epileptic seizures with no evidence of structural epilepsy or metabolic disorders, and for which the underlying cause is therefore unknown.[2,5,6] The proportion of epileptic cats with IE (or EUO or EUC) has been reported as between 22-54%.[2,3,5,6] In a recent study including 188 cats with epileptic seizures and no interictal neurological signs, the MRI of the brain was unremarkable in 165 (88%).[7] It is important that the diagnosis of IE be based on a normal interictal clinical and neurological examination and on the absence of epileptogenic abnormalities after comprehensive diagnostic investigations (e.g., blood and urine tests, MRI of the brain and cerebrospinal fluid [CSF] analysis) (see Chapter 1 for additional details on IE definition and diagnostic criteria). The age at IE onset in cats is likely to be similar to that in dogs (i.e., 6 months–6 years). However, there is less evidence to support this age range in cats than there is in dogs and an upper age limit of 5 or 7 years has been suggested in different studies.[3,7]

It should be borne in mind that there is always a degree of uncertainty involved in the diagnosis of feline IE, as various disorders (such as postencephalitic and posttraumatic seizures in the absence of MRI signal changes) can be challenging to rule out.

DIAGNOSTIC APPROACH TO SEIZURE DISORDERS IN CATS

Due to the limited clinical applicability of electroencephalography (EEG) in veterinary medicine and more particularly in feline epileptology, it is essential to clinically establish whether the cat is experiencing an epileptic or a nonepileptic paroxysmal event. A detailed description and whenever possible a video recording of the seizure should be obtained and carefully reviewed. A detailed seizure disorder questionnaire (see Chapter 1, Fig. 1.3) can guide the practitioner in obtaining all the relevant clinical details. Being familiar with the clinical manifestations of feline epileptic seizures and nonepileptic paroxysmal events is very helpful to discriminate between the two disease groups.

In addition to the disorders that can mimic seizures and the discriminators described in Chapter 1, other feline-specific conditions should be considered. These include:

- Estrus-associated behavior, such as episodic vocalizations, lordosis, purring, and unprovoked aggression.

TABLE 5.1. Feline epilepsy classification (modified after Pakozdy et al., 2014[8]).

Main category	Subcategory	Possible etiology
Idiopathic epilepsy	Idiopathic	Recurrent epileptic seizures in which the nature of the underlying cause is as yet unknown following exclusion of structural epilepsy and reactive seizures

Structural epilepsy	Vascular	Hypertensive encephalopathy Feline ischemic encephalopathy Thromboembolic disorders Polycythemia Coagulopathy
	Inflammatory	Meningoencephalitis of unknown origin Cuterebriasis, dirofilariosis Rabies, pseudorabies Feline immunodeficiency virus Feline leukemia virus Feline infectious peritonitis Cryptococcosis, blastomycosis Voltage-gated potassium channel (VGKC)-associated limbic encephalitis Toxoplasmosis
	Traumatic	Head trauma
	Anomaly	Hydrocephalus Lissencephaly
	Neoplastic	Meningioma, lymphoma, glioma Hypophyseal tumor Metastatic neoplasia
	Degenerative	Hippocampal necrosis Storage disease
Reactive seizures	Metabolic	Hyperthyroidism Renal encephalopathy Thiamin deficiency Hepatic encephalopathy Hypoglycemia Hypocalcemia Electrolyte imbalance
	Toxic	Organophosphates, pyrethroids, Ethylene glycol
Probable symptomatic epilepsy	Post-traumatic, posthypoxic encephalopathy, postencephalytic epileptic seizures	

- Feline orofacial pain syndrome: acute behavioral signs of oral discomfort (e.g., exaggerated licking, chewing movements and pawing at the mouth, typically to one side only) and tongue mutilation, triggered

in many cases by mouth movements (in adult cats) and teeth eruption (in kittens).[9]

- Feline hyperesthesia syndrome: episodes of contraction of the cutaneous trunci muscle resulting in skin rippling over the lumbar area, excessive vocalization, overgrooming and sometimes also self-trauma to the tail.[10]

Feline orofacial pain syndrome (FOPS) and feline hyperesthesia syndrome (FHS) are considered maladaptive pain disorders.[11] Feline orofacial pain syndrome occurs most commonly in Burmese cats, and it has been proposed that it could be an inherited disorder of nociceptive trigeminal information processing. This syndrome can affect kittens at the time of permanent teeth eruption or adult cats of any age. Periodontal disease can be a predisposing factor for FOPS. Feline hyperesthesia syndrome is more common in Siamese, Burmese, Himalayan and Abyssinian cats, and clinical signs typically appear between 1 and 4 years of age. Anxiety and social stress can influence disease expression of both FOPS and FHS.[11] Therefore, addressing environmental stressors and needs is essential for successful management of these conditions, in combination with pharmacological treatment. Good dental care and treatment are required in adult cats with FOPS. Further details on FOPS and FHS can be found in a recent review article.[11]

A thorough clinical and neurological examination is the basis of the diagnostic investigation of cats presenting with a history of paroxysmal events. However, clinical assessment may sometimes be challenging to perform in cats that are anxious or aggressive. It is very important to dedicate sufficient time to making the cat comfortable and to be prepared to perform the examination in short sessions with breaks in between. The neurological signs consistent with forebrain disease are detailed in Box 1.1, Chapter 1. Even subtle signs such as behavioral changes at home or a menace response deficit may indicate structural forebrain disease.

The diagnostic investigations of seizure patients are presented in detail in Chapter 1.

TABLE 5.2. Epileptic and nonepileptic seizures (Modified after Pakozdy et al., 2014).

	Seizures	Important features

Epileptic seizures	Generalized convulsive epileptic seizures	Tonic-clonic seizures
	Focal epileptic seizures	Vocalisation, purring, abnormal head and/or leg movement, rapid running, (secondary generalization is possible)
	Temporal lobe seizures (special form of focal seizure)	Orofacial automatism (salivation, facial twitching, jawing, gagging, lip smacking) (Secondary generalization is possible)
	Feline audiogenic reflex seizures (FARS)	Myoclonus, frequently triggered by sound, usually in old cats
Non-epileptic seizures	Neuromuscular collapse	Exercise induced
	Cardiac syncope	Arrhythmia, other signs for heart disease possible
	Cervical pain	Evidence of cervical pain during examination
	Compulsive disorder	No impairment of consciousness during the seizure, no autonomic signs
	Estrus-associated behavior	Lordosis, purring, aggression
	Vestibular disorder	Nystagmus, head tilt, falling tendency during examination
	Increased intracranial pressure	No fast start and termination
	Feline orofacial pain syndrome (FOPS)	Acute orofacial discomfort, tongue mutilation
	Feline hyperesthesia syndrome (FHS)	Rolling skin in the lumbar area, increased cleaning behavior (may be epileptic)

As with general neurological patients, the diagnostic investigations of cats with seizures should include at least hematology and serum biochemistry tests. A urinalysis may be also beneficial, although the collection of urine is more challenging for cats than for dogs. Blood pressure testing is indicated in adult cats and anytime hypertension is suspected. Serological testing for infectious diseases should be considered,

depending on the local prevalence and the cat's lifestyle. However, serological testing can only confirm seroconversion and contact with the agent, but it cannot establish whether the infection has a role in the pathogenesis of epilepsy. Serological testing is therefore mainly useful if the results of the CSF analysis or MRI are suggestive of encephalitis or meningoencephalitis.

Whether a brain MRI and CSF analysis should be performed is a frequent issue in clinical practice. The decision to perform these procedures should consider not only the risk associated with general anesthesia and the relatively invasive procedure of CSF collection, but also their cost. The IVETF published its recommendation for the diagnostic evaluation of epileptic dogs,[12] which can also be used for cats. Different tier levels were defined for the diagnosis of IE (see Chapter 1, Box 1.4). An MRI scan and CSF analysis are suggested when the age at seizure onset is <6 months and >6 years, when interictal neurological signs are present, when status epilepticus (SE) or cluster seizures have occurred, and in case of ASD resistance. However, because IE in cats is not as well characterized as in dogs, an MRI of the brain may be advisable in any cat with recurrent seizures following exclusion of reactive seizure etiologies.

Some studies have attempted to differentiate clinically between IE and structural epilepsy, but in many cases this was not possible. Even when an abnormal neurological examination is suggestive of structural epilepsy, several limitations should be considered. First, when the clinical examination is performed during the postictal phase, transient abnormalities such as weakness, ataxia, compulsive walking, impaired vision or blindness, and behavioral changes may be present and not associated with structural brain disease. Secondly, structural cerebral disorders are not always associated with neurological deficits detectable upon clinical examination, especially if the lesion is small or in a location that makes it "clinically silent" (e.g., in the olfactory lobe and rostral frontal lobe). Thirdly, some neurological deficits may not be related to the epilepsy and may be caused by an independent condition.

In a multicenter retrospective study including 188 cats with a normal interictal neurological examination, a structural abnormality was identified on MRI as the cause of the seizure disorder in 9.4% (3/32) of cats aged 1 year or younger, in 5.4% (5/92) cats between 1 and 6 years of age, and in 23.1% (15/65) cats older than 6 years at seizure onset.[7] Congenital

malformations were the structural abnormality identified on MRI in cats aged 1 year or younger and neoplastic lesions were the predominant type of structural abnormality in cats older than 6 years at seizure onset. Statistical analyses showed that MRI abnormalities were more likely in cats older than 5 years at seizure onset, with the odds of a significant structural lesion increasing by 14% for each year of older age.[7] Ictal salivation, seizures occurring at rest and ictal rapid running were more frequently observed in cats with IE than in those with structural epilepsy in two studies.[3,13]

Several diagnostic procedures are now available and widely used to evaluate epileptic cats. Some of these diagnostic tools are very sophisticated, but it should be borne in mind that no diagnosis of epilepsy can be made without epileptic seizures. Whether a seizure is epileptic or not is established based on a clinical suspicion. There is no proven method that can differentiate between epileptic and nonepileptic seizures. Electroencephalography in cats (and in dogs) is rarely used in clinical practice for several reasons. There is no clear evidence that an interictal EEG can differentiate between an epileptic and a nonepileptic seizure. However, this may not be due to the EEG per se, because experimental studies with intracranial recording were able to record epileptic discharges in epileptic cats,[14,15] but rather to several circumstances that limit the diagnostic value of EEGs in clinical practice. For cats, sedation or even general anesthesia is necessary, but influences and likely reduces cerebral activity. Furthermore, the cat's brain is so small that a synchronization of 6 cm^2 of the cerebral cortex—which is necessary for a recordable interictal epileptic discharge—rarely occurs.[16]

Feline audiogenic reflex seizures

A unique epileptic clinical syndrome has been described in geriatric cats (median age, 15 years). Feline audiogenic reflex seizures (FARS) are characteristic myoclonic seizures usually elicited by a high-frequency sound such as crinkling of tin foil, a metal spoon dropping into a ceramic feeding bowl, tapping of glass, crinkling paper or plastic bags, tapping the computer keyboard or clicking the mouse, clinking of coins or keys and other types of sounds.[17,18] In the study that first characterized this condition, of the 96 cats included, 33% did not always develop seizures in association with these noises. Avoiding these sounds eliminated seizure occurrence in 75% of cats.[17] In some cats, spontaneous myoclonic jerks (20% of cats) and

generalized tonic-clonic seizures (8% of cats) occasionally occurred without any acoustic trigger. The youngest cat reported with FARS was 10 years old, while the median age at onset was 15 years in a population of 96 cats.[17] Many of these cats have several comorbidities, and, interestingly, many were deaf or had hearing impairment. The etiology of FARS is unclear. Their late onset suggests degenerative changes, but this aspect has not yet been investigated. Levetiracetam (LEV) seems to be much more effective than phenobarbital (PB) in cats with FARS. In a prospective, randomized, open-label trial including 57 cats (28 treated with LEV and 29 treated with PB), all LEV-treated cats improved (>50% reduction in seizure frequency) and about 50% became seizure-free, whereas seizure freedom was not achieved in any of the cats in the PB group and improved seizure control was also very rare (3%).[18]

Temporal lobe epilepsy in cats

There is growing evidence that temporal lobe epilepsy exists in cats, and due to its unique features, this type of epilepsy should receive specific consideration. The clinical manifestations of temporal lobe epilepsy were researched in depth experimentally starting in the 1950s. The temporal lobe structures (hippocampus, amygdala, temporal cortex) were stimulated electrically or chemically, and the clinical signs during stimulation of such structures were very consistent. Orofacial muscle activity is frequently present and includes not only hypersalivation and masticatory movement, but also lip smacking, facial twitching, gagging, and tongue movement. All these signs can be summarized as **orofacial automatism**.[19] Similarities in the sequential progression of these signs were observed, and resulted in a six-stage experimental system,[20] which can also be used clinically (Box 5.1). Knowledge of this system can increase the veterinarian's awareness and recognition of temporal lobe epileptic seizures in cats. The earlier stages are less pronounced, and some seizures do not progress to stage 6 (Videos 5.1 and 5.2).

BOX 5.1. Staging temporal lobe epileptic seizures in cats.

Stage 1	Attention, looking around, sniffing
Stage 2	Arrest (immobility and staring)
Stage 3	Hypersalivation, orofacial automatism, mydriasis, licking, lip

	smacking
Stage 4	Masticatory movement, facial twitching
Stage 5	Head turning, head nodding
Stage 6	Generalized tonic-clonic epileptic seizure

Neutered, 2.5-year-old male domestic shorthair cat with temporal lobe epilepsy in the “arrest phase” (stage 2). Note the immobility and staring.

Video 5.1.



Neutered, 3-year-old male domestic shorthair cat in stage 3 of a temporal lobe epileptic seizures. Note the hypersalivation, orofacial automatism, and mydriasis.

Video 5.2.



Feline temporal lobe epilepsy is a unique entity not only due to its specific clinical manifestations, but also because of its characteristic diagnostic imaging features. The MRI often shows changes in signal intensity in the hippocampal region,[21] which are frequently consistent with hippocampal necrosis on histopathology, but may also be caused by sclerosis, edema, inflammation or a combination thereof (Figs. 5.1a and b).[22]

The hippocampal formation has a special nature; it is susceptible to epileptic seizures and very epileptogenic itself.[23] This means that hippocampal necrosis can develop from different causes and can contribute to the maintenance of epilepsy. In clinical practice, the etiology of

hippocampal necrosis often remains unclear and the primary injury undetermined (Box 5.2).

The prognosis for temporal lobe epilepsy in cats has never been investigated systematically. It is likely that a general prognosis cannot be made due to the many possible causes and highly variable severity of the condition. A previous publication reported a fatal prognosis,[24] but this seems to be an oversimplification, and the real prognosis is likely to depend on many factors. The most important factors are:

- The primary (i.e., underlying) etiology.
- How promptly effective antiepileptic treatment can be started.
- How severe the epileptic seizures are.
- How severe the hippocampal pathology is.[25]

BOX 5.2. Etiology of hippocampal necrosis in cats (modified after Pakozdy et al., 2014).

Etiologic category	Specific disorders
Vascular	Hypoxia, ischemia, anesthesia induced
Inflammatory	LGI1 antibody related encephalitis
Toxic	Jodoxychinolin derivate, kainic acid, tungstic acid
Anomaly	Hippocampal malformation
Metabolic	Polycythemia
Unknown	Many cases
Neoplastic	Secondary to neoplasia

Anti-LGI1 antibody–related encephalitis

Anti-LGI1 encephalitis is an immune-mediated disease that attacks the hippocampus, among other structures.[26] Antibodies in this disorder are directed to the leucine-rich glioma-inactivated 1 (LGI1) region of the voltage-gated potassium channel (VGKC) complex. A very similar disease is known in human patients and a serological test has made the diagnosis possible worldwide in the last decade. Unfortunately, such a test is not available for cats in clinical practice, so the diagnosis cannot currently be confirmed by serology. Anti-LGI1 encephalitis in humans responds to immunosuppressive treatment and this also seems to be the case in cats. Consequently, in drug-resistant temporal lobe epilepsy, immunosuppressive

treatment should be considered. It should be emphasized that unremarkable CSF analysis does not rule out anti-LGI1 encephalitis, as it mainly activates the humoral immune system.[27] Interestingly, the MRI is also unremarkable in many cases, and mild hippocampal inflammation can be suspected based on MRI only in a minority of seropositive cats with limbic encephalitis (unpublished observation). Magnetic resonance imaging characteristics of normal and abnormal hippocampi are presented in Figs. 5.2 (normal hippocampi), 5.3 (hippocampal signal alteration without contrast enhancement) and 5.4 (hippocampal signal alteration with contrast enhancement).

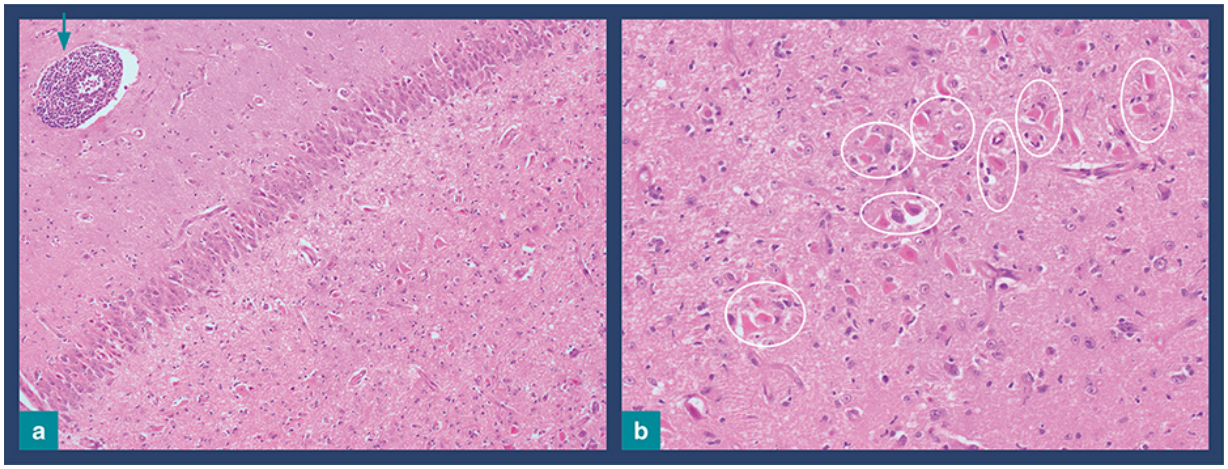


FIGURE 5.1. Degenerative hippocampal changes in a cat with limbic encephalitis. Mononuclear perivascular cuffing (arrow) and neuronal necrosis in the pyramidal and granular cell layer of the hippocampus (a). Hypereosinophilic neuronal necrosis of pyramidal cells, together with mild proliferation of microglial cells and swollen astrocytes (within the circles), which is likely the very early phase of transition to hippocampal sclerosis (b). Hematoxylin & eosin stain. Images courtesy of Andrea Klang.

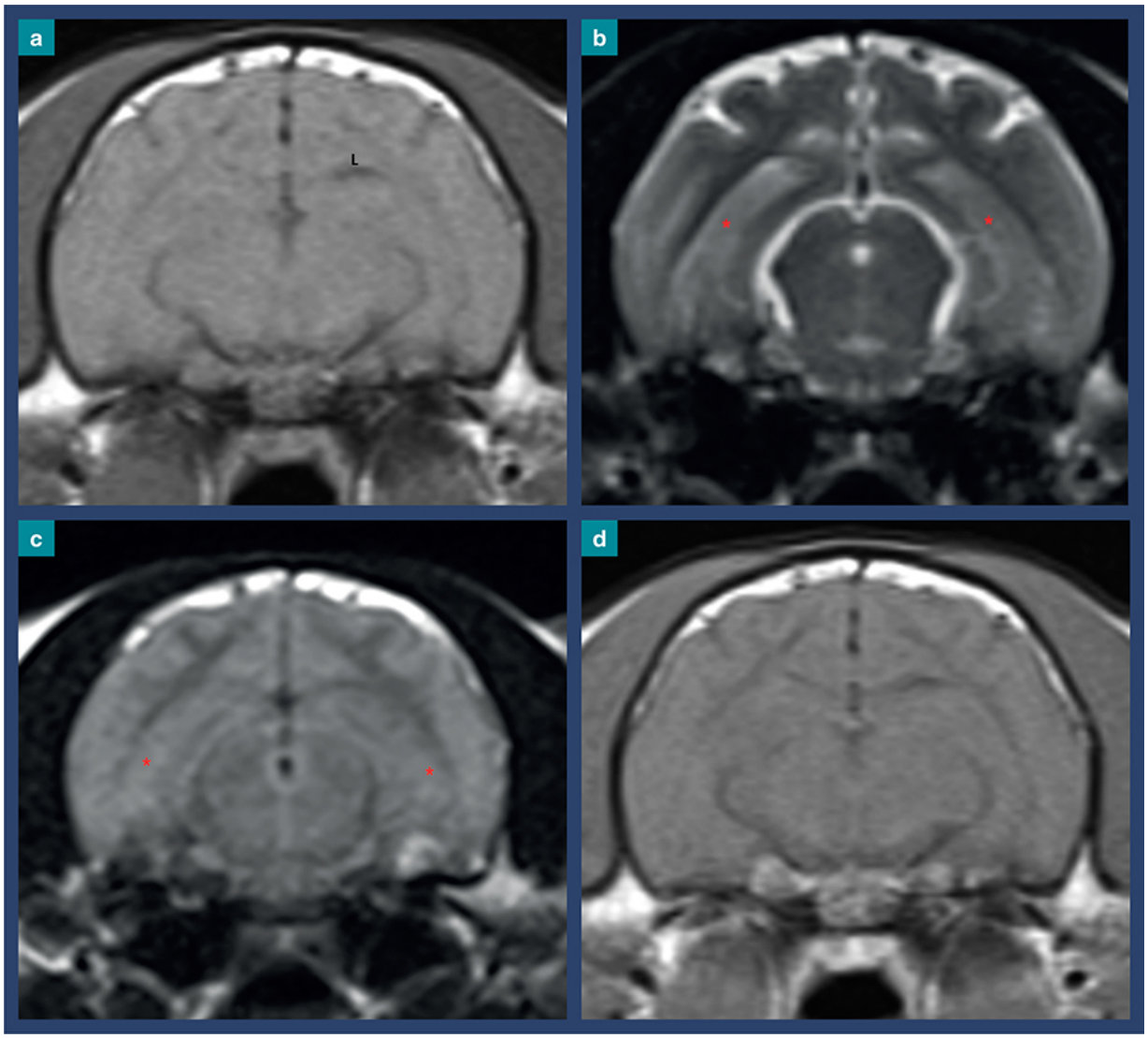


FIGURE 5.2. Transverse T1-weighted (TW1) (a), T2-weighted (TW2) (b), FLAIR (fluid attenuated inversion recovery) (c), and T1W postcontrast (d) magnetic resonance images of the normal feline brain at the level of the hippocampi. Note the mild asymmetry of the almost virtual lateral ventricles (the left [L] is slightly larger than the right one). The hippocampi are isointense to the cerebral grey matter in the T1W images (a) and subjectively slightly hyperintense (red stars) in the T2W and FLAIR images (b, c). There is no contrast enhancement (d). It is not possible to delineate the hippocampi accurately in the T1W images.

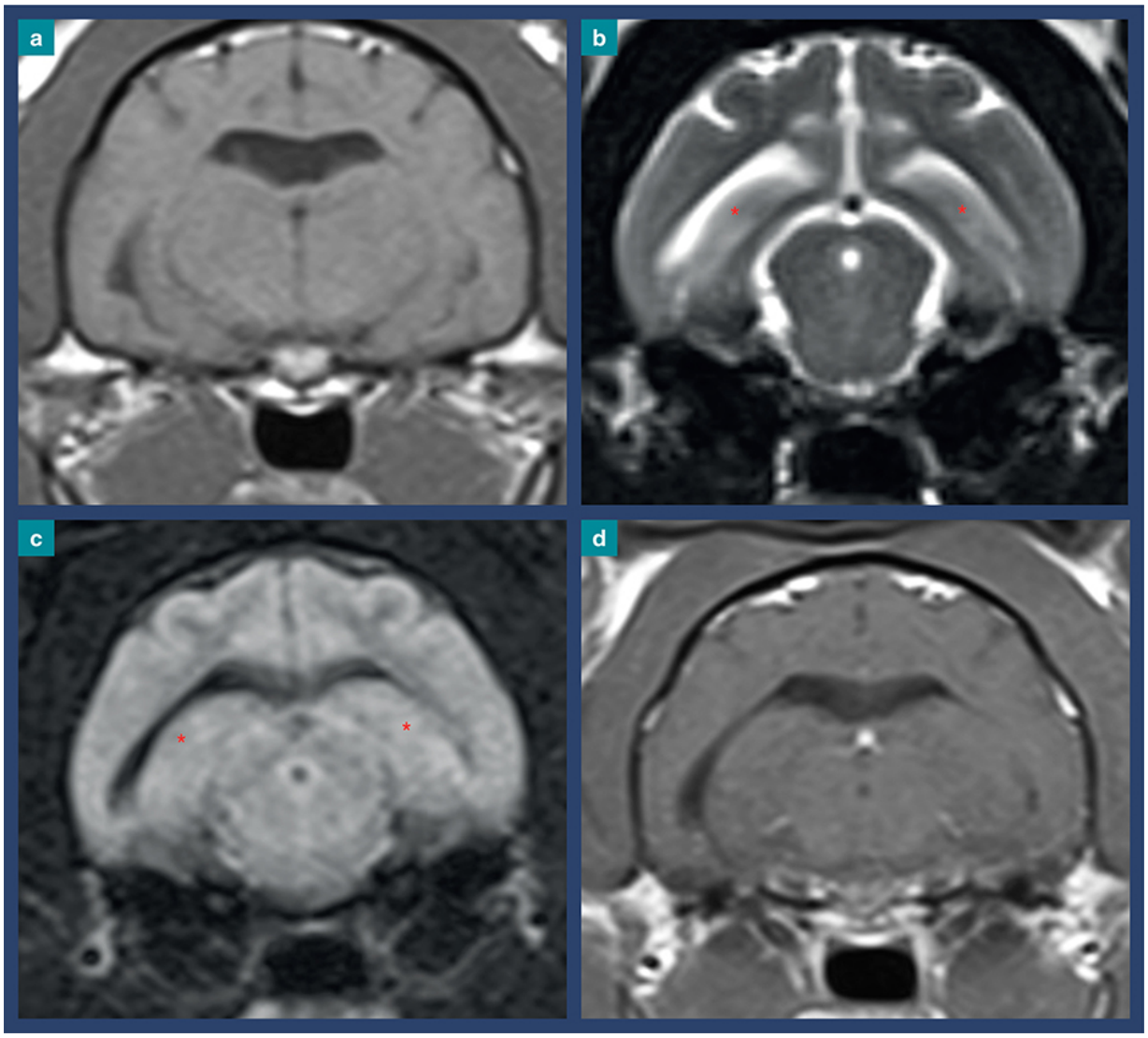


FIGURE 5.3. Transverse T1-weighted (TW1) (a), T2-weighted (TW2) (b), FLAIR (fluid attenuated inversion recovery) (c) and T1W postcontrast (d) magnetic resonance images of the feline brain at the level of the hippocampi with subtle abnormalities in the T2W and FLAIR images (red stars) (b, c). Note the slightly more pronounced hyperintensity of the hippocampi in b) and c) compared to Figs. 5.2b and 5.2c. The hippocampi are isointense to the cerebral gray matter in T1W (a) and do not contrast enhance in T1W postcontrast (d). It is not possible to delineate the hippocampi accurately in the T1W images.

ANTISEIZURE TREATMENT OF FELINE EPILEPSY

The aim of feline epilepsy treatment is to optimize the patient's quality of life by minimizing epileptic seizure occurrence and the adverse effects (AEs) of ASDs.

In cats with structural epilepsy, treatment of the underlying seizure etiology (whenever possible) is required in combination with an ASD.

In cats with IE, similarly to what has been recommended by the IVETF for canine IE,[28] ASD treatment should be initiated when the cat experiences at least one of the following:

- Two or more epileptic seizures within a 6-month period
- Status epilepticus or cluster seizures
- Worsening of epileptic seizure frequency/severity/duration
- Severe or prolonged (i.e., >24 hours) postictal signs

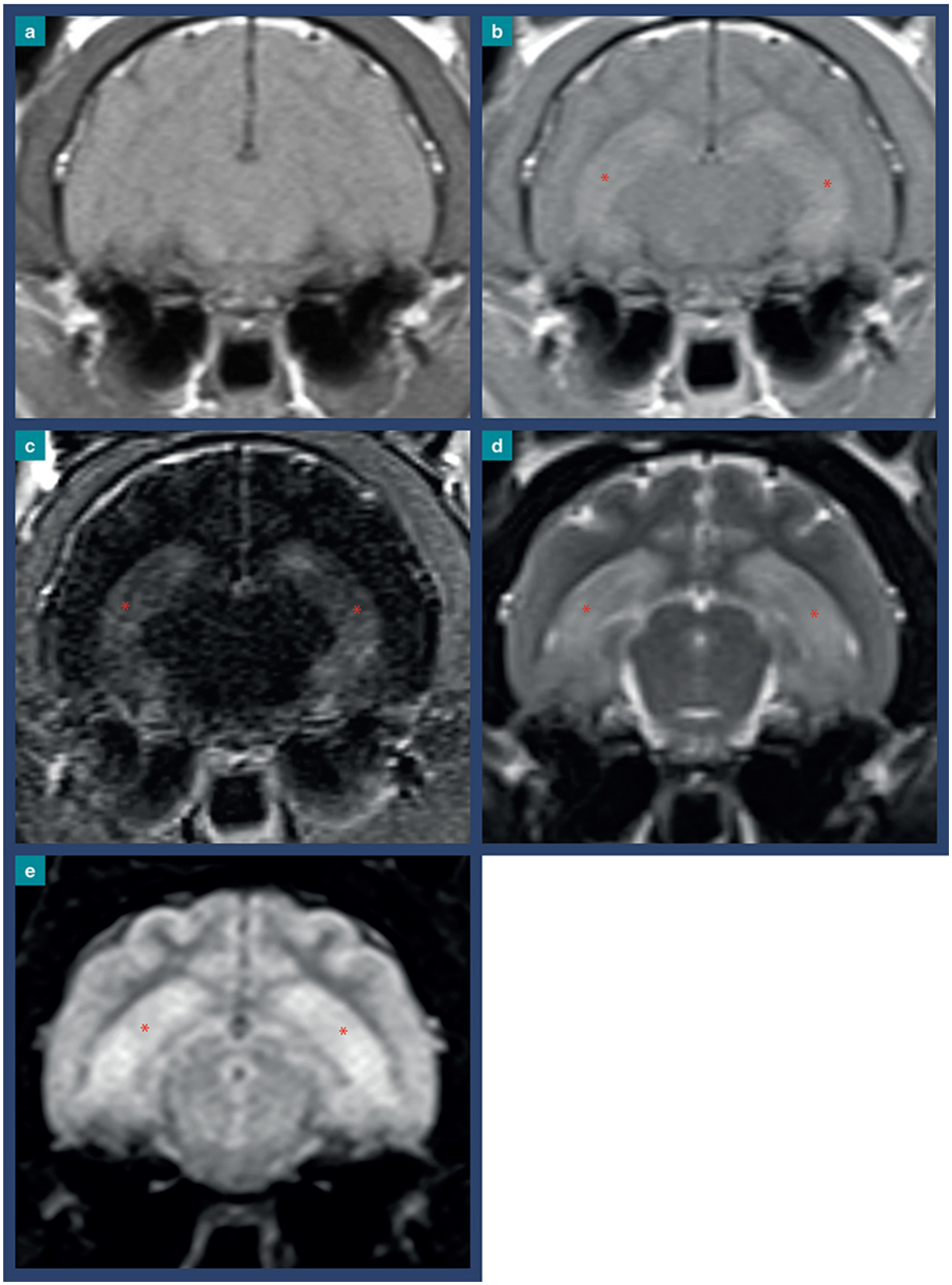

a
b
c
d
e

FIGURE 5.4. Transverse T1-weighted (TW1) (a), T1W postcontrast (b), subtraction (c), T2-weighted (TW2) (d) and FLAIR (fluid attenuated inversion recovery) (e) magnetic resonance images of the feline brain at the level of the hippocampi. Note the marked hyperintensity of the hippocampi (red stars) in the T2W and FLAIR images (d and e) and the marked, slightly heterogenous contrast enhancement in both hippocampi (red stars) (b and c). It is not possible to delineate the hippocampi accurately in the nonenhanced T1W images.

The ASDs that have been shown to be safe and efficacious in cats are limited to PB and LEV (see chapters 9, 10 and 12). A systematic review of the efficacy and safety of ASDs in feline epilepsy concluded that PB might currently be considered the first-line ASD for feline epilepsy (other than FARS).[18] Details on PB efficacy are presented in Chapter 10, in the section *Phenobarbital efficacy in cats*. The recommended initial PB dose in cats is 1.5–2.5 mg/kg every 12 hours. The PB oral dosage is subsequently tailored to the individual based on an accurate epileptic seizure diary, serum PB concentration monitoring, as well as occurrence and degree of AEs (see Chapter 10 for further details on PB).

Despite the relatively limited published data on the efficacy of LEV in feline epilepsy, LEV use in cats is increasing due to its safety and tolerability and the limited ASD options in cats. Results from a prospective, randomized, open-label study suggest that LEV is effective and superior to PB in the treatment of FARS.[19] Levetiracetam has also been evaluated as adjunctive therapy to PB in cats with presumed IE. In this open-label, noncomparative trial, most cats were reported to have a >50% reduction in seizure frequency with LEV administration.[30] The recommended initial dose for LEV as monotherapy or adjunctive therapy in cats is 20 mg/kg every 8 hours (for the immediate-release formulation) (see Chapter 12 for further details on LEV).

OUTCOME OF FELINE EPILEPSY

The outcome of epilepsy in cats depends on the underlying etiology and treatment. The results obtained in the different studies conducted to date are difficult to compare due to differences in inclusion criteria and outcome measures. One study suggested that initiating ASD treatment without delay may have a positive impact on long-term seizure control.[31] Cats with IE (or EUC) are likely to respond to ASD treatment. Several studies have

documented that more than 50% of cats with epilepsy achieve long-term seizure-freedom with the administration of an ASD (most commonly PB).[5,6,31–34] These studies were all retrospective and used different inclusion criteria. The number of included cats in all but two studies were under 50, so further scientific investigation is warranted. However, in the authors' experience, seizure-freedom in cats with IE (or EUC) treated with ASD is much more common than in dogs with IE.

There is limited published data on survival in feline epilepsy. In a retrospective study, which included 81 cats with seizures (18 with IE, 38 with structural epilepsy and 25 with reactive seizures), the one-year survival rate was 73% in the 18 cats with IE, which was significantly higher than the survival rate of cats with structural epilepsy or reactive seizures (35%; 22 of 63 cats).[5] In a retrospective study including 76 cats with EUC presenting over a 15-year period, the median survival time was 4.9 years.[6] This is markedly higher than in studies of canine epilepsy, where in a multi-breed study, the median survival time was 2.3 years.[35] Survival of cats with EUC was significantly associated with age at time of seizure onset and seizure remission (defined as seizure freedom of at least one-year duration with or without ASD therapy). Euthanasia that was motivated by circumstances directly associated with seizures was reported in 21% of cats.[6]

The quality of life of cats receiving treatment for epilepsy has not yet been assessed in a systematic manner, but in the authors' clinical experience, most cats tolerate the long-term ASD treatment well and have a good to excellent quality of life. The aspects that affect quality of life in dogs (see Chapter 3) are likely to also apply to feline epilepsy.

TAKE-HOME MESSAGES

- ✔ It is important that the diagnosis of IE in cats be based on a normal interictal neurological examination and on the absence of epileptogenic abnormalities after comprehensive diagnostic investigations.
- ✔ Being familiar with the clinical manifestations of feline epileptic seizures and nonepileptic paroxysmal events (e.g., estrus-associated behavior, feline orofacial pain syndrome and feline hyperesthesia

syndrome) is very helpful to discriminate between an epileptic or reactive seizure or another nonepileptic paroxysmal event.

- ✔ Feline audiogenic reflex seizures (FARS) are characteristic myoclonic seizures usually elicited by a high-frequency sound. Treatment with LEV seems to be much more effective than PB in cats with FARS.
- ✔ There is growing evidence that temporal lobe epilepsy exists in cats, and due to its unique features, this type of epilepsy should receive specific consideration. Orofacial muscle activity is frequently present and includes not only hypersalivation and masticatory movement, but also lip smacking, facial twitching, gagging, and tongue movement.
- ✔ Anti-LGI1 encephalitis in humans responds to immunosuppressive treatment and this also seems to be the case in cats. In drug-resistant temporal lobe epilepsy, immunosuppressive treatment should therefore be considered.
- ✔ The ASDs that have been shown to be safe and efficacious in cats are limited to PB and LEV. A systematic review of the efficacy and safety of ASDs in feline epilepsy concluded that PB might currently be considered the first-line ASD for feline epilepsy (other than FARS).
  - ✔ The recommended initial PB dose in cats is 1.5–2.5 mg/kg every 12 hours. Treatment should then be tailored to the individual.
  - ✔ The recommended initial dose for LEV as monotherapy or adjunctive therapy in cats is 20 mg/kg every 8 hours.
- ✔ In the authors' experience, seizure-freedom in cats with IE (or EUC) treated with ASD is much more common than in dogs with IE. Most cats tolerate the long-term ASD treatment well and have a good to excellent quality of life.

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REFERENCES

1. O'Neill, DG Phillipps SA, Egan JR et al. Epidemiology of recurrent seizure disorders and epilepsy in cats under primary veterinary care in the United Kingdom. *J Vet Intern Med*. 2020;34: 2582–2594. https://doi.org/10.1111/jvim.15881
2. Schriefl S, Steinberg TA, Matiasek K et al. Etiologic classification of seizures, signalment, clinical signs and outcome in cats with seizure disorders: 91 cases (2000–2004). *J Am Vet Med Assoc*. 2008; 233:1591–1597.
3. Pakozdy A, Sarchachi Ali A, Leschnik M et al. Clinical comparison of primary versus secondary epilepsy in 125 cats. *J Feline Med Surg*. 2010; 12:910–916.
4. Berendt M, Farquhar RG, Mandigers PJJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11:182
5. Wahle AM, Bruhschwein A, Matiasek K et al. Clinical characterization of epilepsy of unknown cause in cats. *J Vet Intern Med*. 2014; 28:182–188
6. Szelecsenyi AC, Giger U, Golini L et al. Survival in 76 cats with epilepsy of unknown cause: a retrospective study. *Vet Rec*. 2017;181(18): 479.
7. Raimondi F, Shihab N, Gutierrez-Quintana R et al. Magnetic resonance imaging findings in epileptic cats with a normal interictal neurological examination: 188 cases. *Vet Rec*. 2017;180(25): 610. doi: 10.1136/vr.104142.
8. Pakozdy A, Halasz P, Klang A. Epilepsy in cats: Theory and practice. *J Vet Int Med*. 2014; 28:255–263.
9. Rusbridge C, Heath S, Gunn-Moore DA et al. Feline orofacial pain syndrome (FOPS): a retrospective study of 113 cases. *J Feline Med Surg*. 2010; 12:498–508.
10. Amengual Batle P, Rusbridge C, Nuttall T et al. Feline hyperaesthesia syndrome with self-trauma to the tail: retrospective study of seven cases and proposal for an integrated multidisciplinary diagnostic approach. *J Feline Med Surg*. 2019; 2:178–185.
11. Rusbridge C. Neurobehavioral disorders: the corticolimbic system in health and disease. *Vet Clin North Am Small Anim Pract*. 2020, 50:1157–1181.
12. De Risio L, Bhatti S, Muñana K et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015;11:148.
13. Stanciu GD, Packer RMA, Pakozdy A et al. Clinical reasoning in feline epilepsy: Which combination of clinical information is useful? *Vet J*. 2017; 225:9–12.
14. Shouse MN, Siegel JM, Wu MF et al. Mechanisms of seizure suppression during rapid-eye-movement (REM) sleep in cats. *Brain Res*. 1989; 505(2):271–282.
15. Mizoguchi S, Hasegawa D, Kuwabara T et al. Magnetic resonance volumetry of the hippocampus in familial spontaneous epileptic cats. *Epilepsy Res*. 2014; 108(10):1940–1944. doi: 10.1016/j.eplepsyres.2014.09.009.
16. Tao JX, Ray A, Hawes-Ebersole A, Ebersole JS. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia*. 2005; 46(5):669–676.
17. Lowrie M, Bessant C, Harvey RJ et al. Audiogenic reflex seizures in cats. *J Feline Med Surg*. 2016; 18(4):328–336.
18. Lowrie M, Thomson S, Bessant C et al. Levetiracetam in the management of feline audiogenic reflex seizures: a randomised, controlled, open-label study. *J Feline Med Surg*. 2017;

19(2):200–206.

19. KITZ S, THALHAMMER JG, GLANTSCHNIGG U et al. Feline temporal lobe epilepsy: review of the experimental literature. *J Vet Intern Med*. 2017; (31):3633–640.
20. SATO M. Hippocampal seizure and secondary epileptogenesis in the "kindled" cat preparations. *Psychiatry Clin Neurosci*. 1975; 29:239–250.
21. CLASSEN AC, KNEISSL S, LANG, J et al. Magnetic resonance features of the feline hippocampus in epileptic and non-epileptic cats: a blinded, retrospective, multi-observer study. *BMC Vet Res*. 2016; 12(1):165.
22. WAGNER E, ROSATI M, MOLIN J et al. Hippocampal sclerosis in feline epilepsy. *Brain Pathol*. 2014; 24:607–619.
23. GIBBS FA, GIBBS EL. The convulsion threshold of various parts of the cat's brain. *Arch Neurol Psychiatr (Chicago)*. 1936; 35:109–116.
24. FATZER R, GANDINI G, JAGGY A et al. Necrosis of hippocampus and piriform lobe in 38 domestic cats with seizures. A retrospective study on clinical and pathologic findings. *J Vet Intern Med*. 2000; 14:100–104.
25. PAKOZDY A, GRUBER A, KNEISSL S et al. Complex partial cluster seizures in cats with orofacial involvement. *J Feline Med Surg*. 2011; 13:687–693.
26. PAKOZDY A, HALASZ P, KLANG A et al. Suspected limbic encephalitis and seizure in cats associated with voltage-gated potassium channel (VGKC) complex antibody. *J Vet Intern Med*. 2013; 27:212–214.
27. KLANG A, SCHMIDT P, KNEISSL S et al. IgG and complement deposition and neuronal loss in cats and humans with epilepsy and voltage-gated potassium channel complex antibodies. *J Neuropathol Exp Neurol*. 2014; 73(5): 403–413.
28. BHATTI SF, DE RISIO L, MUÑANA K et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015; 11:176.
29. CHARALAMBOUS M, PAKOZDY A, BHATTI SFM, VOLK HA. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14(1):64.
30. BAILEY KS, DEWEY CW, BOOTHE DM et al. Levetiracetam as an adjunct to phenobarbital treatment in cats with suspected idiopathic epilepsy. *J Am Vet Med Assoc*. 2008; 232(6):867–72.
31. PAKOZDY A, SARCHAHI AA, LESCHNIK M et al. Treatment and long-term follow-up of cats with suspected primary epilepsy. *J Feline Med Surg*. 2013; 15:267–273.
32. SCHWARTZ-PORSCHE D, KAISER E. Feline epilepsy. In: INDERI RJ (ed.). *Problems in Veterinary Medicine. Vol 1*. Philadelphia: Lippincott; 1989. pp.628–649.
33. BARNES HL, CHRISMAN CL, MARIANI CL, et al. Clinical signs, underlying cause, and outcome in cats with seizures: 17 cases (1997-2002). *J Am Vet Med Assoc*. 2004; 225:1723-1726.
34. FINNERTY KE, BARNES HL, MERCIER MN et al. Evaluation of therapeutic phenobarbital concentrations and application of a classification system for seizures in cats: 30 cases (2004-2013). *J Am Vet Med Assoc*. 2014; 244:195–199.
35. BERENDT M, GREDAL H, ERSBOLL AK et al. Premature death, risk factors, and life patterns in dogs with Epilepsy. *J Vet Intern Med.* 2007; 21:754–759.

Advanced Diagnostic Imaging in Epilepsy

06

Daisuke Hasegawa

Magnetic resonance imaging (MRI) plays an important role in the diagnosis of seizure disorders in dogs and cats. Diagnostic imaging of a veterinary patient with epilepsy mainly involves MRI of the brain, which can serve two purposes:

1. To exclude or detect an underlying structural lesion as the cause of the seizures.
2. To investigate the pathophysiological (functional) mechanisms of epilepsy in the brain and identify epileptogenic foci.

When imaging is performed as part of the diagnostic evaluation of epilepsy, conventional MRI sequences are used (see Chapter 1). These techniques allow any macroscopic morphological or pathological abnormalities to be examined in detail and is therefore also referred to as structural MRI. When the purpose is to evaluate the functional and pathophysiological aspects of epilepsy, the advanced imaging techniques or modalities used include diffusion or perfusion MRI, MR spectroscopy (MRS), blood oxygen level–dependent (BOLD) functional MRI (fMRI), positron emission computed tomography (PET) and single photon emission computed tomography (SPECT), which are considered functional neuroimaging. In veterinary medicine, these advanced imaging techniques are used to a limited extent in clinical practice, with most of their application confined to the research setting at the present time.

BOX 6.1. Abbreviations for the imaging terminology used in this chapter.

ADC: apparent diffusion coefficient

ASL: arterial spin labeling (perfusion MRI)

BOLD: blood oxygen level dependent (fMRI)

CBF: cerebral blood flow

CBV: cerebral blood volume

CE: contrast enhanced/enhancement (e.g., CE-T1W)

CHESS: chemical shift selective (fat suppression sequence)

Cho: choline (MRS metabolite)

Cre: creatinine (MRS metabolite)

DCE: dynamic contrast enhancement (perfusion-weighted imaging)

DMN: default mode network

DSC: dynamic susceptibility contrast (perfusion-weighted imaging)

DTI: diffusion tensor imaging/image

DWI: diffusion-weighted imaging/image

FA: fractional anisotropy

FDG: [18F] fluoro-2-deoxyglucose (radiotracer for PET)

FID: free induction decay

FLAIR: fluid-attenuated inversion recovery (imaging/image)

fMRI: (BOLD) functional MRI

Gd: gadolinium

GRE: gradient echo (sequence) = T2*W or T2* GRE

MPG: motion probing gradient

MRS: magnetic resonance spectroscopy

MTT: mean transit time (a parameter of perfusion imaging)

NAA: N-acetylasparate (MRS metabolite)

NMR: nuclear magnetic resonance (phenomenon)

PET: positron emission computed tomography

PDW: proton density-weighted (imaging)

PWI: perfusion weighted imaging

rCBF: relative cerebral blood flow (a parameter of perfusion-weighted imaging)

rCBV: relative cerebral blood volume (a parameter of perfusion-weighted imaging)

ROI: region of interest

rs-fMRI: resting-state fMRI

SNR: signal-to-noise ratio

SPECT: single-photon emission computed tomography

STIR: short-T1 (or tau) inversion recovery (imaging/image)

SWI: susceptibility weighted imaging

T: Tesla (unit of magnetic strength; 1T = 10,000 Gauss)

TTP: time to peak (a parameter of perfusion imaging)

T1: longitudinal relaxation time

T1W: T1-weighted (imaging/image)

T2: transverse relaxation time

T2W: T2-weighted (imaging/image)

T2*: T2*(star) or effective T2; exponential time constant of free induction decay (FID)

T2*W: T2*(star)-weighted (imaging/image) = GRE or T2* GRE

VBM: voxel-based morphometry

2D: two-dimensional

3D: three-dimensional

^{99m}**Tc**: technetium-99m (radiotracer for SPECT)

This chapter describes the basic information needed to interpret conventional/structural MRI as a diagnostic tool in a dog or cat with epilepsy and provides an overview of the use of functional imaging in epilepsy. In addition, the characteristic MRI findings in structural epilepsy will be described. A list of abbreviations for the imaging terminology used in the chapter are included in Box 6.1.

CONVENTIONAL MRI

Overview of MRI and magnetic field strength

Magnetic resonance imaging is a diagnostic imaging modality that utilizes the nuclear magnetic resonance (NMR) phenomenon generated by a proton (^{1}H) in a strong magnetic field. The principles of NMR and the data processing that produces the MR image are complicated and beyond the scope of this chapter. The reader is referred to any standard MRI textbook for further information on this. Numerous imaging techniques called pulse sequences (such as spin-echo, fast spin-echo, gradient echo, and echo-planar imaging) and image contrast weighting options (such as T1-weighted [T1W], T2-weighted [T2W], T2*-weighted [T2*W], fluid-attenuated inversion recovery [FLAIR] and diffusion-weighted imaging [DWI]) exist, and the field continues to advance and develop day by day.

In general, image quality (spatial resolution and signal-to-noise ratio [SNR]), scanning speed, and the availability of various imaging techniques depends on the strength of the magnetostatic field of the machine. The magnetostatic field strength of MRI machines commonly used in clinical practice is classified as low-field (0.2–1.0 Tesla [T]) permanent magnet type and high-field (1.5–3.0 T) superconducting magnet type. The ultra-high-field MRI of over 3.0 T is used primarily for research purposes. Due to its comparatively low cost, low-field MRI is commonplace in veterinary clinical practice. However, it has several disadvantages, which include:

1. A difficulty in obtaining high-resolution three-dimensional (3D) data, T2*W and/or other advanced MRI sequences of sufficient diagnostic quality.
2. The need for a large slice thickness (3.0–4.0 mm) for sufficient SNR.
3. Longer scanning times, which require prolonged anesthesia.

On the other hand, although high-field MRI requires a specialized shielded room and is associated with high installation and operational costs, it produces high quality images and many advanced sequences can be obtained relatively quickly. It is also adequate for many research applications. Therefore, high-field MRI is typically available in secondary or tertiary care facilities such as neurology referral centers and academic teaching hospitals.

Basic knowledge for interpretation of conventional MRI

Conventional MRI typically involves the acquisition of the following sequences: T1W with and without paramagnetic contrast administration (also known as a contrast enhanced [CE] study), T2W, FLAIR, and T2*W (also known as gradient echo; GRE) imaging. Other sequences may also be performed, including proton density–weighted (PDW) imaging, and fat suppression sequences (short T1 inversion recovery [STIR] for low-field MRI, chemical shift selective [CHESS] for high-field MRI). DWI is also used routinely in high-field MRI, and is described in the *Diffusion MRI* section. Images are assessed for changes in symmetry and signal intensity. Signal intensities of normal canine and feline adult brain structures and common pathological lesions are summarized in Tables 6.1 and 6.2, respectively. As a general rule, the reference intensity on brain MRI, i.e., isointensity, is the signal intensity (color) of normal gray matter regardless of the sequence. Accordingly, "hyperintensity" ("high signal intensity") denotes an appearance that is brighter than normal gray matter, while "hypointensity" ("low signal intensity") refers to an appearance that is darker than normal gray matter.

T1-weighted imaging and contrast enhanced studies

T1W (including T1W-based sequences such as T1-FLAIR and T1-inversion recovery [IR]) is routinely obtained in MRI studies of the brain regardless of magnetic field strength. In general, a tissue can be characterized by different relaxation times: T1 and T2. Tissues with a shorter T1 (longitudinal relaxation time), such as lipids and fat, appear hyperintense (bright) on T1W images, while water (including cerebrospinal fluid [CSF]), which has a long T1 value, appears hypointense (dark). Imaging characteristics are easy to understand if one remembers that T1W images evaluate the distribution of lipids and fats in the tissue. Therefore, white matter, which is composed of bundles of myelin (i.e., lipids), is more hyperintense (whiter) than gray matter, which contains neuronal cells (i.e., water-rich). Aside from lipids and fat, the only other hyperintense structure in the normal brain is the posterior lobe of the pituitary, which contains vasopressin. Paramagnetic substances, such as ferric (Fe^{3+}) or manganese (Mn^{2+}) ions, and melanin appear hyperintense on T1W images, and can be seen in certain lesions such as hemorrhage (methemoglobin, hemosiderin)

(Fig. 6.1), hepatic encephalopathy (Mn^{2+} accumulation in the basal nuclei)[1] and melanoma.

TABLE 6.1. Signal intensities of normal brain structures on conventional MRI.

	T1W	CE (Gd)	T2W	FLAIR	T2*W
Gray matter[1]	iso	none	iso	iso	iso
White matter	mild hyper	none	mild hypo	mild hypo	mild hypo
CSF (ventricle)	hypo	none	hyper	hypo	mild hyper
Choroid plexus	slight hypo – iso	moderate	slight hypo – iso	iso - slight hyper	slight hypo – iso
Thalamus-medulla	slight hyper – mild hyper	none	slight hypo – mild hypo	slight hypo – mild hypo	slight hypo – iso
Pituitary–anterior lobe	iso	moderate	iso	iso	iso
Pituitary–posterior lobe[2]	mod hyper	slight	slight hypo	slight hypo	iso – slight hypo
CN II–IV, VI–XII	iso	none	slight hypo – mild hypo	slight hypo – mild hypo	(iso – mild hypo)[3]
CN V	iso	mild	slight hypo – mild hypo	slight hypo – mild hypo	(iso – mild hypo)[3]
Vessels	(hypo – iso)[4]	mild – moderate	signal void	signal void	signal void
Meninges[5]	(iso)	(slight hyper – mild hyper)	(slight hypo – iso)	(slight hypo – iso)	(iso – slight hyper)
Bone (cortex)[6]	signal void	none	signal void	signal void	signal void
Bone (fatty marrow)[7]	hyper	none – slight	mod hyper	mod hyper	mod hypo – hypo
Muscle	slight hypo – iso	slight	hypo	hypo	slight hypo
Fat (subcutaneous and intermuscular)	hyper	none – slight	mod hyper	mod hyper	mod hypo – slight hypo

CSF, cerebrospinal fluid, CN, cranial nerve; Iso, isointense (= gray matter); slight hypo, slightly hypointense; mild hypo, mildly hypointense; mod hypo, moderately hypointense; hypo, hypointense (= CSF on T1W, hemosiderin on T2W); signal void, no signal (= cortical bone, air); slight hyper, slightly hyperintense; mild hyper, mildly hyperintense; mod hyper, moderately hyperintense; hyper, hyperintense (= fat on T1W, CSF on T2W)

[1] Normal gray matter is the reference signal intensity in the brain

[2] In cats and small breed dogs, the pituitary gland is occasionally affected by a susceptibility artifact due to air within the nasopharyngeal meatus and may not be identified on T2*W images.

[3] CNs may not be identified on T2*W due to susceptibility artifacts caused by bone and air within the tympanic bulla.

[4] Vessels are rarely seen as hypo- to isointense on T1W.

[5] Meninges are generally undetectable.

[6] Cortical bone has no ^1H, and creates no signal on MRI

[7] The diploe of the skull normally contains fatty marrow

Gadolinium (Gd^{3+})-based agents such as gadopentetate meglumine (Gd-DTPA), gadoteridol (Gd-HP-DO3A) and gadodiamide hydrate (Gd-DTPA-BMA), are commonly used for MRI diagnostic investigations. These Gd-based contrast mediums effectively shorten T1 values (and also have a slight effect on T2 shortening); therefore, contrast enhanced (CE) (or postcontrast) studies with MRI are primarily performed on T1W imaging.

In general, CE-T1W images are acquired by performing T1W imaging following intravenous administration of 0.1–0.2 mmol/kg of a Gd agent. In the normal brain, the brain parenchyma is not enhanced due to the presence of an intact blood–brain barrier (BBB), whereas the choroid plexus, pituitary, trigeminal nerves and meninges enhance on CE-T1W.

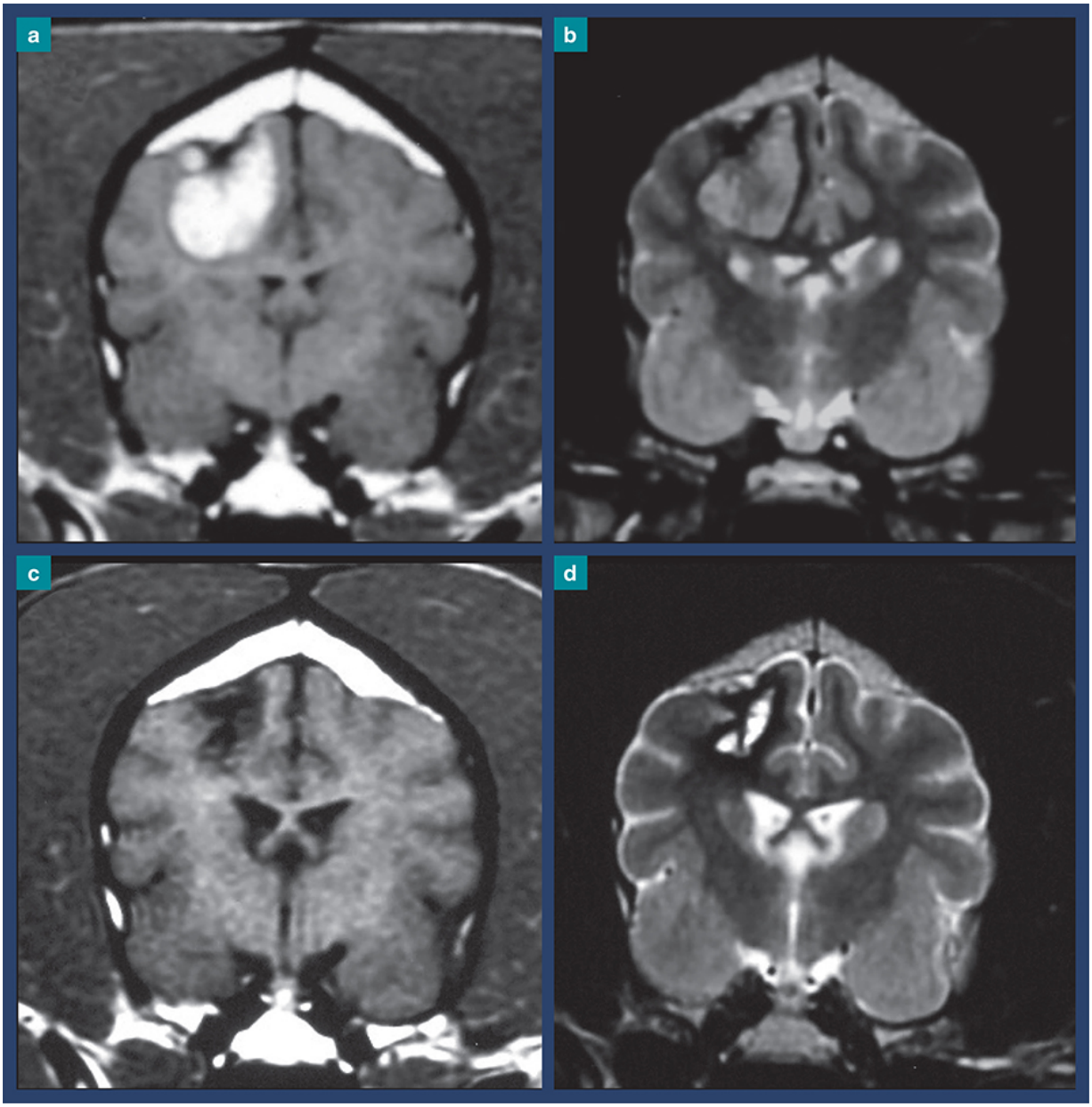


FIGURE 6.1. MR images from a 5-year-old, neutered male Shetland Sheepdog with left hemiparesis that had developed acutely 1 month previously, and then gradually improved. The dog had also experienced two convulsive seizures within a month and had been prescribed zonisamide. A large mass lesion appearing hyperintense on T1W (a) and hyperintense with a rim of low intensity on T2W (b) was observed in the right frontoparietal cortex, with minimum mass effect and no perilesional

edema. The lesion was observed to be mildly hyperdense on CT. The signal pattern of this lesion is consistent with subacute hemorrhage (hematoma). Three months later (4 months after the onset), the dog displayed only reduced proprioception in the left thoracic and pelvic limbs, and the lesion was noted to be reduced in size, hypointense on T1W (c) and hyperintense surrounded by a hypointense capsule on T2W (d). (Images obtained with a 1.5T scanner.)

T2-weighted imaging and fluid-attenuated inversion recovery imaging

T2W imaging is also routinely obtained regardless of the field strength. Tissues with longer T2 (transverse relaxation time), such as fluid (water) appear hyperintense (high signal intensity, bright) on T2W images, while tissues with short T2 values such as white matter and meninges appear hypointense (low signal intensity, dark). T2W images evaluate the distribution or content of water in the tissue. Therefore, the highest signal in the brain is CSF. Gray matter, comprised of neuronal cells (i.e., water-rich), has a higher signal intensity (bright) than the white matter that is comprised of bundles of axons (i.e., low in water). Note that fat also appears hyperintense on T2W, although it is less bright than CSF.

Fluid-attenuated inversion recovery (FLAIR or T2-FLAIR) is a T2W-based image in which the signal intensity of water, i.e., CSF is suppressed. Therefore, interpretation of FLAIR images is almost the same as T2W, except that CSF and other free fluid is dark. FLAIR is useful to detect or distinguish hyperintense lesions around or within the CSF-filled ventricular system. In addition, only normal CSF is suppressed on FLAIR images, and therefore, abnormal CSF such as with severe pleocytosis or marked elevations in protein (i.e., central nervous system form of feline infectious peritonitis [CNS-FIP]) is incompletely suppressed and remains gray in color.[2]

T2*-weighted imaging (hemosiderin and calcification sensitivity sequences)

T2*W imaging is obtained with gradient echo (or gradient recalled echo, GRE) pulse sequences. A GRE sequence image is based on the principle of free induction decay (FID) that is seen in a homogenous magnetic field in the absence of any magnetic gradients. In reality, magnetic susceptibility differences exist between tissues, and GRE is very sensitive to magnetic field heterogeneity, also known as magnetic susceptibility effects (please refer to a general MRI textbook for details on T2*, FID and GRE). T2*W

imaging is available on high-field MRI machines. In general, a low-field machine (usually open-MRI) has difficulty maintaining a homogenous field, resulting in low sensitivity for T2* decay.

Based on the magnetic susceptibility of iron in hemoglobin, T2*W imaging is sensitive to the presence of hemorrhage. On T2*W images, hemorrhage is visualized as a signal void (markedly hypointense) area, regardless of the oxygenated state of hemoglobin. It is important to note that the area seen on imaging is larger than the actual size of the lesion, due to the susceptibility artifact caused by iron (Fig. 6.2). In addition, T2*W images are easily affected by the presence of air (due to its heterogenous magnetic field), so that areas surrounding the frontal sinus and tympanic bulla have a low signal intensity, or are "blacked out".[3]

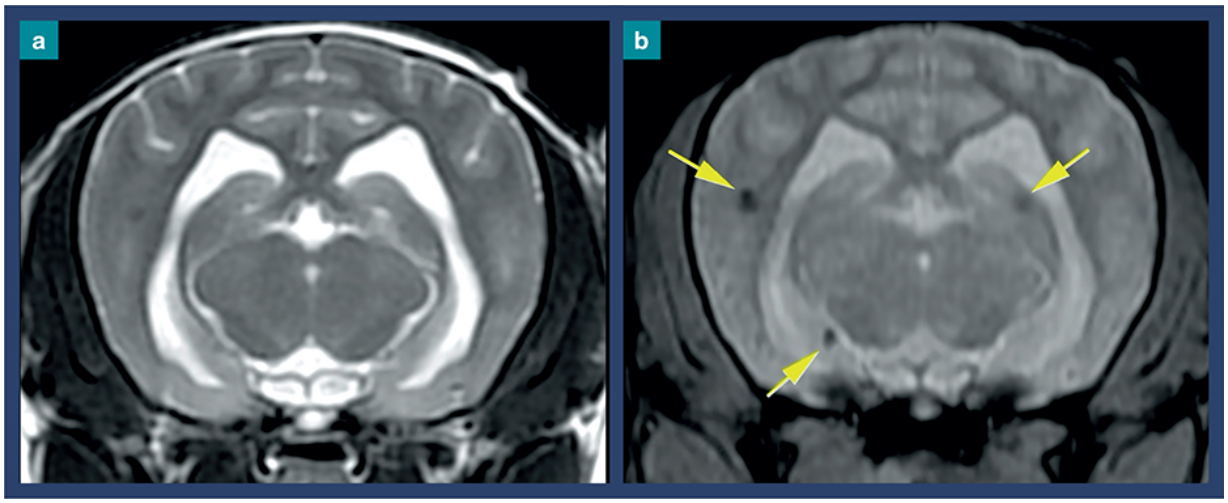


FIGURE 6.2. T2W (a) and T2*W (b) transverse images at the level of the hippocampus in a 13-year-old, female neutered Chihuahua with a recent onset of epileptic seizures. Multiple hypointense, round to oval, small lesions (arrows) suggesting microhemorrhages are visible on the T2*W image, while they are not evident on the T2W image. Note that the microhemorrhages are visible in both hippocampi. Courtesy of CAMIC, co. Ltd. (Images obtained with a 3T scanner.)

Susceptibility-weight imaging (SWI) is another imaging sequence to detect hemorrhage. SWI is acquired with GRE, BOLD, and flow (velocity)-compensation techniques, and consequently is only available with high-field MRI. SWI reveals not only hemorrhage or iron, but also is very sensitive for imaging venous blood. In a retrospective study comparing the ability of SWI and T2*W sequences to detect venous structures and signal void lesions in dogs with intracranial disease using 1.5 T MRI, SWI was

significantly superior to T2*W in detecting vessels and hemorrhage, leading the researchers to recommend the addition of SWI to standard protocols.[4]

Interpretation of conventional MRI with T1W, T2W/FLAIR and CE-T1W

Signal patterns

Signal patterns of common lesions are summarized in Table 6.2.

- The most frequently encountered pathological pattern on MRI of the brain is an iso- to hypointensity on T1W and hyperintensity on T2W/FLAIR (Fig. 6.3). This pattern occurs in lesions with a high water content (water-rich), such as edema, inflammation, infarction, many tumors, and necrosis. If these lesions are accompanied by breakdown of the BBB, the lesion will enhance on CE-T1W (Fig. 6.3).
- A mass with a lower water content, such as a solid meningioma, or a highly vascularized mass, such as an inflammatory granuloma (i.e., granulomatous meningoencephalomyelitis) or histiocytic sarcoma, often appears iso- to hyperintense on T1W, iso- to hypointense on T2W/FLAIR, with mild to strong enhancement on CE-T1W.
- A fully necrotic lesion that has been replaced with CSF or interstitial fluid will appear markedly hypointense on T1W, hyperintense on T2W and hypointense on FLAIR. Such a pattern would be observed in a chronic infarction, necrotizing encephalitis (NE), chronic cortical laminar necrosis, and chronic seizure-induced changes.
- The signal patterns of a cystic lesion depend on the nature of its fluid contents.
  - If it contains CSF or fluid that is similar in cellularity and protein content to CSF, as is seen with arachnoid cyst/diverticula or large (extratumoral) cystic meningiomas, the signal pattern will be the same as CSF. Such a cyst often has a well-circumscribed border, but its integument (wall) is usually unrecognized on conventional MRI and does not enhance.
  - If the content has high cellularity and/or high protein concentration, such as an abscess or otitis media, the signal pattern is typically iso- to hyperintense on both T1W and T2W/FLAIR. However, the degree of signal intensity apparent on each sequence varies depending on the pathological stage or its water content. The integument of an abscess or inflammatory cyst is often hypertrophied and markedly enhanced

on CE-T1W. If the content of a cyst is secretory fluid (e.g., intratumoral cyst) or an effusion, includes subtle hemorrhage, or is in the process of necrosis, then its signal pattern will be complex, but usually appears diffusely hypointense (but to a lesser degree than CSF) on T1W, iso- to mild hyperintense on T2W and incompletely suppresses on FLAIR.

- Hemorrhagic lesions show various patterns depending on the time course (state of hemoglobin or iron) of the bleeding event.
  - Hyperacute (0–12 hours): oxyhemoglobin (Fe^{2+}) is isointense on both T1W and T2W images.
  - Acute (1–3 days): deoxyhemoglobin (Fe^{2+}) is isointense on T1W and hypointense on T2W images.
  - Subacute (3 days–few months): methemoglobin (Fe^{3+}) is hyperintense on T1W and hypointense on T2W images (see Figs. 6.1a and 6.1b).
  - Chronic (>2 weeks, or margin of lesion): hemosiderin is isointense on T1W and hypointense on T2W images (see Figs. 6.1c and 6.1d).

When hemorrhage occurs within the ventricular system, the signal of CSF within the ventricle becomes cloudy on each sequence in the acute phase, but in the chronic phase, clots (appearing isointense on T1W and hypointense on T2W) can settle to the bottom of the ventricle or become trapped within the foramen of the ventricular system.

However, in high-field MRI, hemorrhage is also detected by hemosiderin- and calcification-sensitive sequences such as T2*W or SWI regardless of the stage, as described above.

TABLE 6.2. Signal intensities of pathological lesions on conventional MRI.

	T1W	CE (Gd)	T2W	FLAIR	T2*W
Cytotoxic edema[1]	iso – slight hypo	none	iso – slight hyper	iso – slight hyper	iso – slight hyper
Vasogenic/interstitial edema	slight hypo – mod hypo	none – slight	slight hyper – mod hyper	slight hyper – mod hyper	slight hyper – mild hyper
Necrosis (malacia)	mod hypo – hypo	none[2]	mod hyper – hyper	mild hypo – hypo	slight hyper – mild hyper
Gliosis	iso – slight hypo	none	slight hyper – mod hyper	slight hyper – mod hyper	iso – slight hyper
Hyperacute hemorrhage	iso	slight – moderate	iso	iso	mod hypo – hypo
Acute hemorrhage[3]	iso	slight – moderate	slight hypo – mod hypo	slight hypo – mod hypo	mod hypo – hypo
Subacute hemorrhage[4]	slight hyper – mod hyper	slight – moderate	slight hypo – hypo	slight hypo – hypo	mod hypo – hypo
Chronic hemorrhage[5]	slight hypo – slight hyper	slight – moderate	mod hypo – hypo	mod hypo – hypo	mod hypo – hypo
Abscess[6]	slight hypo – mod hyper	slight – moderate	mild hypo – mod hyper[6]	iso – mod hyper	iso – slight hyper
Inflammatory	mild hypo – slight hyper	none – mild	slight hyper – mod hyper	slight hyper – mod hyper	slight hyper – mild hyper
Granuloma (GME)	slight hypo – slight hyper	slight – marked	mod hypo – mod hyper[7]	mod hypo – mod hyper	mod hypo to mild hyper
Meningioma	mild hypo – slight hyper	slight – marked[8]	mild hypo – mod hyper	mild hypo – mod hyper	mild hypo – slight hyper
Glioma (astrocytoma and oligodendroglioma)	iso – mod hypo	none – moderate[9]	slight hyper – mod hyper	slight hyper – mod hyper	slight hyper – mild hyper
Choroid plexus tumor	mild hypo – iso	moderate – marked	slight hyper – mod hyper	slight hyper – mod hyper	iso – slight hyper

Iso, isointense (= gray matter); slight hypo, slightly hypointense; mild hypo, mildly hypointense; mod hypo, moderately hypointense; hypo, hypointense (= cerebrospinal fluid on T1W, hemosiderin on T2W); slight hyper, slightly hyperintense; mild hyper, mildly hyperintense; mod hyper, moderately hyperintense; hyper, hyperintense (= fat on T1W, CSF on T2W)

[1] Cytotoxic edema is DWI hyperintense, with low signal on ADC.

[2] The margin of a necrotic lesion can enhance.

[3] Signal characteristics are due to deoxyhemoglobin (Fe^{2+}); seen 1–3 days after a hemorrhage.

[4] Signal characteristics are due to methemoglobin (Fe^{3+}); seen 3 days to 2–3 months after a hemorrhage.

[5] Signal characteristics are due to hemosiderin; seen >2 weeks after a hemorrhage.

[6] Ring enhancement is observed, with the abscess capsule usually hypointense on T2W, FLAIR, and T2*W.

[7] Signal intensity on T2W is variable depending on the site.

[8] Meningiomas often have a dural tail sign on CE; ring enhancement in meningiomas does not suggest malignancy.

[9] Contrast enhancement is more common in malignant gliomas and is typically heterogenous or ring enhancing.

Morphological changes and typical abnormal findings on brain MRI

The brain is a symmetric structure; therefore, the easiest way to identify abnormalities is to look for asymmetry in anatomical structures or signal intensity, e.g., unilateral hippocampal atrophy. However, it is important to always be aware that there are interbreed and interindividual differences and/or breed- (or species-) specific findings. For example, asymmetry of the

lateral ventricles is common in small breeds, and the shape and position of the olfactory lobes are different between brachycephalic and dolichocephalic breeds. Furthermore, it is important to be aware that certain conditions appear as symmetric or bilateral abnormalities without apparent signal changes, such as generalized brain atrophy associated with cognitive dysfunction, lissencephaly, and midline defects such as agenesis of the corpus callosum and quadrigeminal arachnoid diverticula. The primary structural abnormalities related to epilepsy are described in the section on structural epilepsy. Common abnormal findings, and the terms used to describe these abnormalities, are detailed below.

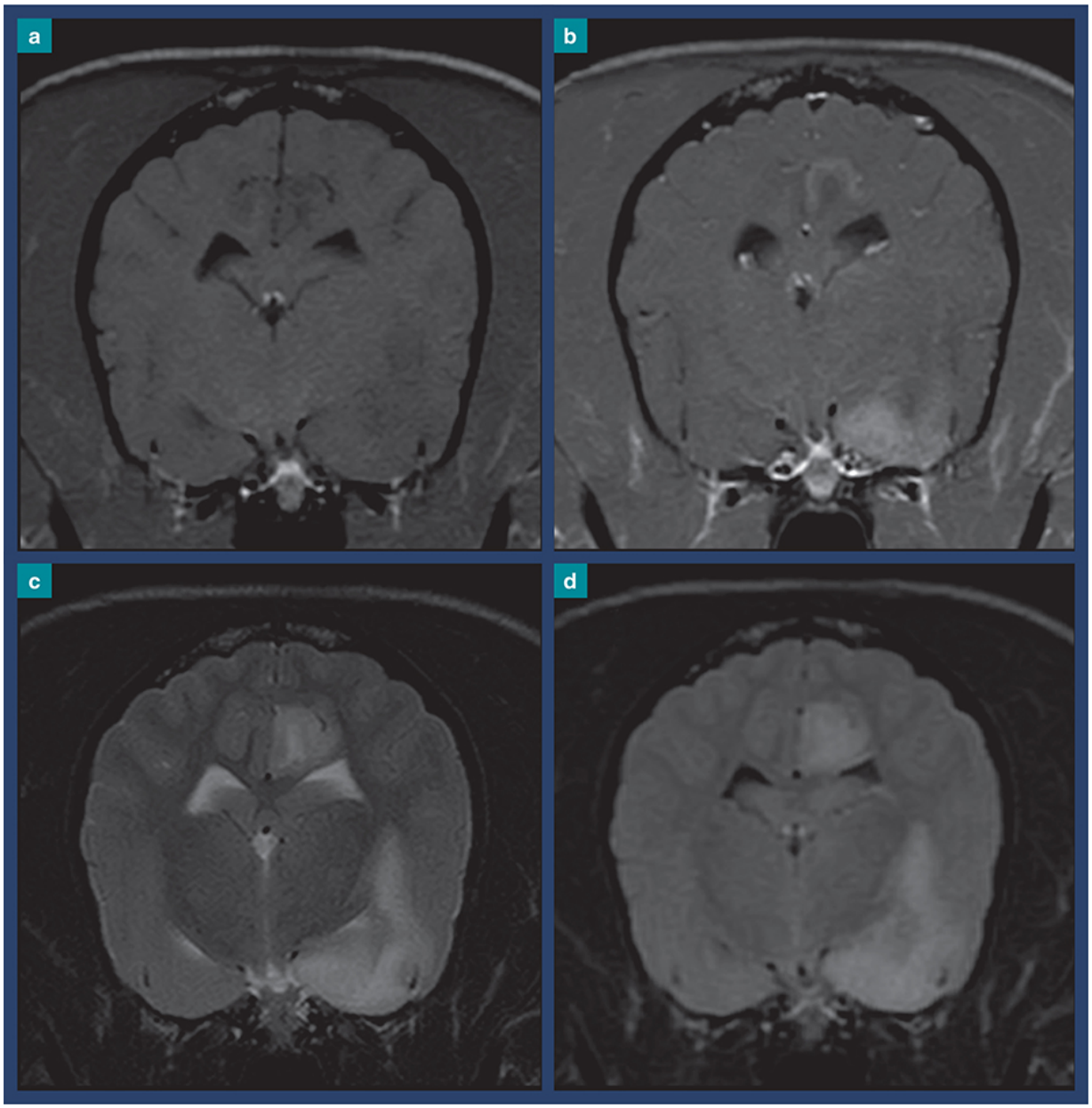


FIGURE 6.3. MR images from a 3-year-old, male Beagle with idiopathic epilepsy (diagnosed at 1 year of age and treated with zonisamide) that developed sustained nonconvulsive status epilepticus of more than 8 hours in duration. A lesion is present in the left cingulate gyrus and piriform lobe including the amygdala, that appears mildly hypointense on T1W (a), hyperintense on T2W (c) and FLAIR (d) with partial contrast enhancement on CE-T1W (b) and slight mass effect. The signal pattern of the lesion is consistent with focal edema due to prolonged seizure activity, and the lesion was attributed to seizure-induced changes. Contrast enhancement in this case is thought to suggest focal impairment of the blood–brain barrier. (Images obtained with a 1.5T scanner.)

- **Edema.** Brain edema refers to an increased water content in the brain parenchyma, which can be focal or generalized, and is further classified

as cytotoxic, vasogenic, or interstitial edema.

- Cytotoxic edema (increased intracellular water) is observed in the acute phase of ischemia/infarction (hypoxia), hypoglycemia, and with severe seizure activity (hypermetabolism). It typically does not manifest as signal changes on conventional MRI but can be detected by DWI (see section on DWI).
- Vasogenic edema (increased water in the extracellular space) is observed in the subacute/chronic phase of the abovementioned pathology (i.e., secondary to cytotoxic edema), in the peritumoral area (due to direct or indirect compression of peritumoral vessels), and in inflammatory lesions (encephalitis), and appears as focal or diffuse hypointensity on T1W and hyperintensity on T2W/FLAIR with structural swelling (see Fig. 6.3).
- Interstitial edema is characterized by CSF leakage into the periventricular white matter via the ependymal layer of the ventricles due to increased intraventricular pressure, as is observed in obstructive hydrocephalus. Interstitial edema is identified as a periventricular (along the rim of the ventricles) hyperintense line on FLAIR images. Note that this periventricular T2W/FLAIR hyperintensity due to interstitial edema must be distinguished from leukoaraiosis observed in older animals.

- **Mass effect.** A space-occupying extra-axial mass lesion (e.g., a meningioma [Fig. 6.4] or abscess), an intra-axial mass lesion (e.g, a glioma), or an area of swelling or enlargement (e.g., focal edema [see Fig. 6.3] or inflammation) causes the surrounding brain tissue to be compressed by the lesion and displaced from its normal position. This shifting of normal brain structures by the mass lesion is referred to as "mass effect". Midline shift is a type of mass effect, in which a unilateral lesion compresses the ipsilateral hemisphere and shifts the midline to the opposite side (see Fig. 6.4a). The final form of mass effect is brain herniation, which includes subfalcian (cingulate), transtentorial, and foramen magnum herniation (see Fig. 6.4b). Mass effect is considered a sign of increased intracranial pressure.
- **Increased intracranial pressure (ICP)** (or intracranial hypertension [ICH]). Various pathologies can increase ICP. Typical MRI findings of increased ICP include a mass effect with or without brain herniation, narrowing of the cisterns and subarachnoid space resulting in

undefinable sulci (sulci effacement) and fissures (Figs. 6.4 and 6.5), and focal or diffuse parenchymal T2W/FLAIR hyperintensity (perilesional/vasogenic edema) that results in blurring of the gray-white matter definition. Additional findings such as rounding or enlargement of the ventricular system, decreased size or area of the interthalamic adhesion (third ventricular compression), and periventricular hyperintensity on T2W/FLAIR (interstitial edema) are occasionally observed (Fig. 6.5).[5,6]

- **Dural tail sign.** A dural tail sign is seen on contrast-enhanced images (CE-T1W) as partially hypertrophied meninges adjacent to a mass located on the brain surface, which gradually regain their normal thickness. A dural tail sign is often seen with meningiomas (Fig. 6.4d), but it is not specific for this type of brain tumor. Histiocytic sarcomas, gliomas, lymphoma, abscesses or cystic lesions that are located on the brain surface have the potential to be associated with a dural tail sign.
- **Ring (or peripheral/marginal) enhancement.** Ring enhancement is used to describe a mass, cyst or other focal lesion with a peripherally enhanced portion and a centrally unenhanced portion on CE-T1W images (Fig. 6.4d). If associated with a tumor, the peripherally enhanced portion is the tumor parenchyma, while the centrally unenhanced portion is thought to be necrosis or fluid accumulation. The presence of ring enhancement increases the possibility of malignancy in gliomas, but this does not apply to other tumor types.

Volumetry and voxel-based morphometry

The computational postprocessing of structural MRI is useful to obtain an objective and statistical analysis of morphological changes. For example, hippocampal volume is often evaluated with this technique. To measure hippocampal volume from conventional MRI data, the outline of the hippocampus must be traced manually as the region of interest (ROI) in each slice and each side, and the volume (mm^3) is then calculated by summing up the areas obtained (mm^2) from each slice and multiplying it by the sum of slice thickness and slice gap (mm). The accuracy of volumetry depends on the spatial resolution of images, especially the slice thickness and slice gap. Therefore, it is recommended that volumetric studies be performed with a data set acquired with thin slice thickness, i.e., high-field MRI, although it is possible to perform these studies in low-field MRI.

Because the data set of a routine two-dimensional (2D) sequence has a small number of slices (e.g., the hippocampus appears on 5–6 slices of the data with 2.5 mm slice thickness and 0.5 mm slice gap), the ROI method is comparatively easy to perform; however, the results are less accurate than with three-dimensional (3D) data with a 1.0 mm slice thickness without a slice gap. On the other hand, the ROI method using 3D data is more challenging and time consuming (e.g., the hippocampus appears on 15–18 slices). Therefore, in some studies of hippocampal volumetry using 3D (or 2D) data, semiautomatic ROI tracing based on specific software has been used (Fig. 6.6).[7–9] Even when using 3D data and/or semiautomatic ROI tracing, human error or variations in tracing the boundary of the hippocampus can still affect results. Therefore, results of volumetry should be interpreted cautiously, especially when comparing different studies. The approximate unilateral hippocampal volume in normal (nonepileptic) adult dogs has been estimated as 0.50–0.65 cm^3,[8–12] and the mean unilateral hippocampal volume in normal cats (calculated from only 8 domestic shorthair cats) is estimated at 0.23 cm^3.[7]

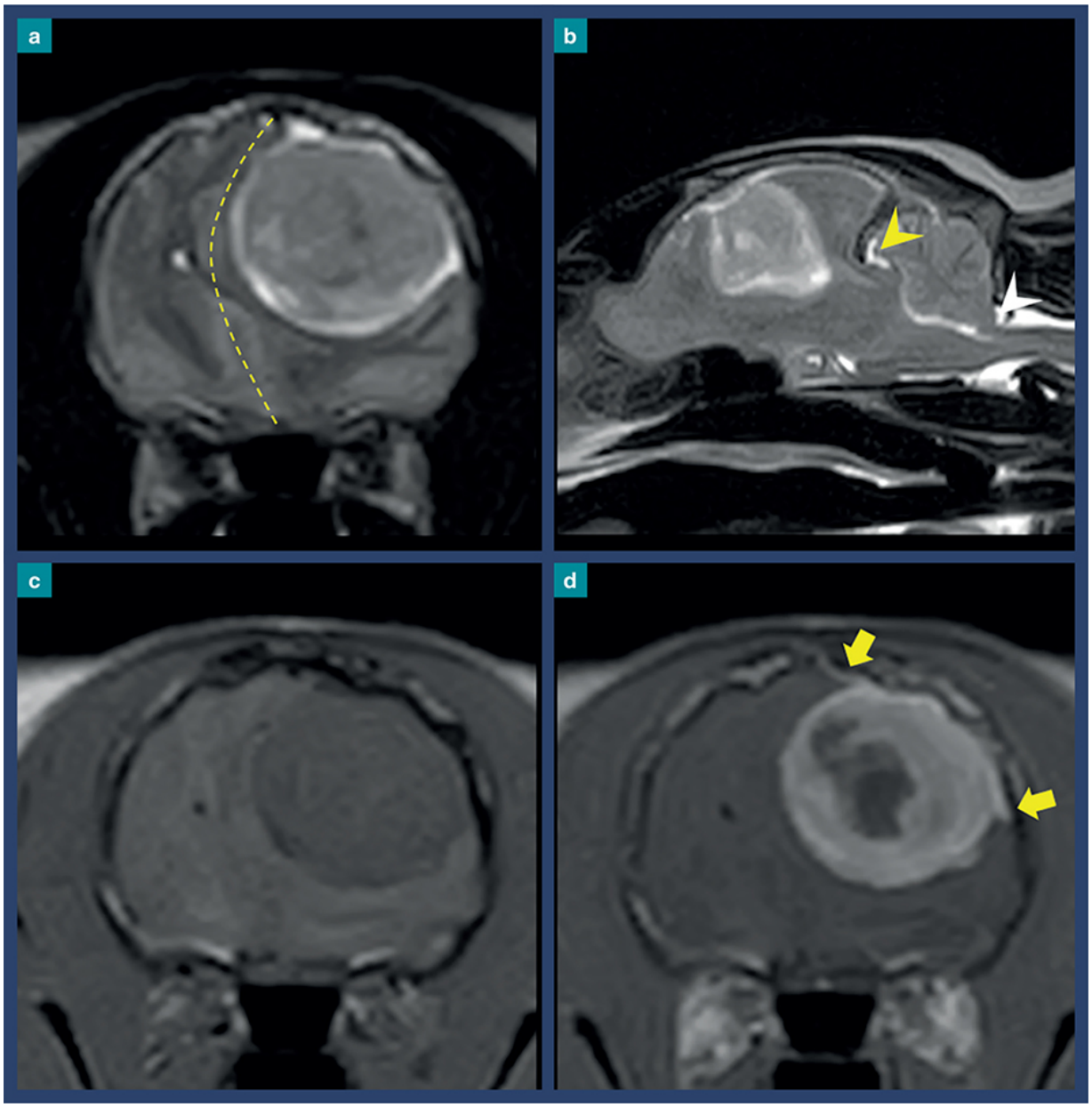


FIGURE 6.4. MR images from a 14-year-old, neutered male American Shorthair cat with obtundation, left circling with ataxia, and a single epileptic seizure. A large extra-axial mass lesion in the left parietotemporal region, which appears heterogeneously hypo- to hyperintense on T2W (a, b), hypointense on T1W (c), and ring-enhancing on CE-T1W (d) with a dural tail sign (d, arrows). A mass effect is seen as a midline shift on the transverse images (a, dotted line), and transtentorial herniation (b, yellow arrowhead) and incomplete foramen magnum herniation (b, white arrowhead) on the parasagittal T2W image. Narrowing of the superficial subarachnoid space and cisterns, leading to decreased conspicuity of the sulci, was also observed and is indicative of increased intracranial pressure. Perilesional edema was not evident, even though the mass was large enough to induce herniation, suggesting that the mass was very slow growing and less invasive in nature. The mass was surgically removed and confirmed to be a benign (transitional) meningioma histologically. The center of the lesion that did not contrast enhance on CE-T1W was intratumoral necrosis containing malacic tissue. (Images obtained with a 0.3T scanner.)

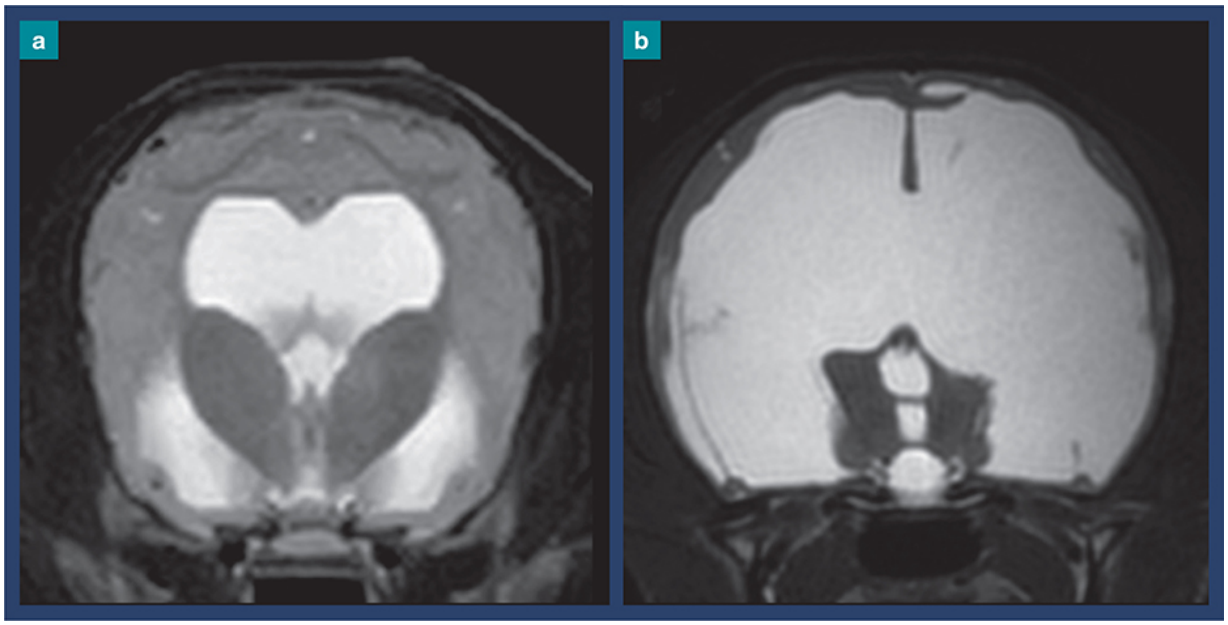


FIGURE 6.5. Transverse T2W images at the level of the thalamus in two dogs with congenital hydrocephalus. a) Three-month-old male Border Collie with clinical signs of depression, blindness, ataxia and seizures. The dog had a normally developed cortex, and imaging findings suggestive of severe increased ICP as described in the text are present. b) Three-year-old male Maltese showing abnormal behavior, blindness, ataxia, and seizures. Findings compatible with increased ICP can also be seen in this image, but the cortex is extremely thin, and the cortex and thalamus may be hypoplastic. Hydrocephalus and seizures in a case such as that depicted in a) may be treatable with decompressive therapy, such as diuresis or ventriculoperitoneal shunting, while clinical signs in a case such as that depicted in b) may not respond to decompressive therapy, and antiseizure drugs are likely needed for seizure control. (Images obtained with a 3.0T scanner.)

In human medicine, to avoid various errors from manual methods and objectively detect any morphological changes, the statistical imaging analysis method referred to as "voxel-based morphometry (VBM)" has been developed. In VBM, numerous 3D MRI data sets from a normal population (e.g., Asian adult males) are gathered, and then averaged and normalized to produce one standard template (e.g., Asian adult male standard brain template), with further segmentation into tissue probability maps for gray matter, white matter, and CSF space. This standard template and tissue probability maps can be used for voxel-based statistical comparison with an individual patient or another population with a certain disease (e.g., Asian adult male standard template vs. one Asian adult male patient with epilepsy, or vs. Asian adult epileptic patient group). Therefore, once a standard template has been developed, the statistical analysis can be performed automatically and the results are objective. In addition, VBM

analysis has also been applied to other functional MRI modalities such as diffusion MRI and BOLD-fMRI.

There are challenges in the application of VBM in veterinary patients, particularly due to differences in the shape of the brain in the various canine breeds. To perform an accurate VBM analysis, the standard template should be breed-specific, and this involves performing MRI in a sufficient number of normal dogs of the same breed. Other challenges include morphological variability (for example ventricle size, position of the olfactory lobe, absence/presence of quadrigeminal diverticula) in a particular breed. A pilot study of VBM showed a significant volume reduction of the gray matter in the olfactory bulb, cingulate gyrus, hippocampus, and cortex of the temporal and parietal lobes in 5 Beagles with idiopathic epilepsy (IE) compared with 5 control Beagles.[13] Nevertheless, such studies involving a specific breed will have limitations in terms of sample size and the time required to collect sufficient cases. Therefore, in order to resolve the issue of breed-specific or interbreed differences, two ambitious studies have been reported. The first study by Milne et al. created four templates for brachycephalic, mesaticephalic, dolichocephalic, and combined mesati- and dolichocephalic skull types.[14] A second study by Johnson et al. developed a canine standard template from 30 mesati- and dolichocephalic dogs, and demonstrated a method to transform data from dogs with a different skull type into the canine standard template.[12] Compared to dogs, cats have a more uniform shape and size of the brain, with the exception of brachycephalic breeds such as the Persian. Therefore, developing accurate standard templates for VBM analysis seems more achievable in cats than in dogs. A 7T MRI-based feline template from 8 cats[15] and a 3T MRI-based feline template from 14 cats (38 data sets) have been developed[16]. The latter study also compared VBM analysis between familial epileptic cats and normal controls, and demonstrated volume reduction of the hippocampus and amygdala, which was suspected to represent the epileptogenic zone in 20% of the epileptic cats.[16]

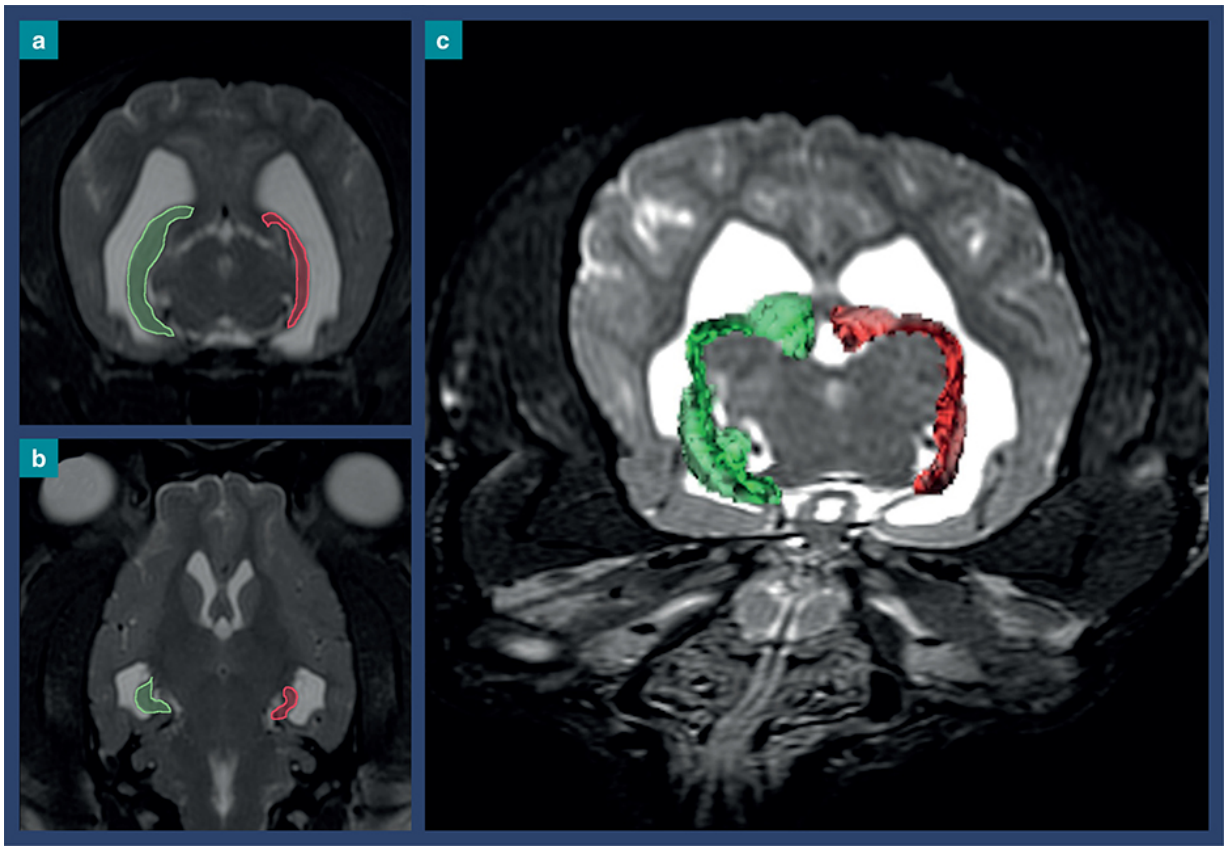


FIGURE 6.6. Hippocampal volumetry using 3D T2W data on an imaging workstation in a 4-year-old, female neutered Cavalier King Charles Spaniel with drug-resistant epilepsy and left hippocampal atrophy. Transverse (a) and dorsal (b) planes acquired in accordance with the International Veterinary Epilepsy Task Force epilepsy-specific protocol, produced from 3D data by multiplanar reconstruction, showing the traced ROIs for the left (red) and right (green) hippocampi. Volume rendering (c) provides a 3D reconstruction of each traced hippocampus. The volume of the left (red) and right (green) hippocampus were 0.23 cm^3 and 0.52 cm^3, respectively. (Images obtained with a 3.0T scanner.)

STRUCTURAL MRI FOR DIAGNOSIS OF EPILEPSY

Veterinary epilepsy-specific MRI protocol developed by the International Veterinary Epilepsy Task Force

As mentioned in Chapter 1, MRI examination is included in the Tier 2 confidence level diagnosis of IE. The International Veterinary Epilepsy Task Force (IVETF) has recommended performing imaging according to "the

veterinary epilepsy-specific MRI protocol" to optimize and standardize the quality of MR images and facilitate lesion detection in patients with suspected IE.[17] Practically, although a presumed diagnosis of IE can be made if a Tier 1 level of confidence is met, performing a structural MRI utilizing the epilepsy-specific protocol should be considered in a dog with an age of onset of epileptic seizures of <6 months or >6 years, if any abnormal neurological findings are present interictally, or if the owner desires a more accurate diagnosis, i.e., Tier 2 confidence level. In addition, MRI should also be considered in patients that present with cluster seizures or status epilepticus at the onset of epilepsy diagnosis, or in animals previously diagnosed with IE based on Tier 1 criteria but that demonstrate drug-resistance to first-line antiseizure drugs administered at therapeutic doses.[18]

The veterinary epilepsy-specific MRI protocol is shown in Table 6.3 for low-field MRI (0.2–1.0T) and Table 6.4 for high-field MRI (1.5–3.0T).

TABLE 6.3. Veterinary epilepsy-specific MRI protocol for low-field MRI.[2] (modified)

Slice thickness of 4 mm or less for all sequences	
T1W	1. Sagittal – scan initially to identify the long axis of the hippocampus 2. Dorsal – perpendicular to the long axis of the hippocampus as identified on the sagittal plane 3. Transverse – parallel to the long axis of the hippocampus as identified on the sagittal plane
T2W	4. Dorsal – same as T1W dorsal 5. Transverse – same as T1W transverse
FLAIR	6. Dorsal – same as T1W dorsal 7. Transverse (optional) – same as T1W transverse
CE-T1W (optional)	8. Acquisition of CE-T1W in one or more planes is indicated based on the detection of cerebral pathology or clinician's preference

TABLE 6.4. Veterinary epilepsy-specific MRI protocol for high-field MRI.[2] (modified)

Slice thickness of 3 mm or less for all sequences If using 3D sequence, 1 mm isotropic voxel is recommended	
T2W	1. Sagittal – scan initially to identify the long axis of the hippocampus 2. Dorsal – perpendicular to the long axis of the hippocampus as identified on the sagittal plane

	3. Transverse – parallel to the long axis of the hippocampus as identified on the sagittal plane OR obtain as a 3D-T2W sequence, and then reconstruct the above three planes using multiplanar reconstruction (MPR)
FLAIR	4. Dorsal – same as T2W dorsal 5. Transverse (optional) OR obtain as a 3D-FLAIR sequence, and then reconstruct the three planes using MPR
T1W§	6. 3D-T1W sequence, and then reconstruct the three planes using MPR OR usual (2D) T1W dorsal same as T2W dorsal
Hemo/calc†	7. Transverse – same as T2W transverse
CE-T1W (optional)	8. Acquisition of CE-T1W in one or more planes is indicated based on the detection of cerebral pathology or clinician's preference

§ T1W may be replaced by T1-FLAIR or T1-inversion recovery (IR) depending on the manufacturer of the machine.
† Hemo/calc, hemosiderin and calcification sensitive sequences such as T2* gradient echo (T2*W or GRE) or susceptibility weighted imaging (SWI).

The first key point of the IVETF epilepsy-specific protocol is to initially identify the long axis of the hippocampus in the sagittal plane (T1W for low-field, T2W for high-field). This is necessary to set the slice angulation of the dorsal and transverse planes, respectively, parallel and perpendicular to the long axis of the hippocampus rather than the hard palate (Fig. 6.7). Orientating the angles of the transverse and dorsal planes to the long axis of the hippocampus identified in the sagittal plane allows for optimal visualization of the hippocampus. Both the traditional (e.g., hard palate–based) and the IVETF epilepsy-specific protocols are affected by skull types (brachycephalic, mesocephalic, and dolichocephalic). However, the latter minimizes the effect of skull shape on the hippocampal appearance.

The second peculiarity of the IVETF epilepsy-specific protocol is that CE-T1W is suggested as an optional sequence. In imaging of the brain to evaluate diseases other than epilepsy, it is thought that administration of contrast medium is generally essential for a complete investigation. In dogs with a diagnosis of IE with a Tier 1 level of confidence, it is debatable whether contrast administration is essential. If a lesion is seen or suspected on an unenhanced study, CE-T1W should be obtained. The author of this chapter prefers to obtain CE-T1W images when initially scanning an animal

with recurrent epileptic seizures, to rule out the possibility of structural brain disease.

A hemosiderin and calcification sensitive imaging sequence such as T2*W or SWI is suggested in the high-field IVETF epilepsy MRI protocol, but not in the low-field. The reason for this is the low sensitivity for hemorrhage (T2* decay) of the low-field magnet as described previously; however, the quality of T2*W is improved in recently marketed low-field machines. Therefore, if possible (allowing the extended scanning/anesthetic time), T2*W should also be added to the low-field protocol. It is thought that hemorrhage, followed by iron liberation from hemoglobin, and hemosiderin deposition can play an important role in the development of epileptogenesis.[19] Therefore, a hemosiderin sensitive imaging sequence should be incorporated in the MRI evaluation of epileptic patients whenever possible, especially in traumatic (including post-neurosurgery), cerebrovascular and elderly cases (see also the *Trauma and posttraumatic epilepsy* and *Vascular diseases* sections) (see Fig. 6.2).

Seizure-induced MRI changes

Repeated and/or prolonged seizures, as is seen with severe cluster seizures and status epilepticus, can induce temporary (reversible) or permanent MRI changes, referred to as "seizure-induced (MRI) changes". This is synonymous with "peri-ictal changes", "postictal changes", "seizure-associated changes", or "epileptic brain damage". Seizure-induced changes can occur both in IE and structural epilepsy. The pathophysiology of seizure-induced changes is not fully understood; however, it seems that excessive seizure activity induces excitotoxicity due to excessive release of glutamate, an imbalance between energy demand and supply, local hypoxia, lactic acidosis, depletion of adenosine triphosphate (ATP) and sodium–potassium (Na/K) pump failure that results in cytotoxic and vasogenic edema, intracellular Ca^{2+}-dependent signal cascade and finally cell death (Fig. 6.8). During these processes, hyperperfusion is present due to the hypermetabolism associated with excessive seizure activity in the hyperacute (ictal) phase, then cytotoxic and vasogenic edema occurs in the acute to subacute phase (ictal to early postictal), and finally hypometabolism, hypoperfusion, and higher diffusivity due to neuronal dysfunction or death and gliosis are observed in the chronic (postictal or interictal) phase.

In general, late acute to chronic seizure-induced changes are visualized on conventional/structural MRI. Typically, seizure-induced changes can be unilateral or bilateral (more common), and are observed in the limbic system, primarily the hippocampus, piriform lobe including the amygdala, cingulate gyrus and dorsal parts of the thalamus. They manifest as hyperintensity on T2W and FLAIR images and iso- to hypointensity on T1W images with slight to mild or no contrast enhancement, and often a slight mass effect (see Fig. 6.3). The findings that can be observed on conventional MRI are thought to be subacute changes, corresponding to the phase of cytotoxic and vasogenic edema. In a multicenter, retrospective, cross-sectional study investigating seizure-induced MRI changes in 81 dogs with suspected IE,[20] MRI was performed in 53% of dogs within 24 hours of epileptic seizure activity and in 79% of dogs within 48 hours. Bilateral lesions were identified in 88% of dogs, 85% of which were symmetric; this may be a reflection of seizure type, as 86% of dogs had generalized seizures. The findings of local mass effect and contrast enhancement were less frequent, but were observed in 28% and 15% of dogs, respectively. Repeat (follow-up) imaging was conducted in only 3 of 81 dogs in this study; the lesions in 2 of the dogs were completely resolved (1 week and 10 months after initial MRI) and the other dog showed marked improvement. The reversible nature of seizure-induced changes has been reported previously,[21,22] and because of this, the IVETF recommends that MRI be repeated after a period of seizure control (>10–16 weeks) in order to help differentiate seizure-induced changes from other pathologies such as inflammation or neoplasia.[18] However, seizure-induced changes can be chronic (irreversible) and result in necrosis with or without cavity formation (polioencephalomalacia). In the study mentioned above, 2 of 81 dogs had bilateral necrotic cavitated lesions on MRI (i.e., T2W-hyperintense, T1W-hypointense, and FLAIR-hypointense) in the piriform lobes including the amygdala, although detailed information on seizure type, duration and interval from seizures to the time of imaging is not provided.[20] Such irreversible lesions in the limbic system of dogs have also been reported and confirmed histologically in an experimental study[23] and in clinical studies[21,24,25]. In the more chronic stage of irreversible changes, or in the situation in which reversible changes occur repeatedly, the author believes that seizure-induced changes of neuronal loss with no apparent cavity formation and/or signal changes can progress to chronic atrophic lesions,

such as hippocampal atrophy with hypometabolism, hypoperfusion and hyperdiffusivity, as described in the next section.

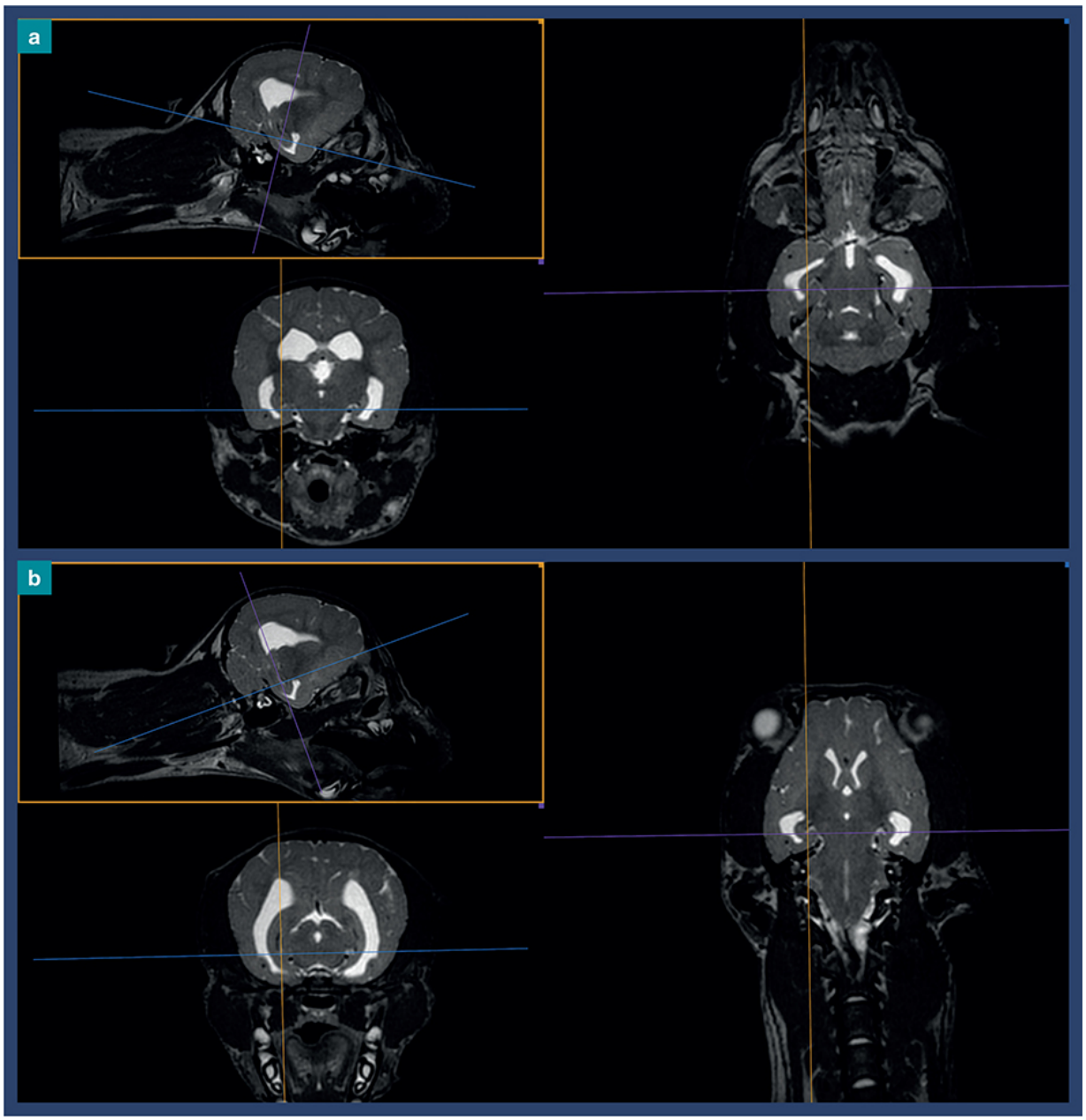


FIGURE 6.7. Three-axis (multiplanar reconstruction) MRI images acquired with traditional orientation (e.g., based on the hard palate) (a) and the IVETF epilepsy-specific protocol (e.g., based on the long axis of the hippocampus) (b) from a 4-year-old, neutered female Cavalier King Charles Spaniel with drug-resistant epilepsy. Images a) and b) were reconstructed from the same 3D-T2W data, with the intersection of the axis lines placed at the same level (the ventral part of the right hippocampus). This imaging revealed left hippocampal atrophy (contralateral to the intersection of the axis lines). (Images obtained with a 3T scanner.)

The hyperacute phase of seizure-induced pathophysiology (from hypermetabolism and hyperperfusion during the seizure to the generation of cytotoxic edema) cannot be detected by conventional MRI. In this phase, functional imaging including diffusion/perfusion MRI and ictal SPECT is indicated as explained later (Fig. 6.8).

Hippocampal changes

The hippocampus is the most affected and studied region in the epileptic brain of both humans and animals. Hippocampal sclerosis (HS) is the typical imaging and pathological finding observed in humans with epilepsy, especially in drug-resistant temporal lobe epilepsy (TLE). Hippocampal sclerosis is generally unilateral and characterized by neuronal loss of the pyramidal cell layers (CA1, CA3 and CA4) and astrogliosis on histopathology. It is typically visualized on MRI as hyperintensity on T2W and FLAIR images with volume loss (atrophy).[26] In some cases with TLE/HS, the atrophic changes with gliosis extend to the surrounding limbic structures such as the amygdala, parahippocampal gyrus, fornix and cingulate gyrus; therefore, these changes are synonymously referred to as mesial temporal sclerosis (MTS).

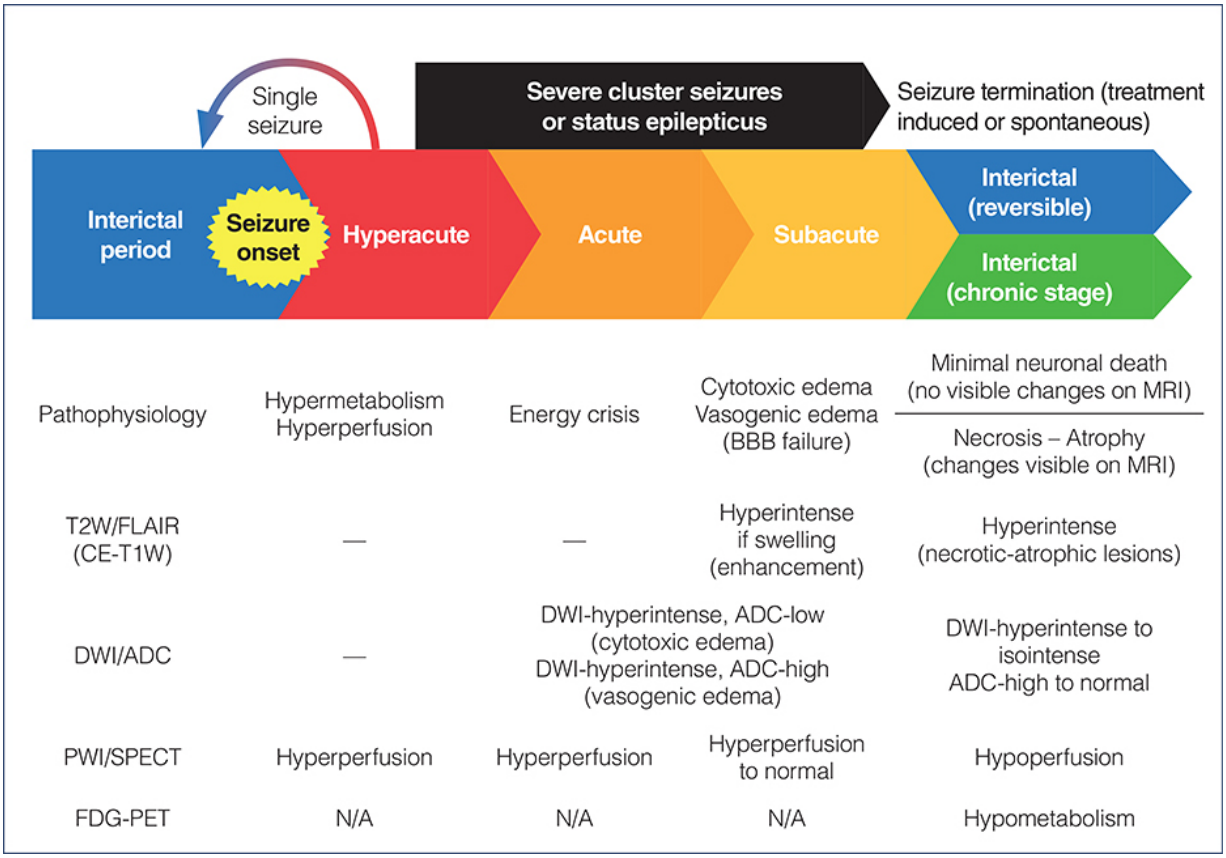


FIGURE 6.8. Schema of the pathophysiology and recommended imaging protocols associated with different stages of seizure-induced changes.

BBB, blood–brain barrier; MRI, magnetic resonance imaging; T2W, T2-weighted; FLAIR, fluid-attenuated inversion recovery; CE, contrast-enhanced; T1W, T1-weighted; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; PWI, perfusion-weighted imaging; SPECT, single-photon emission computed tomography; FDG, fluoro-2-deoxyglucose; PET, positron emission tomography; N/A, not applicable.

As described above, the hippocampus is the focus of imaging in the veterinary epilepsy-specific protocol and is also affected by seizure-induced changes in dogs and cats with epilepsy. The imaging finding that is typical of human HS (T2W/FLAIR-hyperintensity with atrophy) is rarely observed in dogs with epilepsy; however, several retrospective volumetric studies have demonstrated asymmetric hippocampal volume loss with or without signal changes, and therefore the term "hippocampal atrophy" (HA) is commonly used (see Fig. 6.6).[8–11] In the first MRI study investigating hippocampal volume in 58 dogs with IE using the classical ROI method, 48% of dogs had unilateral HA when applying an asymmetric ratio (calculated by dividing the absolute volume difference between the right

and left hippocampi by the volume of the larger hippocampus) of 6% as a cutoff value, although only 12% of dogs had visually recognized HA with T2W/FLAIR hyperintensity.[10] In a study investigating an association between HA and electroencephalography (EEG) using a cutoff value of 6% for the asymmetric ratio, 56% (23/41) of epileptic dogs had unilateral HA and 35% (8/23) of those had epileptiform discharges in the temporal region.[9] Another study using an advanced 3D volumetric method evaluated 100 dogs with presumptive IE and compared their imaging findings to 41 nonepileptic dogs.[8] In this study, the epileptic group had significantly greater hippocampal asymmetry compared to the nonepileptic group. Furthermore, 42% of dogs in the epileptic group (versus 15% in the nonepileptic group) had a hippocampal ratio >1.16 (equal to the previous asymmetric ratio of 12.6%) that was shown to have an 85% specificity for epilepsy-associated HA. The results of these studies suggest that HA will occur in dogs with epilepsy in the same way as HS in humans, although its association with the duration, severity, and type of epileptic seizures requires additional investigation. On the other hand, signal changes (hyperintensity on T2W/FLAIR) consistent with HA have not yet been documented in canine IE, although a study of T2 relaxometry in a small population of dogs suggested these changes might occur, as described later.[27]

In cats, TLE, HA, feline hippocampal necrosis (FHN) and HS have been documented with MRI and pathological studies.[7,28–31] Cats with TLE have predominant hippocampal abnormalities on MRI and present with focal seizures characterized by altered mentation, hypersalivation, orofacial automatism, mydriasis, licking, lip smacking, facial twitching, head nodding or turning and secondary generalization (see Chapter 5, Videos 5.1 and 5.2 and Box 5.1).[30] In a retrospective study investigating MRI findings in 188 epileptic cats with a normal interictal neurological examination, 5 of 23 epileptic cats with structural epilepsy had FHN.[31] Imaging findings of FHN are similar to the seizure-induced MRI changes mentioned above, such as unilateral or bilateral hippocampal hyperintensity on T2W and FLAIR, and iso- to hypointensity on T1W with or without contrast enhancement, sometimes extending to the amygdala/piriform lobe. In contrast to canine epilepsy, volumetric studies are limited to laboratory familial epileptic cats that were shown to have unilateral HA without signal changes.[7,16] Studies evaluating both signal changes and volumetry in a large

cohort of cats are therefore needed to further investigate HS in feline epilepsy.

There is an argument as to whether HS/HA is the cause or the result of epilepsy and/or epileptic seizures, and both scenarios are considered possible. The author thinks that in the majority of cases, HA in dogs (and in many cats) with epilepsy is more likely to be the result of recurrent epileptic seizures, i.e., chronic seizure-induced changes rather than the primary cause of the epileptic seizures.

ADVANCED AND FUNCTIONAL IMAGING

T2 relaxometry

T2 relaxometry is a method of measuring T2 relaxation time (T2 value) from T2 map imaging (T2 mapping). In general, T2 relaxometry is performed with high-field MRI. T2 relaxometry can be used to increase the sensitivity of T2 hyperintensity above the detectable level of conventional MRI; therefore, it is expected that T2 relaxometry may allow the identification of signal changes associated with an epileptic (atrophic) hippocampus in dogs and cats, for which evidence is currently lacking, as mentioned above. A retrospective study compared T2 relaxation time in various brain regions between 31 dogs with IE and 15 nonepileptic control dogs.[27] Although no significant difference was identified between the groups, a tendency for higher T2 values in the hippocampus of the epileptic group was observed, and 6 of 31 epileptic dogs had increased hippocampal T2 values that exceeded two times the standard deviation. Therefore, T2 relaxometry may be helpful to detect hippocampal signal changes in patients with epilepsy, although further studies investigating the correlation between T2 values and histopathological changes are needed to establish its reliability.

Diffusion MRI

Diffusion MRI is a specific sequence that detects and quantifies the molecular motion (Brownian movement) of water (i.e., water diffusivity) that represents an intrinsic characteristic of tissues. Free water molecules like CSF in the ventricles can diffuse equally in all directions (isotropic)

with a certain speed (units expressed in $\times 10^{-3}$ mm^2/s), whereas intracellular water molecules are restricted in their diffusivity. Diffusion MRI is obtained using a spin echo or echo planar sequence, and the application of a pair of strong gradient magnetic fields, referred to as "motion-probing gradients" (MPGs), in the direction of three or more axes. At present, there are two types of diffusion MRI, namely DWI and diffusion tensor imaging (DTI), which are mainly performed for evaluation of epilepsy and other brain diseases. Diffusion MRI is frequently performed as part of conventional MRI in veterinary practice. In general, diffusion MRI is easily performed with high-field MRI machines, but it can also be performed with some newer low-field machines.

Diffusion-weighted imaging and apparent diffusion coefficient

DWI is acquired with and without applying MPGs along three (x, y, z) axes, and the raw images are fused and shown as an isotropic DW image for visual assessment.[32] The apparent diffusion coefficient (ADC), a major parameter of DWI, is calculated voxel by voxel from the raw data set and shown as an ADC map. ADC is an absolute value with units usually expressed in mm^2/s, indicating the diffusion speed of water molecules. Therefore, low ADC values signify restricted (water) diffusivity and high ADC values signify freely moving water. ADC values of the cerebral cortex, hippocampus, amygdala/piriform lobe, and white matter in the normal canine brain are approximately 0.8–0.9, 0.9–1.2, 0.8–1.0, and 0.7–0.8 $\times 10^{-3}$ mm^2/s, respectively.[32–34]

An area of cytotoxic edema, in which water movement is restricted within the cells, appears hyperintense on isotropic DWI and has low ADC values (DWI-high/ADC-low), while CSF (free water) appears hypointense on DWI and has high ADC values (DWI-low/ADC-high). However, because DWI is based on T2W sequences, hyperintense lesions on T2W that consist of partially restricted water such as vasogenic edema also appear hyperintense on isotropic DWI with high ADC values (DWI-high/ADC-high). This phenomenon is referred to as "T2 shine-through".

In the diagnostic imaging of epilepsy, DWI is used to detect acute seizure-induced changes and/or to identify the epileptogenic area. Conceptually, as described in the section on seizure-induced changes, severe or prolonged seizure activity can induce cytotoxic and vasogenic edema in the acute–subacute phase, with the affected regions appearing

DWI-high/ADC-low (Fig. 6.9) or DWI-high/ADC-high. In the chronic or interictal phase, or in structurally changed (necrotic or atrophic) lesions, DWI will appear iso- to hyperintense with normal to high ADC values due to neuronal loss (increased extracellular space) and gliosis. In the previously described retrospective study that investigated seizure-induced changes in dogs with IE, DWI was conducted in 21/81 cases, and ADC values in 38 lesions from 19 cases were analyzed, revealing a mixed pattern of restricted (low ADC; 14/38), facilitated (high ADC; 19/38) and normal (4/38) diffusivity.[20] In another prospective study that investigated interictal DWI changes (scanned 1–9 days after the last seizure) in 17 dogs with IE, significant increases in ADC values were observed in the piriform lobe including the amygdala (mean, 0.96×10^{-3} mm^2/s) compared with normal dogs (n = 10; mean, 0.92×10^{-3} mm^2/s).[33,34] In addition, studies evaluating changes in hippocampal DWI/ADC values from the interictal to the early postictal (<20 min) phase of a single generalized seizure in familial epileptic cats (n = 6) identified a higher ADC in the interictal phase than in healthy controls, and a significantly lower ADC in the early postictal phase than in the interictal phase.[35] These studies demonstrate the utility of DWI in veterinary patients with epilepsy; however, the interpretation of results should be considered with respect to the time interval between the last seizure and MRI scanning.

Diffusion tensor imaging

Even in the normal brain, water molecules within a restricted space such as neuronal fibers are hindered from moving in directions other than the fiber direction. These differences in diffusivity depending on the direction are referred to “anisotropic diffusion”, and diffusion tensor imaging (DTI) evaluates anisotropic diffusion using “tensor”, which is a mathematical vector function. While DWI is obtained by applying three MPG axes, six or more axes are needed for DTI. The most well-known appearance of DTI is “tractography” or “fiber tracking”, in which sequential fiber tracts of the white matter appear as a 3D image (Fig. 6.10). Tractography is useful in identifying white matter abnormalities and avoiding important pathways during brain surgery. Fractional anisotropy (FA) is the most widely used parameter to express the strength of anisotropic diffusion; it is a unitless value ranging from 0.0 (isotropic) to 1.0 (completely anisotropic). FA values in the brain of normal dogs are approximately 0.2 for gray matter

and 0.3–0.6 for white matter; they tend to be greater in massive tracts such as the internal capsule, fornix, and corpus callosum.[36] In human epileptology, DTI and its parameters have been used to evaluate hippocampal or limbic changes and connectivity (epileptic network), and to detect epileptogenic lesions such as focal cortical dysplasia. Currently, there is no information on its utility in canine and feline epileptic patients except in experimental studies.[35]

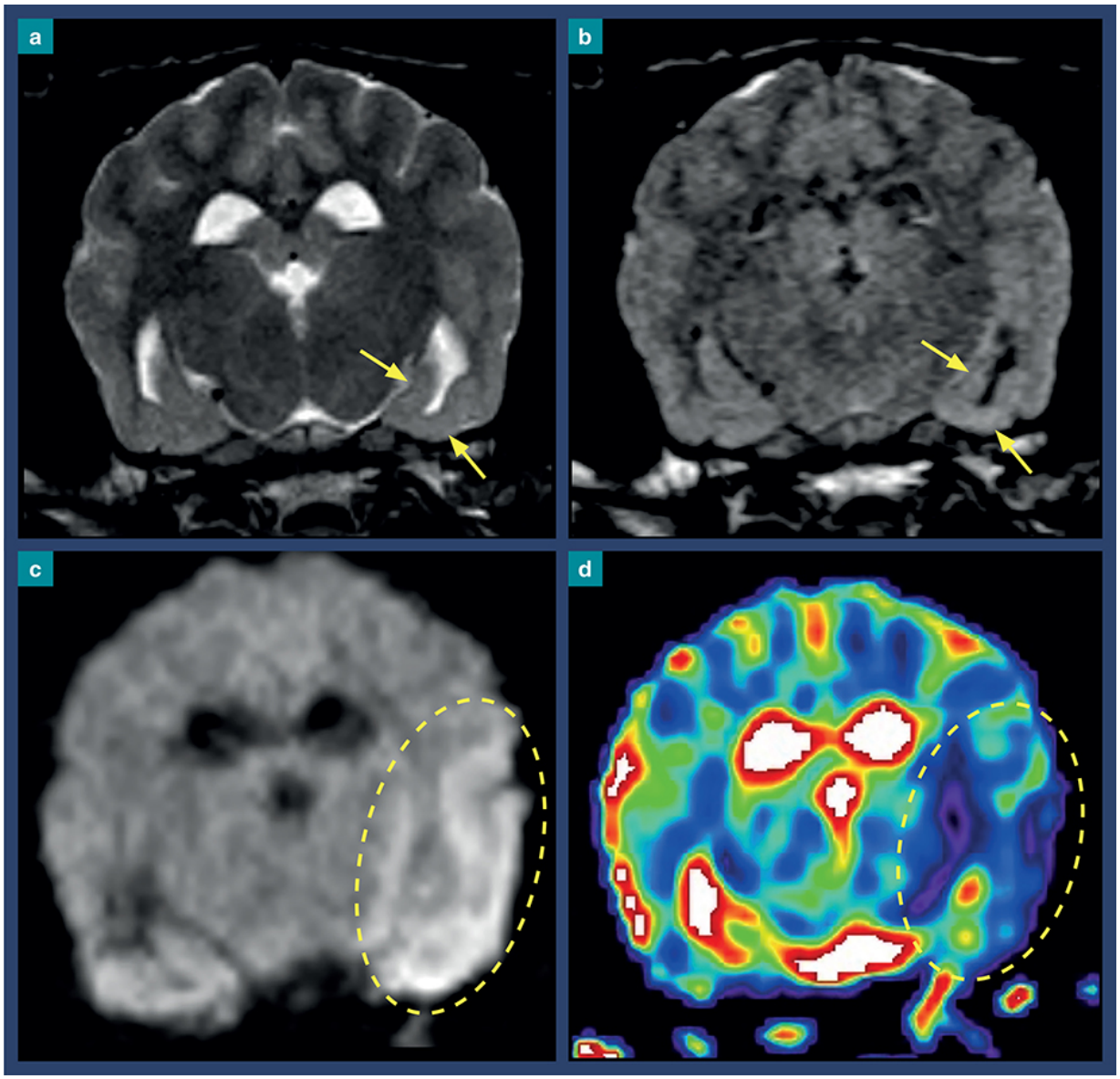


FIGURE 6.9. Transverse T2W (a), FLAIR (b), isotropic DWI (c) images and ADC color map (d) at the level of the hippocampus in a 6-year-old, male mongrel dog with a high frequency of focal seizures evolving into generalized tonic-clonic seizures. The dog had a seizure during preoxygenation prior to anesthesia induction for MRI. The left hippocampus and parahippocampal

gyrus are mildly atrophied with slight hyperintensity on T2W/FLAIR (arrows). Volume reduction of the left hippocampus was approximately 20% compared to the right hippocampus. DWI reveals hyperintensity in the left medial and lateral temporal lobes with low ADC values (dark blue to purple on ADC map, dot enclosure). (Images obtained with a 1.5T scanner.)

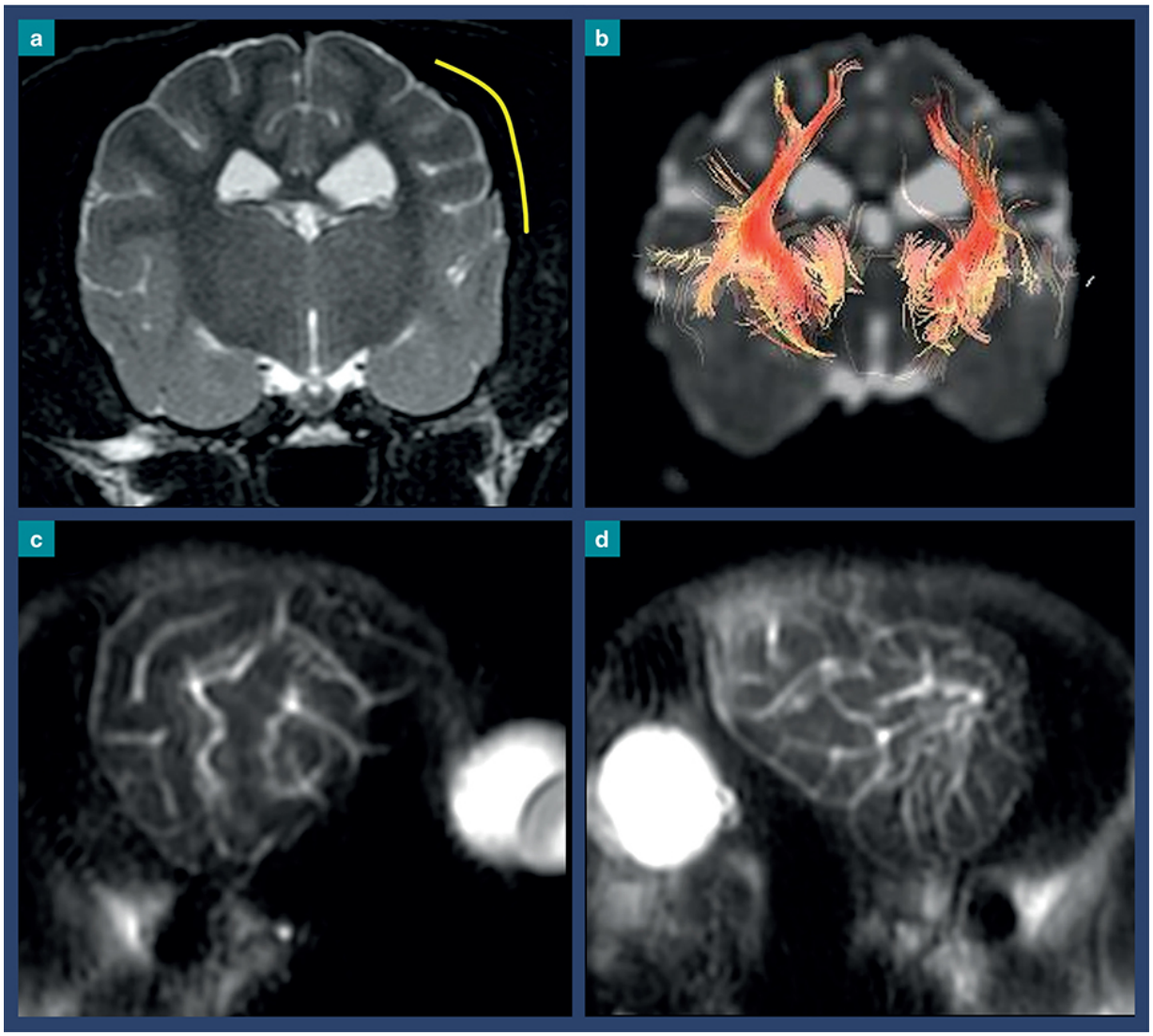


FIGURE 6.10. MR images from a 7-year-old, male Papillon with structural epilepsy caused by polymicrogyria in the left perisylvian area. a) Multiple small gyri are observed in the left temporoparietal region on a transverse T2W image (area under yellow line). b) Tractography created from DTI reveals the subcortical white matter of those small gyri is hypoplastic when compared to the right hemisphere. Abnormal gyration (polymicrogyria) of the left perisylvian area was clearly recognized by comparing the right (c) and left (d) hemispheres on a 3D surface anatomy scan. (Images obtained with a 3.0T scanner.)

Perfusion MRI

Perfusion MRI or perfusion-weighted imaging (PWI) are specific sequences that evaluate cerebral perfusion with an estimation of hemodynamic parameters. There are three main methods for acquiring PWI: two of them utilize a contrast agent (i.e., Gd) and are referred to as dynamic susceptibility contrast (DSC) PWI and dynamic contrast-enhanced (DCE) MRI, while the third method, arterial spin labeling (ASL), is an MRI-specific sequence that does not require the administration of a contrast agent. DCE-PWI sequences are used to assess BBB integrity and analyze the microenvironment of brain tumors; they are not commonly used for epilepsy.

Dynamic susceptibility contrast- perfusion-weighted imaging

DSC-PWI is obtained by rapid sequential image acquisition during an intravenous bolus injection of Gd-based contrast, with subsequent analysis of a time-concentration curve created from the susceptibility effect of Gd on T2*W imaging. DSC-PWI allows for measurement of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT) and time-to-peak (TTP), similarly to computed tomography (CT) perfusion imaging. However, absolute evaluation of flow requires an arterial input function, which is difficult for PWI. Therefore, each parameter on DSC-PWI is a relative value and is referred to as relative CBV (rCBV) or relative CBF (rCBF).

The hemodynamics of the epileptic brain described in the section on seizure-induced changes (see Fig. 6.7), with hyperperfusion in the ictal and subsequent acute phase, normalization in the postictal–interictal phase, and hypoperfusion in the chronic (structurally-changed) interictal phase, have been confirmed at the epileptogenic zone in familial epileptic cats.[35] Furthermore, in a prospective study evaluating interictal DSC-PWI in 12 dogs with IE (all dogs had recurrent generalized tonic-clonic seizures during the 4 weeks prior to MRI), epileptic dogs showed a significantly greater MTT and lower CBF than healthy controls, especially in the piriform lobe, thalamus, and temporal cortex, suggesting that dogs with IE have decreased cerebral perfusion compared to healthy dogs.[37]

Arterial spin labeling

ASL is a comparatively new perfusion MRI technique that utilizes magnetically labeled (tagged) arterial blood as an endogenous tracer instead

of a contrast agent. It is noninvasive, easy to perform and provides high resolution images compared to DSC-PWI. Consequently, ASL has become routine in human medicine. However, ASL evaluates CBF only (although the methodology to evaluate other parameters is currently being developed) and requires high-field MRI. To date, there is only one case report of ASL use in a dog, which revealed hyperperfusion within a lesion of hypoxic cortical laminar necrosis.[38]

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a unique MR technique that obtains the local spectrogram of metabolites in vivo using chemical shift properties of protons such as ^{1}H, ^{13}C and ^{31}P. Clinical MRS uses mostly ^{1}H, and is also referred to as ^{1}H-MRS. Since ^{1}H protons exist in combination with various other atoms, the rotation frequency of precession differs for each substance containing a proton (chemical shift), and this is detectable by high-field (>1.5T) MRS sequences. There are two main sequences with different imaging parameters that are used in the acquisition of MRS, with advantages and disadvantages of each technique. The reader is referred to a standard MRI text for additional information on MRS sequences.

The commonly measured metabolites in MRS are summarized in Table 6.5. Each metabolite has a concentration peak (amplitude, vertical axis) and an individual resonance frequency (ppm, horizontal axis) against the reference (tetramethylsilane, TMS). In general, three main metabolites, i.e., N-acetylaspartate (NAA), creatinine (Cr) and choline (Cho), are commonly evaluated in MRS and are expressed as ratios, with NAA/Cr, NAA/Cho, NAA/Cr+Cho, Cho/Cr, and Cho/NAA reported routinely.

A prospective, cross-sectional study evaluated the interictal metabolic activity of the temporal lobe in 27 dogs with IE and 10 healthy control dogs, using ^{1}H-MRS. The NAA/Cr, NAA/Cho, Cho/Cr, and Cho/NAA ratios were determined in both hemispheres. No significant differences in all metabolite ratios were identified between epileptic and healthy dogs. No correlation was identified between metabolite ratios and age or sex. A time-dependent decrease in the NAA/Cho ratio as well as an increase in the Cho/NAA ratio was found to be associated with proximity in time to the last epileptic seizure.[39]

TABLE 6.5. Summary of the detectable main metabolites and their significance in ^{1}H-MRS.

Abbreviation	Metabolite	ppm	Significance
Lac	Lactate	1.3	■ Marker of anaerobic metabolism ■ Not detected in normal brain ■ With long echo time (TE), the peak is inverted (negative peak)
NAA	N-acetylaspartate	2.0	■ Most prominent positive peak in the normal brain ■ Marker of neuronal density ■ Decreased peak signifies decreased number of neurons; loss of peak is observed in gliomas, meningiomas, etc.
Glx	Glutamate (Glu) and glutamine (Gln) complex	2.3–2.5	■ Irregular, unstable and broad peak next to NAA ■ Indicates excitatory neurotransmitters
GABA	γ-aminobutyric acid	2.9	■ Unclear in common MRS ■ Requires higher magnetic field (≥3T) and specific sequence such as MEGA PRESS to identify
Cr	Creatine and phosphocreatine	3.0	■ Prominent and stable positive peak in the normal brain ■ Indicates energy metabolism of neurons (energetic marker) ■ Used as the internal reference, as /Cr ■ Lost in tissue without creatine kinase, such as meningiomas
Cho	Choline and phosphocholine	3.2	■ Prominent and stable positive peak next to Cr in the normal brain ■ Indicates metabolism (synthesis and decomposition) of cell membrane ■ Increased in tissues with active cytokinesis and/or necrosis such as tumors and demyelination
mIns (Ins)	Myo-inositol	3.5	■ Detectable using short TE ■ High concentration in astrocytes; increasing mIns signifies proliferation of astrocytes such as gliomas

Blood oxygen level–dependent functional MRI and electroencephalography-functional MRI

BOLD-fMRI is synonymous with brain functional imaging in current neuroscience. In an active brain area, increased regional blood flow (functional hyperemia) occurs. At the region, deoxyhemoglobin (paramagnetic) and oxyhemoglobin (diamagnetic) are sequentially increased with a 1–2 second delay from the neuronal activity, and fMRI detects these changes of magnetism between the activation (task) phase and resting phase, and data is processed to produce an image map. Since imaging is acquired during the performance of a certain task, it is difficult to get reliable fMRI data in anesthetized animals. Some researchers have made great efforts to acquire fMRI in awake trained dogs to obtain information on canine brain function, although this is not practical for veterinary clinics.

In human epileptology, BOLD-fMRI combined with concurrent EEG recording (EEG-fMRI) has been developed to detect the epileptogenic

zone.[40] In this way, BOLD-fMRI is obtained simultaneously with EEG recording, and then, during postprocessing, the spikes or epileptiform activity can be identified on EEG after noise removal and BOLD changes before and after the EEG events can be analyzed. There are no reports of the use of EEG-fMRI in veterinary patients; however, as canine and feline EEG is generally performed under sedation or light anesthesia, EEG-fMRI may be applicable for veterinary clinical cases.

In addition, another form of fMRI called resting-state fMRI (rs-fMRI) analyzes the default mode network (DMN) and/or functional connectivity between certain areas of brain, and is an active area of research in human medicine and the neuroscience field, as well as in dogs.[41,42] Epilepsy is a functional brain disorder, with changes in DMN and/or functional connectivity expected, although currently there are no studies evaluating this MRI technique in canine or feline epilepsy.[43]

Positron emission tomography

PET is a nuclear imaging modality based on the capture of radiation from an administered radioisotope. Compared to SPECT (discussed below), PET is superior in spatial resolution and quantitative analysis, but inferior in temporal resolution. Therefore, PET imaging is generally performed in the interictal phase. Commonly, PET images are combined (superimposed) with CT (PET-CT) or MRI (PET-MRI). The most frequently used radioisotope agent is [18F] fluoro-2-deoxyglucose (FDG), which has a similar structure to glucose and is taken up by cells and metabolized analogously to glucose. FDG-PET is a form of saccharometabolic imaging, in which regional metabolic activities in the brain are evaluated. In the epileptogenic zone, interictal hypometabolism (decreased uptake of FDG) is typically observed due to neuronal loss, diaschisis, and decreased density of synapses.

Two interictal FDG-PET studies in dogs with epilepsy have been reported. A prospective blinded study investigated FDG-PET in 6 Lagotto Romagnolos with familial juvenile focal epilepsy, 2 dogs with adult-onset focal epilepsy and 5 control dogs of the same breed of different ages, and compared those findings with EEG findings.[44] In this study, hypometabolic regions were detected visually in 5/6 dogs with juvenile epilepsy and corresponded with EEG abnormalities in 3 of the 5 dogs. However, semiquantitative analysis of the relative standard uptake value (an indicator of radioactivity) did not detect a significant difference between epileptic

and control dogs. A second prospective, randomized, blinded study evaluated FDG-PET and EEG in 11 Finnish Spitz dogs with focal IE and 6 healthy dogs.[45] A hypometabolic area was identified in 9/11 epileptic Finnish Spitz dogs and 4/8 healthy dogs, and those findings in the occipital lobe were significantly related with epilepsy (Fig. 6.11). Additionally, sensitivity to visually detect lateralization of the epileptogenic focus in FDG-PET was superior to that in EEG.

Single photon emission computed tomography

The diagnostic purpose of SPECT in epilepsy is commonly to evaluate cerebral blood flow (CBF) using Technetium-99m (^{99m}Tc) radiotracer. Due to its rapid labeling and distribution (1–2 min after administration), ^{99m}Tc-SPECT has been used for ictal perfusion imaging (ictal SPECT) in human medicine. As mentioned in the above sections (see Fig. 6.8), the epileptogenic area consumes a large amount of oxygen and glucose, so that ictal SPECT will demonstrate hyperperfusion (increased CBF). On the other hand, similarly to PWI, interictal SPECT will show hypoperfusion in the epileptogenic zone, but the sensitivity of interictal SPECT for detecting the epileptogenic zone is inferior to interictal FDG-PET and ictal SPECT. Therefore, when evaluating SPECT in human epileptology, an image processing technique that subtracts the interictal images from the ictal images and coregisters it to the MRI, called SISCOM (subtraction of ictal and interictal SPECT coregistered to MRI), is used to increase the sensitivity of visualizing the epileptogenic focus.

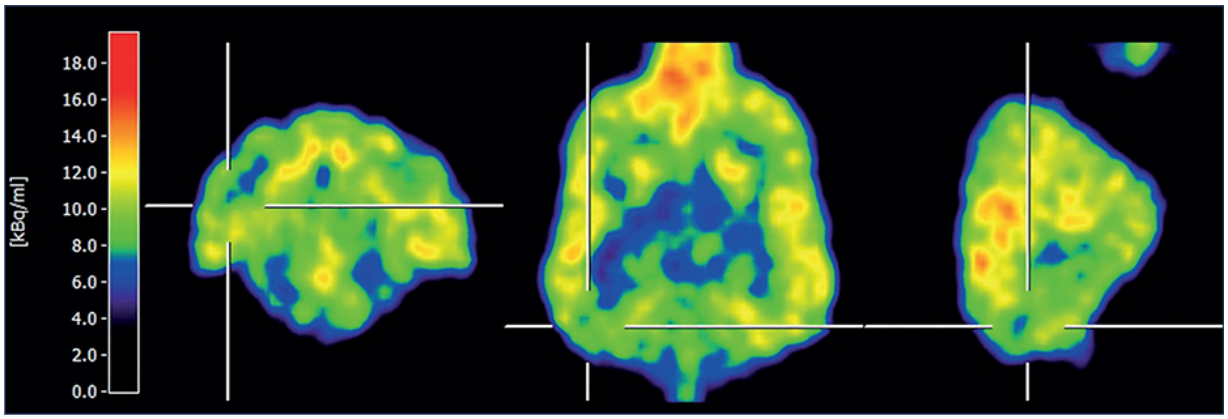


FIGURE 6.11. Interictal FDG-PET in a Finnish Spitz with focal idiopathic epilepsy. An area of decreased glucose uptake (hypometabolic), suspected to be the epileptogenic zone, is observed in the

left occipital lobe (at the intersection of the axis lines). Courtesy of Drs. Ranno Viitmaa and Tarja Jokinen.

No ictal SPECT studies have yet been conducted in veterinary medicine, but two interictal studies have been reported. Twelve dogs with IE underwent interictal ^{99m}Tc-SPECT of the brain, and different ROIs were evaluated by semiquantitative analysis and compared with a control group (18 dogs). Significant hypoperfusion was present in the subcortical area of epileptic dogs, that was not associated with seizure frequency, age at onset of seizures, duration of epilepsy, or time from the last seizure. Hence, the subcortical area may play an important role in the pathophysiology of canine IE.[46] Another study investigated interictal ^{99m}Tc-SPECT in dogs with drug-resistant (n = 7) and non-drug-resistant (n = 7) IE.[47] In this study, all dogs in both groups showed one or more areas of hypoperfusion in various sites, but hypoperfusion in the temporal lobe was more frequently observed in the drug-resistant group (5/7 dogs) compared to the non-drug-resistant group (1/7 dogs). Although both studies showed interictal hypoperfusion in certain areas, further studies in which results are correlated with EEG findings are required in veterinary medicine.

IMAGING FINDINGS OF STRUCTURAL EPILEPSIES

Structural epilepsy can result from various intracranial conditions. The following section briefly describes the MRI findings of different types of structural cerebral disease that have been reported to cause recurrent epileptic seizures in dogs and cats.

Degenerative diseases

Typical MRI findings of canine and feline lysosomal storage diseases such as GM1- or GM2-gangliosidosis, globoid cell leukodystrophy, and mucopolysaccharidosis include bilateral and symmetric T2W hyperintensity in the white matter, hypoplasia of commissural fibers such as the corpus callosum, and generalized brain atrophy. However, epileptic seizures are rarely observed in these diseases.[48] Neuronal ceroid lipofuscinosis is a

neurodegenerative disease with epileptic seizures as a common clinical sign, and typically appears on MRI as brain atrophy without any signal changes. Recurrent epileptic seizures are also a chief complaint in young dogs (or cats) with certain **inherited inborn errors of metabolism** such as Alaskan Husky encephalopathy,[49] L-2-hydroxyglutaric aciduria[50] (Fig. 6.12), and neonatal encephalopathy with seizures in standard Poodle puppies[51] (Fig. 6.13). These diseases also have characteristic abnormal MRI findings, including marked bilateral and symmetric T2W hyperintensity and T1W hypointensity without contrast enhancement identified in either specific brain regions or involving the whole brain.

Geriatric dogs and cats with **cognitive dysfunction syndrome** (CDS), a disorder with similarities to Alzheimer's disease and vascular dementia in humans, will occasionally present with recurrent epileptic seizures. MRI findings of CDS include:

1. Cortical (particularly frontal lobe and hippocampus) or whole brain atrophy, resulting in widened sulci and subarachnoid space
2. Compensatory enlargement of the ventricular system (hydrocephalus ex vacuo)
3. Indistinct boundary between gray and white matter
4. Decreased thickness and area of the interthalamic adhesion
5. Diffuse T2W/FLAIR hyperintensity in the white matter (especially around the lateral ventricles; also known as leukoaraiosis)[52]

In addition, multiple microbleeds identifiable on T2*W or SWI and/or lacunar infarcts are often observed incidentally (see Fig 6.2).[53]

Progressive myoclonic epilepsy (PME), also known as Lafora disease, is a genetic degenerative disease that is classified as structural epilepsy, but no abnormality is typically identified on conventional MRI aside from age-related atrophy. However, MRS has demonstrated decreased NAA and glutamine–glutamate complex and increased Cho and Cre in the thalamus of a 6-year-old Beagle dog with reflex myoclonic seizures and generalized tonic-clonic seizures that was genetically confirmed to have Lafora disease.[54]

Anomalous, congenital and developmental diseases

In humans, congenital anomalous or developmental diseases involving the cortex are known to have high epileptogenicity, resulting in structural epilepsy.[55] These congenital diseases are relatively rare in dogs and cats and are often breed-related, with the exception of hydrocephalus, which occurs in toy and small breed dogs (see Fig. 6.5).

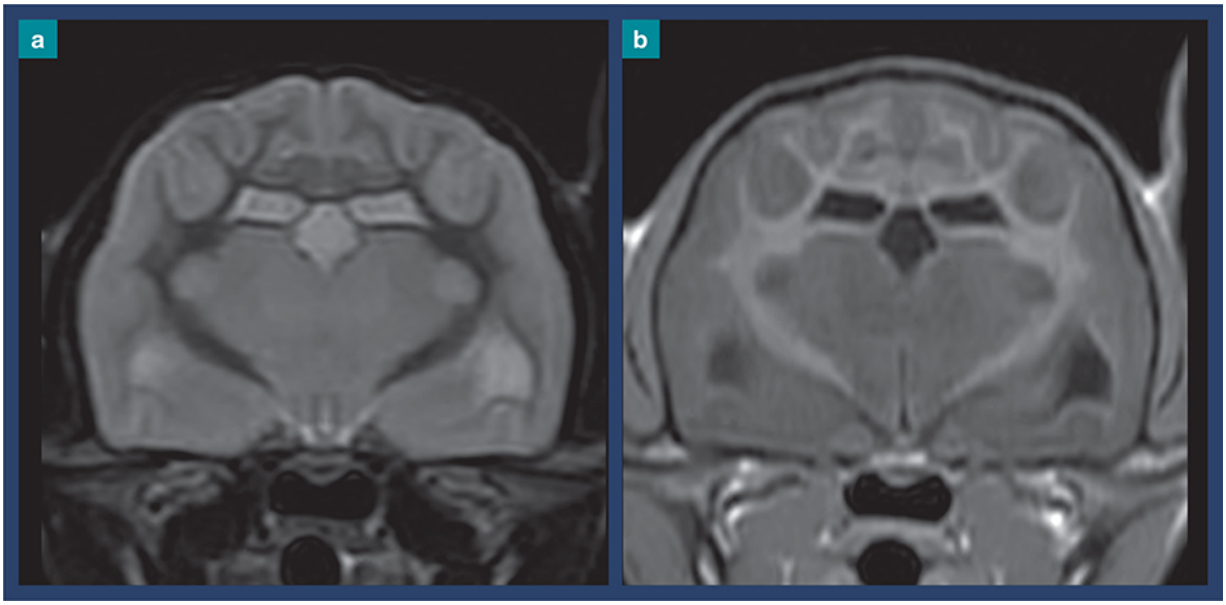


FIGURE 6.12. Transverse T2W (a) and T1W (b) images at the level of the thalamus in a 10-month-old, female Persian-cross cat with cluster seizures and multiple neurological deficits. The entire gray matter of the brain including the cerebral cortex and subcortical nuclei are hyperintense on T2W and hypointense on T1W, which results in accentuation of the white matter. Postmortem histology confirmed spongiform degeneration in the gray matter that is consistent with organic aciduria, an inborn error of metabolism. Courtesy of Dr. Kengo Suzuki. (Images obtained with a 0.2T scanner.)

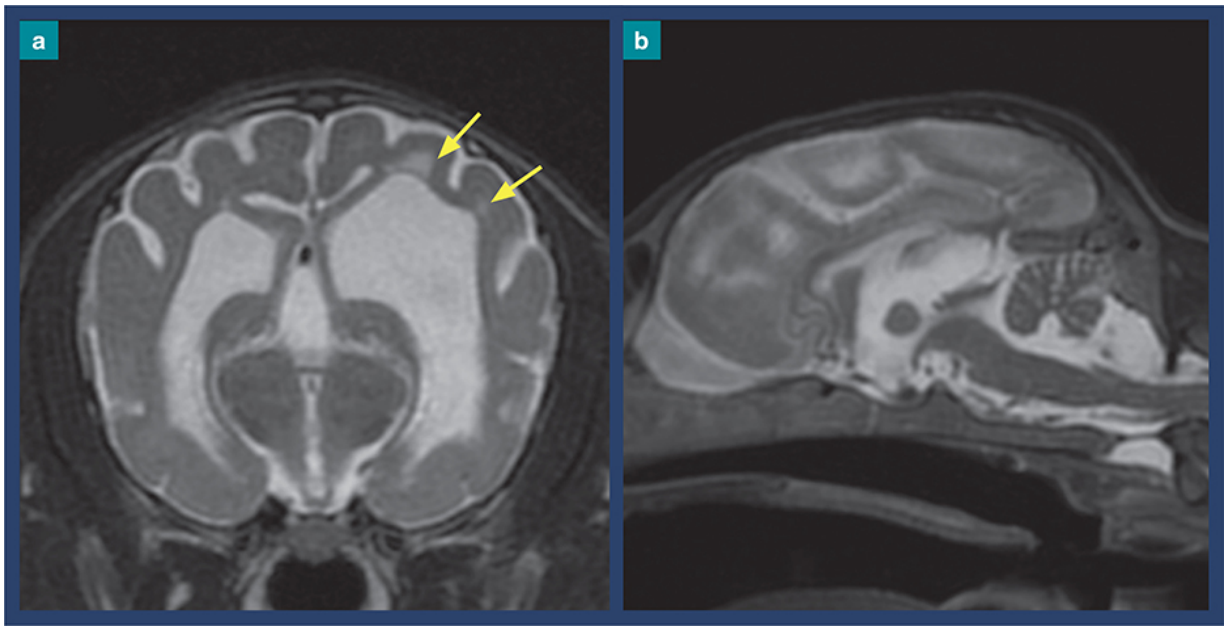


FIGURE 6.13. Transverse image (a) at the level of the thalamus and midline sagittal T2W image (b) of a 2-month-old, female standard Poodle puppy with neonatal encephalopathy with seizures (NEWS). Generalized brain atrophy and white matter hypoplasia are observed. Contrast between the gray and white matter is indistinct, and focal T2W hyperintensities are observed in the periventricular area (a, arrows). On the sagittal image (b), the corpus callosum appears incomplete and the cerebellum is atrophied with a ventral defect; this latter finding can be seen with Dandy-Walker-like syndrome. (Images obtained with a 3.0T scanner.)

Encephalocele or meningoencephalocele is characterized by the extrusion of brain tissues through a cranial defect. Epileptic seizures are most common with encephaloceles involving the olfactory and frontal lobe areas (intranasal or frontal sinus).[56] Extruded brain and meninges appear T2W hyperintense with contrast enhancement on CE-T1W in most cases, with or without a meningeal sac that has the same intensity as CSF (Fig. 6.14).

Holoprosencephaly is sporadically reported in dogs, with a breed predisposition in Staffordshire Bull Terriers and miniature Schnauzers. Affected dogs frequently present with seizures, tremors and hypernatremia, and MRI reveals hypoplasia or agenesis of the corpus callosum (corpus callosum abnormalities) and fornix, and a fused (butterfly-shaped) lateral ventricle with or without a thickened cingula due to white matter remodeling (called Probst bundles).

Lissencephaly, polymicrogyria, schizencephaly and (gray matter) heterotopia are rare MRI-detectable cortical malformations in dogs and

cats. In human medicine, these conditions are known as common epileptogenic diseases, due to abnormal neuronal migration and/or cortical organization (sulcation). Classical lissencephaly (type 1) is characterized by a symmetric smooth and thickened cerebral cortex (pachygyria), with rare and shallow gyri and undeveloped subcortical white matter. Although cobblestone lissencephaly (type 2) has not been reported in veterinary medicine, the author examined a dog with clinical findings closely resembling this condition (Fig. 6.15). Imaging of **polymicrogyria** reveals focal multiple small gyri with undeveloped subcortical white matter (see Fig. 6.9), and **schizencephaly** shows abnormal slits or clefts lined with gray matter in the hemisphere. The **heterotopia** reported in dogs is of the subventricular nodular type. These cortical lesions generally are not accompanied by any signal changes, i.e., they are isointense to normal gray matter on each sequence. Note that **porencephaly**, which refers to a CSF-containing cavitary lesion with smooth and well-defined borders surrounded by brain tissue, is sometimes described as a congenital anomaly, but it actually results from a focal injury (vascular accident, infarction, or trauma) having caused complete loss of a part of the brain during the perinatal period, and therefore should be differentiated from other cortical malformations.

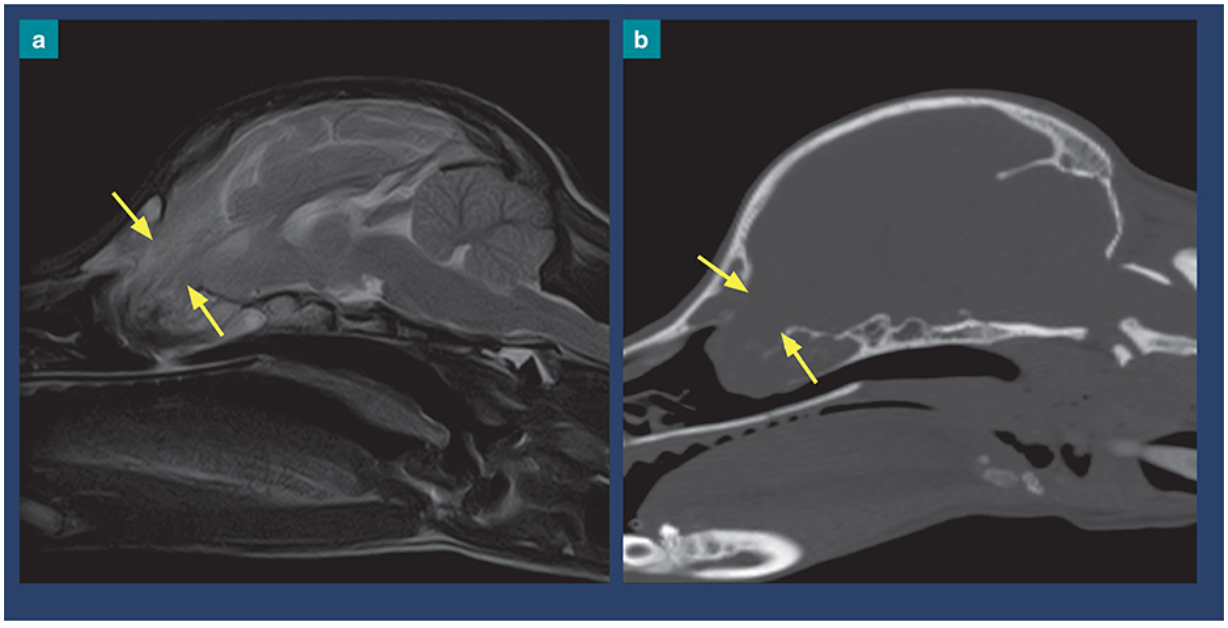


FIGURE 6.14. Parasagittal T2W (a) and CT (b) images of a 4-month-old, male cross-breed dog with an ethmoidal meningoencephalocele and recurrent epileptic seizures including status epilepticus. The

olfactory bulb and the rostral part of the frontal lobe extrude into the nasal cavity through the defect in the ethmoid bone (arrows). Courtesy of Dr. Miyoko Saito. (MR image obtained with a 3.0T scanner.)

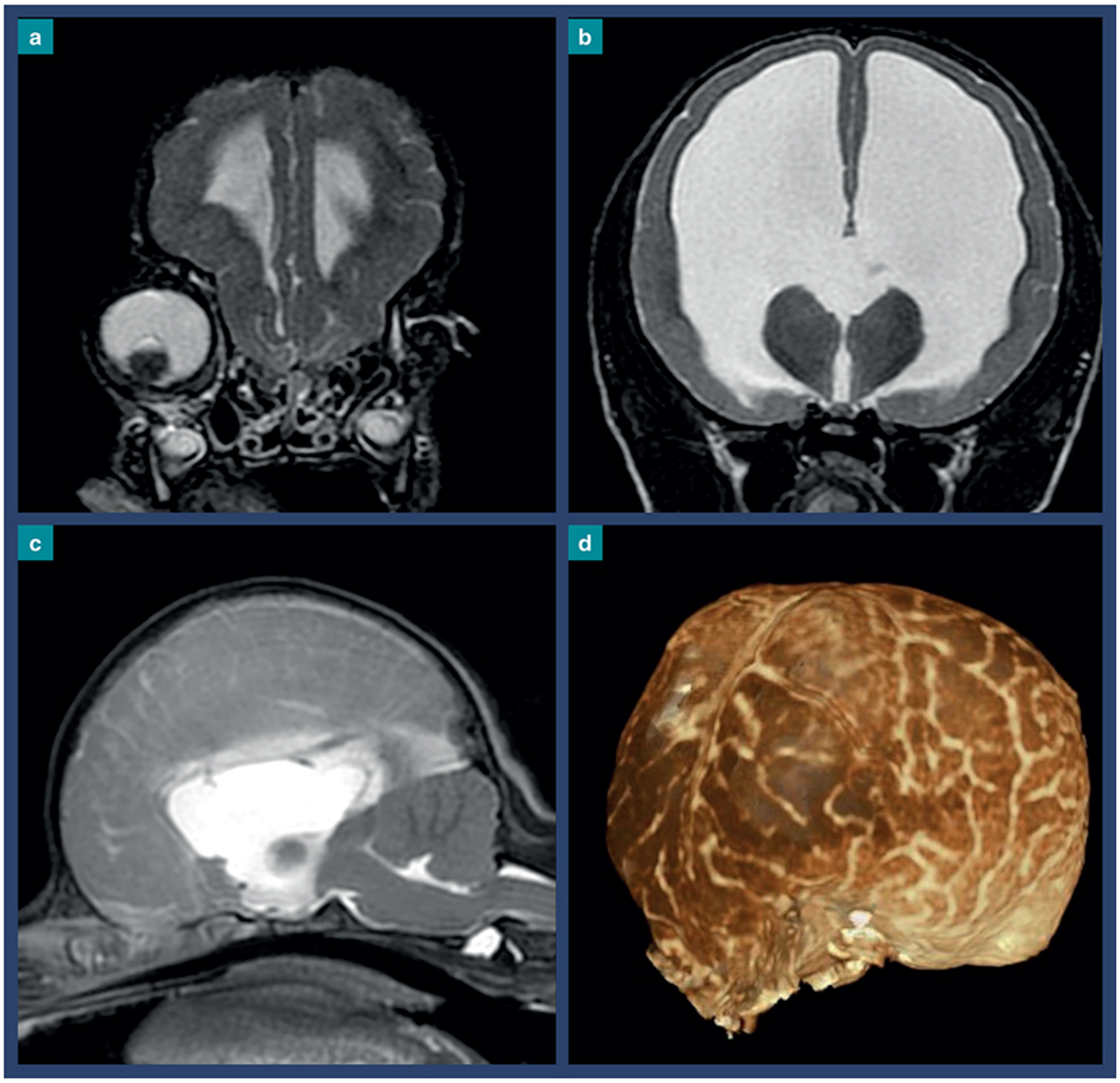


FIGURE 6.15. Transverse T2W images at the level of the orbit (a) and thalamus (b), midline sagittal image (c), and volume rendering image (d) from 3D-T2W data in a 4-year-old, male toy Poodle with cobblestone lissencephaly (type 2)-like diplogenesis. The left eyeball is completely lacking congenitally, and congenital abnormalities were also noted in the right eye; the eye was small and a cataract with a persistent hyaloid artery was present (confirmed with ultrasound). A dome-shaped cranium, polymicrogyria, significant ventriculomegaly (severe hydrocephalus), hypoplastic white matter and agenesis of the corpus callosum and anterior commissure were observed. (Images obtained with a 3.0T scanner.)

Neoplastic diseases (brain tumors)

Brain (or intracranial) neoplasia is the most common cause of structural epilepsy in dogs[57] and cats[31], especially in middle-aged to older patients. A brain tumor can be epileptogenic itself (so called "epileptogenic tumor)", such as a glioma in the amygdala, or it can affect the surrounding brain tissue causing it to become epileptogenic, such as a meningioma in the frontal lobe. An overview of imaging findings will be provided in this section. A more detailed description of imaging findings for specific tumor types can be found in review articles[58] and diagnostic imaging textbooks.

Clinically (imaging) diagnosed **gliomas**, which are histologically confirmed as **astrocytomas** or **oligodendrogliomas**, are common causative lesions of structural epilepsy in dogs. Brachycephalic breeds such as the French Bulldog, English Bulldog and Boxer are predisposed to gliomas. These tumors occur frequently in the frontal, temporal and piriform lobes including the amygdala and hippocampus.[58–60] General MRI findings of gliomas include focal parenchymal swelling that is hyperintense on T2W/FLAIR and hypointense on T1W with variable strength and/or a pattern of contrast enhancement and slight to mild mass effect (Fig. 6.16). Intratumoral necrosis, hemorrhage, calcification, and contrast enhancement characteristics such as ring enhancement are associated with malignancy.

Meningiomas are the most common brain (extra-axial) tumors in dogs and cats with (and also without) epileptic seizures. When a meningioma develops adjacent to a seizure-prone area such as the olfactory, frontal, temporal or piriform lobe, it can be associated with a higher risk of generating seizures. Epileptic seizures in patients with meningiomas can also occur as one of the clinical signs resulting from increased ICP. Typical MRI findings of meningiomas include a broad-based extra-axial mass lesion, with mass effect, variable hypo- to hyper-, or heterogenous intensity on T2W/FLAIR and iso- to hypointensity on T1W, with relatively strong contrast enhancement and a dural tail sign (see Fig. 6.4). The presence and degree of peritumoral edema associated with meningiomas is variable, but may depend on the location, rate of growth, and invasive nature of the tumor, and can also be affected by the administration of certain medications (such as corticosteroids).

Inflammatory diseases (encephalitis)

Inflammatory disease of the brain, i.e., (meningo-)encephalitis, is the second most common cause of structural epilepsy in dogs,[57] but is comparatively rare in cats except in CNS-FIP.[31] Encephalitis can be classified as infectious, and idiopathic or immune-mediated. The latter has been referred to as "meningoencephalitis (or meningoencephalomyelitis) of unknown origin (MUO)/etiology (MUE)/aetiology (MUA)", which is a clinical term used to denote an antemortem diagnosis of inflammatory CNS disease that has not been proven to be due to infectious causes. In cases of encephalitis that resolve with treatment, recurrent epileptic seizures may occur as a sequela, and this condition is called "postencephalitic epilepsy" (PEE).

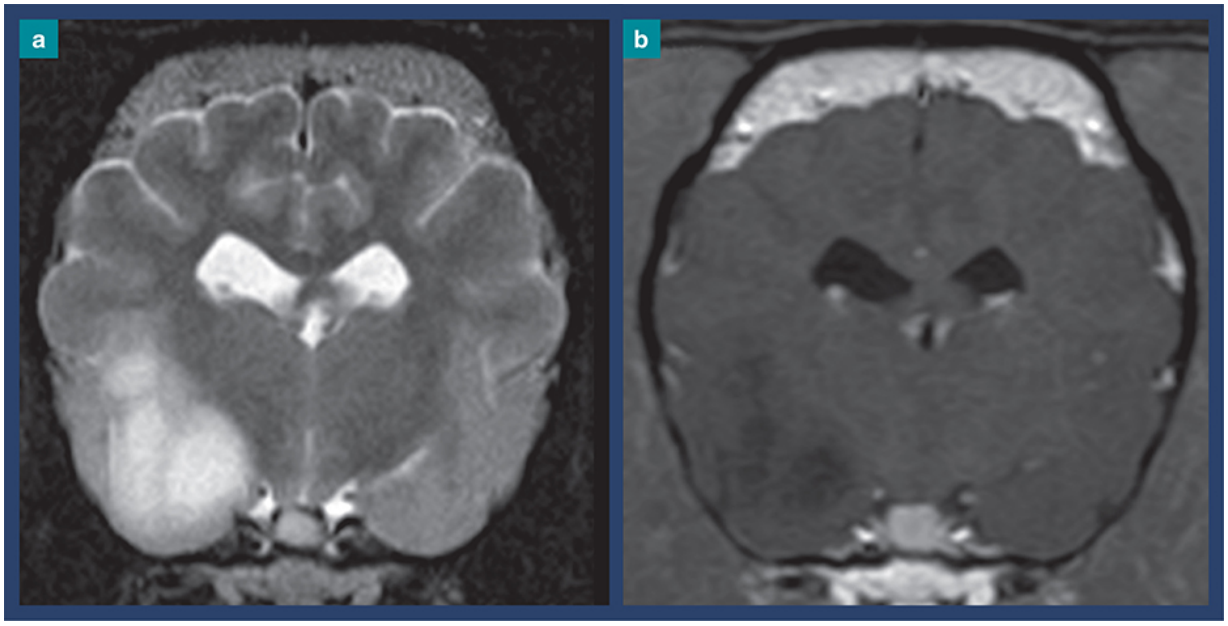


FIGURE 6.16. Transverse T2W (a) and CE-T1W (b) images at the level of the thalamus in a 9-year-old, neutered male French Bulldog with recent-onset epileptic seizures. An intra-axial mass lesion involving the right hippocampus, amygdala and piriform lobe appears hyperintense on T2W and hypointense on T1W without contrast enhancement. This dog was treated with radiation and lomustine and survived for 3 years. An anaplastic (grade III) oligodendroglioma was histologically diagnosed on necropsy, although a low-grade (grade II) tumor was suspected based on the imaging findings. (Images obtained with a 1.5T scanner.)

Bacterial and fungal encephalitis is often caused by infiltration of pathogens into the CNS from an intranasal (including sinus) infection or otitis media/interna. At the site of infiltration, osteolysis (sometimes destructive) of a part of the skull such as the cribriform plate, foramina of the temporal bone, or tympanic bulla can be observed and is well visualized

with CT. On MRI, the meninges can appear hypertrophied and contrast enhance, and diffuse T2W/FLAIR hyperintensity in the adjacent brain parenchyma is generally observed spreading from the site of infiltration, but formation of a single or multiple abscesses is also sometimes found. In general, a bacterial abscess forms a well-defined and extra-axial round or convex encapsulated mass showing variable signal intensity (depending on the nature or stage of its contents) on T1W and hyperintensity on T2W, and peripheral (capsule) enhancement on CE-T1W (Fig. 6.17). DWI is useful in differentiating an abscess from other mass lesions, as an abscess typically shows strong DWI-high/ADC-low. On the other hand, a fungal abscess, such as with *Aspergillus* or *Cryptococcus*, will tend to form intra-axial multiple and miliary cysts that will appear hyperintense on T2W and hypointense on T1W with ring enhancement of each cyst (Fig 6.18).

Feline infectious peritonitis virus infection in the CNS is the most common viral encephalitis in cats, especially under 3 years old. In a typical case, characteristic MRI findings are secondary to obstructive hydrocephalus/ventriculomegaly and/or syringomyelia, with meningeal and ependymal enhancement (meningitis and ependymitis) observed. The CSF within the ventricular system is occasionally partially or completely not suppressed on FLAIR, due to a high protein concentration or increased cellularity. Note that MRI findings can also be normal in CNS-FIP.

Meningoencephalitis of unknown origin (MUO) includes the diseases granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE), which are common idiopathic, suspected immune-mediated encephalitides in dogs. Epileptic seizures are a frequent clinical sign of MUO, especially in NME that mainly affects the cerebral cortex. Typical MRI findings of NME include focal and/or multiple mild to marked T2W hyperintense lesions located at the gray–white matter border of the cortex in the early/acute stage, and marked T2W-hyperintense/T1W-hypointense lesions involving the gray and white matter, suggestive of necrosis, in the chronic stage (Fig. 6.19). Slight to mild contrast enhancement can be occasionally observed around the necrotic lesions. In NLE, necrotic lesion(s) similar to those seen with NME are observed in the deep white matter or thalamic region. Imaging findings of GME are variable and differ depending on its pathological forms. Focal or multifocal granuloma(s)—which are typically either T2W hypointense (in the chiasm or spinal cord) or hyperintense (in

other sites) on T2W, iso- to hypointense on T1W, and strongly or uniformly enhanced on CE-T1W, with or without perilesional edema—are observed in the visual pathway (optic nerve, chiasm, optic tract, lateral geniculate body) in the ocular form of disease, and in the white matter or gray–white matter border of the cerebrum, cerebellum, brainstem, or spinal cord in the focal form. In diffuse (disseminated) GME, diffuse T2W-hyperintense/T1W-iso- to hypointense lesions are mainly observed in the white matter extensively, but can also be seen in the gray matter. Meningeal contrast enhancement is not typical for MUO, but is occasionally observed. Status epilepticus and/or severe cluster seizures are common manifestations in dogs with MUO, especially in the early or acute stage of disease. In these cases, the seizure-induced changes coexist with the original encephalitic lesions, so that it is often difficult to distinguish the pathology of each (Fig. 6.19).

Recently, **autoimmune limbic encephalitis** (LE) has been recognized in some cats with FHN (see also Chapter 5).[31,61] Most cats with LE have antibodies directed against proteins in the voltage-gated potassium channel (VGKC) complex, principally anti-leucine-rich glioma inactivated 1(LGI1) autoantibodies, although some cats can have another type of antibodies, such as netrin-1 receptor antibodies.[62] Cats with LE show drug-resistant focal status epilepticus with or without secondary generalization and bilateral T2W/FLAIR hyperintensity in the hippocampus with or without contrast enhancement, which resembles seizure-induced changes (see Figs. 5.2 and 5.3 in Chapter 5). Differentiation between LE and seizure-induced changes is difficult on imaging alone; therefore, detecting autoantibodies and/or observing response to immunosuppressive therapy is needed.

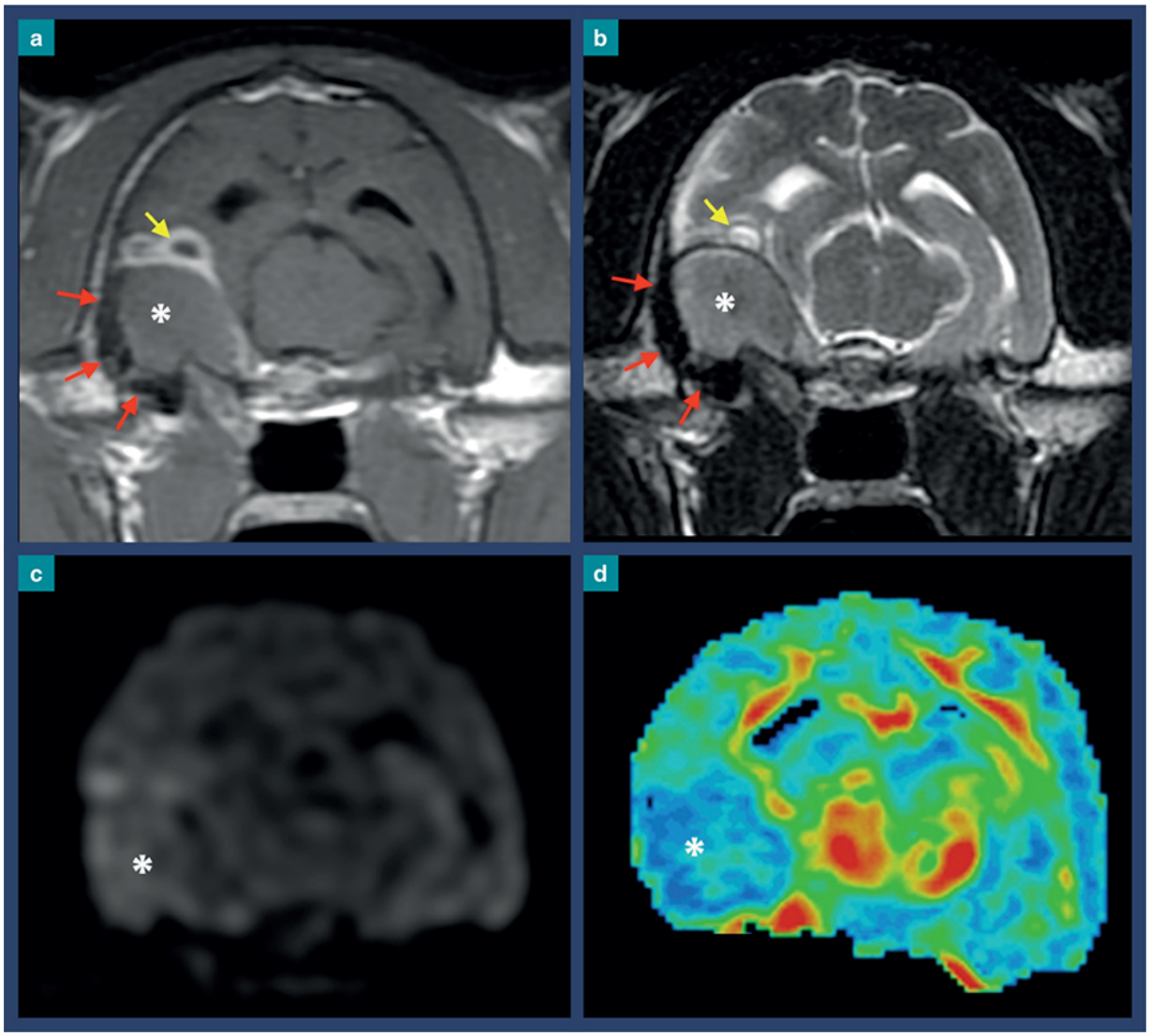


FIGURE 6.17. Images of a surgically confirmed bacterial abscess due to extension from otitis media/interna in a 6-year-old, male domestic shorthair cat with recurrent focal seizures typical of feline temporal lobe epilepsy. Note the large mass lesion (asterisk) that is T1W isointense with peripheral contrast enhancement (a) and T2W iso- to hyperintense (b). The mass appears to arise from the tympanic bulla (not shown) and occupies the ventrolateral portion of the right temporo-occipital region, causing compression of the temporal lobe and hippocampus (mass effect). The mass lesion is hyperintense on DWI (c) and has a low ADC value (d), suggestive of a suppurative abscess. The capsule is contrast enhancing, with a small cavitated lesion showing T2 hyperintensity and T1 hypointensity and ring enhancement (yellow arrow). Note that the inner layer of the temporal bone overlying the abscess is hypertrophied (red arrows). (Images obtained with a 3.0T scanner.)

Trauma and posttraumatic epilepsy

Head trauma can cause damage to the brain (traumatic brain injury,TBI) resulting in acute and/or chronic epileptic seizures, referred to as posttraumatic epilepsy (PTE). Posttraumatic epilepsy is divided into

immediate seizures (<24 hours after the accident), early seizures (24 hours to 1 week) and late PTE (≥1 week).[63] Traumatic brain injury may or may not be visible on imaging. In the early stage of TBI, corresponding to the stage of immediate/early seizures, variable changes from the primary or secondary injury can be observed, including various types of skull fractures (more visible on CT), intra- (epidural, subdural, subarachnoid, intracerebral)/extracranial hemorrhage or hematoma (high density on CT and signal void on T2*W/SWI), brain contusion including edema and swelling, and diffuse axonal injury (Fig. 6.20).[64,65] Minor brain injury may not be visible on imaging, and even if lesions are visible, it is difficult to determine which lesion is responsible for immediate/early seizures in this stage. A retrospective study that investigated the prognostic value of MRI within 14 days after TBI reported that severe intraparenchymal lesions, herniation at the fracture site and transtentorial herniation were significantly associated with the occurrence of seizures.[64] In (late) PTE, postcontusion changes such as focal atrophy, gliosis (T2W/FLAIR-hyperintensity), hemosiderin deposition (T2W hypointensity or signal void on T2*W/SWI), or porencephaly are observed with or without contrast enhancement. These changes are often similar in appearance to a chronic infarction, and the history of TBI and associated findings such as evidence of skull fractures and hypertrophic meninges, or the presence of a lesion in an area supplied by vessels will be differentiating features.

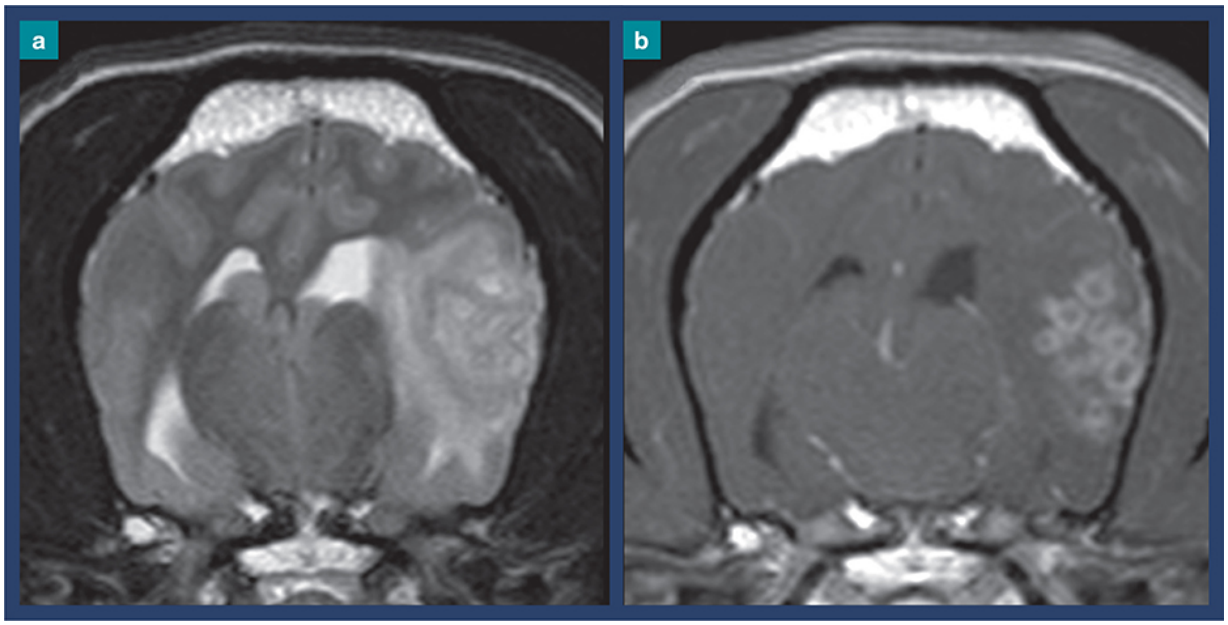


FIGURE 6.18. Images of fungal meningoencephalitis (multiple cystic abscesses) in an 8-year-old, male American Cocker Spaniel with bilateral otitis externa/media/interna and recent-onset epileptic seizures. a) The left temporal cortex appears swollen with heterogenous intensity on T2W. b) CE-T1W reveals multiple, military, ring-enhanced cystic appearing structures within the cortex. Courtesy of CAMIC, co. Ltd. (Images obtained with a 1.5T scanner.)

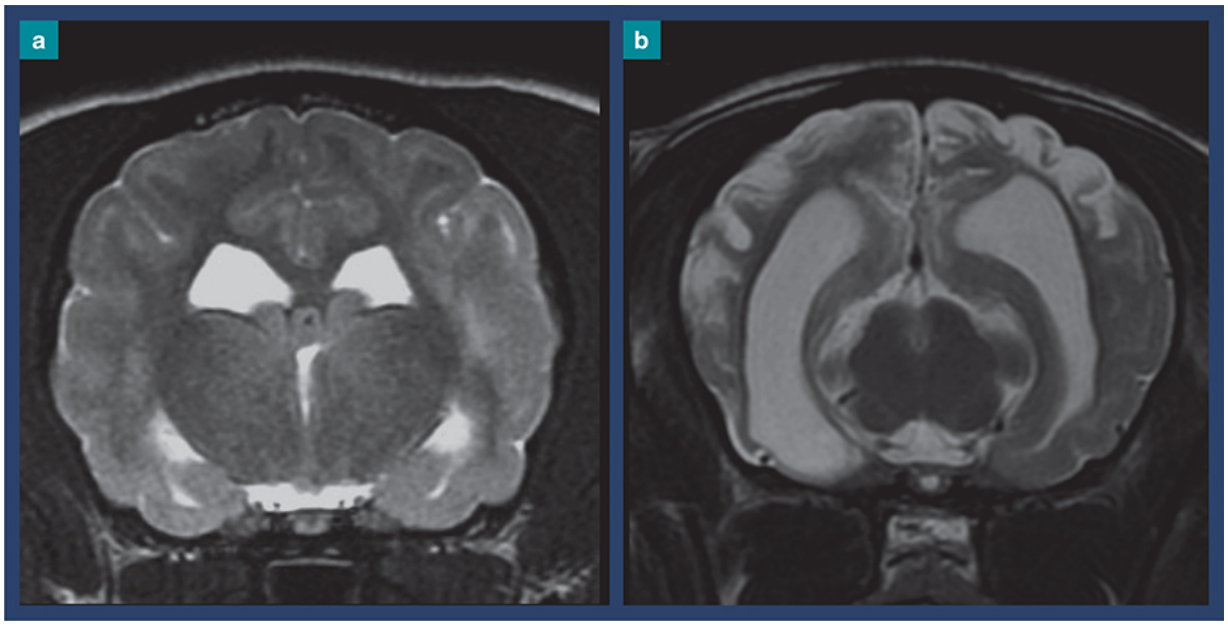


FIGURE 6.19. Transverse T2W images demonstrating different stages of necrotizing meningoencephalitis (NME). a) Image from a 3-year-old, neutered female Pug with recent-onset epileptic seizures. T2W hyperintense lines at the border between the gray and white matter are observed bilaterally in the parietal cortex. This finding is characteristic of early-stage NME. b) Image from another 3-year-old, intact female Pug with acute onset of bilateral blindness that developed after experiencing prolonged status epilepticus 2 months prior to the MRI scan. The dog had recurrent epileptic seizures that were treated with antiseizure drugs since 1 year of age. Necrosis is noted in the parietal cortex bilaterally, with marked hyperintensity suggestive of the chronic stage of NME. Note that the right hippocampus, parahippocampal gyrus, and temporal lobe of this dog are severely atrophied; this is considered to be a chronic seizure-induced change secondary to status epilepticus. (Images obtained with a 3.0T scanner.)

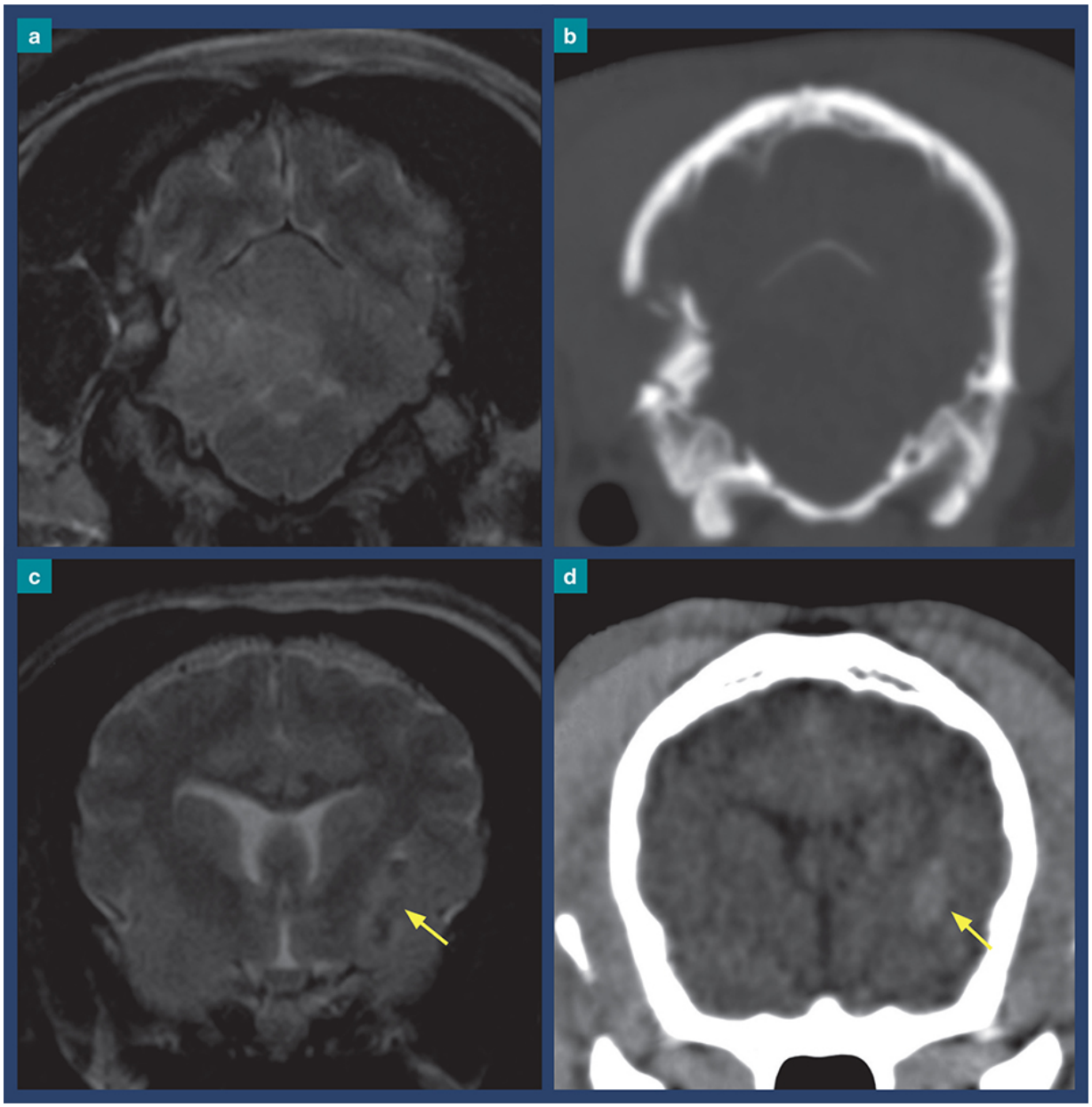


FIGURE 6.20. Transverse T2W images at the level of the cerebellum (a) and piriform lobe (c) and corresponding CT images (b; bone window, d; brain window) obtained the day following head trauma due to a road traffic accident in a 4-year-old, female miniature Dachshund with an early posttraumatic seizure. The direct (primary) lesions are observed in the right occipitocerebellar region, and include a depressed fracture and contusion of the cerebellum (a, b). An indirect (secondary) hemorrhagic lesion is observed on the opposite side in the left frontotemporal region (c, d, arrows), and may be the cause of the early seizure. Such a secondary lesion is referred to as a "countrecoup injury". (MR images obtained with a 3.0T scanner.)

Vascular diseases

Cerebrovascular accident/attack (CVA) is a synonym for stroke and can be subclassified as ischemic or hemorrhagic. The pathophysiological course and/or imaging timing in CVA is similar to seizure-induced changes; however, the onset of the cascade is initiated by hypoxia and hypoglycemia due to the CVA. Therefore, the clinical course of CVA can be classified into hyperacute (<24 hours), acute (1–7 days), subacute (1–3 weeks) and chronic (>1 month) stages. As occurs with head trauma, CVA can induce epileptic seizures both in the acute stage (poststroke or early seizures; <2 weeks after the CVA) and chronic stage (poststroke epilepsy or late seizures).

Conventional MRI findings of the acute to subacute stages of ischemic stroke are a focal, well-defined, wedge- to fan-shaped T2W/FLAIR-hyperintense and T1W-hypointense gray matter lesion that is associated with the affected vascular territory, with or without a slight to mild mass effect.[66] The lesion often involves the subcortical white matter. Contrast enhancement is not typical, but weak and diapedetic contrast enhancement is occasionally observed. Over time, the lesion (T2W/FLAIR-hyperintense) is gradually reduced and the affected area becomes atrophic or necrotic with minimal T2W/FLAIR-hyperintense signal, suggestive of gliosis. Conventional MRI, however, cannot capture the lesion in the hyperacute stage; DWI and PWI (or CT perfusion) are therefore applied. In a hyperacute lesion, DWI-high/ADC-low (cytotoxic edema) and hypoperfusion would be evident (Fig. 6.21). In addition, MR angiography and/or CT angiography may detect the infarcted vessel.[67]

In hemorrhagic stroke, the bleeding site or hematoma is revealed as a markedly hypointense lesion (signal void) on T2*W/SWI and/or a hyperdense lesion on CT in the hyperacute stage. Time-course changes in the signal pattern of hemorrhage are shown in Table 6.2. In the acute stage, a large hemorrhagic lesion may be associated with perilesional edema or an ischemic area that is distal to the bleeding site. Such an edematous area around the lesion is typically resolved by the subacute–chronic stage (see Fig. 6.1). In addition, microhemorrhages are found in older dogs with or without clinical signs, including recent-onset seizures (see Fig. 6.2). Although hemorrhage and hemosiderin deposition are known to be related with epileptogenicity in humans, the relationship between CVA and epilepsy in dogs and cats is still unclear.[53,68]

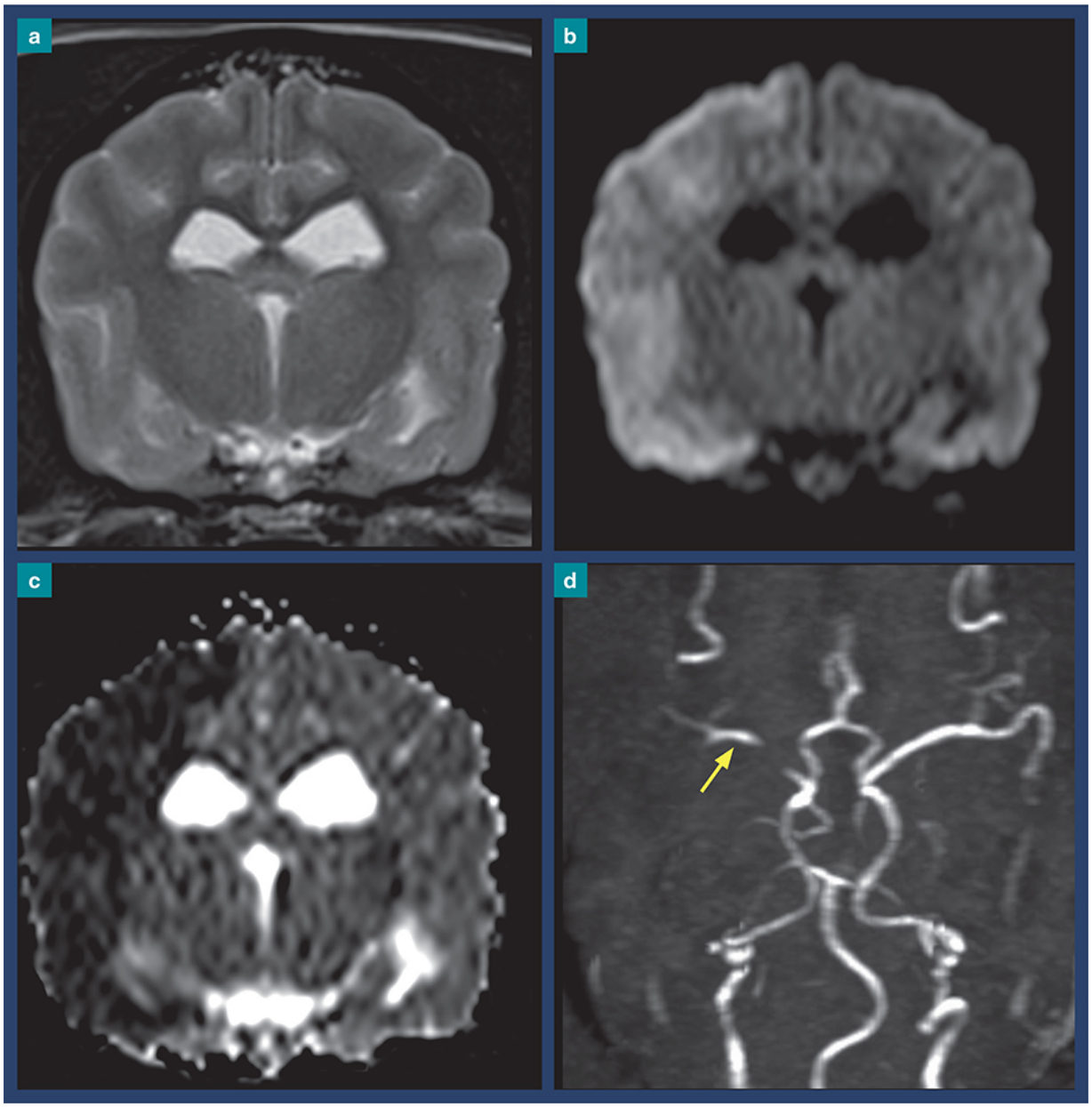


FIGURE 6.21. Transverse T2W image (a), isotropic DWI (b), ADC map (c) at the level of the pseudosylvian fissure, and dorsal view of MR angiography (d) from a 6-year-old, neutered female Welsh Corgi with acute onset of left hemiparesis of 2 days' duration. Although there is no apparent lesion on T2W (a), significant hyperintensity on DWI (b) and low ADC values (c) were observed in an extensive area of the right cerebral cortex. On MR angiography (d), the majority of the course of the right middle cerebral artery (MCA) was inapparent, with only a small portion remaining (arrow). From these findings, the hyperacute stage of a territorial infarction of the right MCA was considered, and the obstruction of the MCA was suspected to have occurred immediately before or during the anesthesia for MRI scan (at least 60 min had elapsed, as the spinal cord had been imaged before the brain study). Another focal T2W-hyperintense lesion (not shown) was identified in the right internal capsule area, which is supplied by blood flow from the striate branch of the MCA, and may have been the cause for the hemiparesis. Courtesy of Dr. Eiji Koyama. (Images obtained with a 1.5T scanner.)

TAKE-HOME MESSAGES

- ✔ MRI is essential in excluding structural abnormalities of the brain as a cause of epileptic seizures, and also provides important evidence to support a diagnosis of idiopathic epilepsy.
- ✔ Use of the IVETF epilepsy-specific MRI protocol is recommended for dogs and cats with epilepsy.
- ✔ A hemosiderin-sensitive sequence such as T2*W or SWI, and DWI should also be acquired when imaging a veterinary patient with epilepsy. These should be performed regardless of the field strength of the magnet, if such sequences are available for the machine.
- ✔ Seizure-induced changes, which are occasionally observed in animals after severe seizures, typically distribute in the limbic structures such as the hippocampus and piriform lobe, including the amygdala, cingulate gyrus, and epithalamic region, and manifest as hyperintensity on T2W and FLAIR images and iso- to hypointensity on T1W images with slight to mild or no contrast enhancement, and often a slight mass effect. These changes can be reversible or permanent.
- ✔ Hippocampal sclerosis, a common finding in humans with temporal lobe epilepsy, is rare in dogs and in cats with epilepsy. However, hippocampal atrophy (or asymmetry) can be seen in dogs with epilepsy, and hippocampal sclerosis or necrosis can be identified in epileptic cats, although it is uncertain whether these changes are related to the cause or the result of recurrent epileptic seizures.
- ✔ Advanced and functional imaging for epilepsy, including T2 relaxometry, diffusion and perfusion MRI, fMRI, and nuclear imaging such as FDG-PET, are used in the diagnostic investigation of humans with epilepsy and are currently being studied in the veterinary field. These imaging modalities have become more readily available and have the potential to improve our understanding and refine the diagnosis of epilepsy in veterinary patients.
- ✔ The timing of image acquisition is key to understanding seizure-induced changes on conventional and functional imaging. The temporal relation to the last epileptic seizure should be considered

(interictal, ictal, or postictal) as well as the phase of the seizure-induced pathology (hyperacute, acute, subacute, or chronic).

- ✔ Structural epilepsy can develop in association with various intracranial diseases. It is important for veterinarians to have a fundamental knowledge of MRI interpretation and an understanding of characteristic findings with each encephalopathy when performing a diagnostic investigation on such a case.

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REFERENCES

1. Torisu S, Washizu M, Hasegawa D, Orima H. Brain magnetic resonance imaging characteristics in dogs and cats with congenital portosystemic shunts. *Vet Radiol Ultrasound*. 2005; 46(6):447–451.
2. Crawford AH, Stoll AL, Sanchez-Masian D et al. Clinicopathologic features and magnetic resonance imaging findings in 24 cats with histopathologically confirmed neurologic feline infectious peritonitis. *J Vet Intern Med*. 2017;31(5):1477–1786.
3. Hodshon AW, Hecht S, Thomas WB. Use of the T2*-weighted gradient recalled echo sequence for magnetic resonance imaging of the canine and feline brain. *Vet Radiol Ultrasound*. 2014; 55(6):599–606.
4. Weston P, Morales C, Dunning M et al. Susceptibility weighted imaging at 1.5 Tesla magnetic resonance imaging in dogs: Comparison with T2*-weighted gradient echo sequence and its clinical indications. *Vet Radiol Ultrasound*. 2020; 61(5):566–576.
5. Bittermann S, Lang J, Henke D et al. Magnetic resonance imaging signs of presumed elevated intracranial pressure in dogs. *Vet J*. 2014; 201(1):101–108.

6. Giannasi S, Kani Y, Hsu FC, Rossmeisl JH. Comparison of direct measurement of intracranial pressures and presumptive clinical and magnetic resonance imaging indicators of intracranial hypertension in dogs with brain tumors. *J Vet Intern Med*. 2020; 34(4):1514–1523.
7. Mizoguchi S, Hasegawa D, Kuwabara T et al. Magnetic resonance volumetry of the hippocampus in familial spontaneous epileptic cats. *Epilepsy Res*. 2014; 108(10):1940–1944.
8. Estey CM, Dewey CW, Rishniw M et al. A subset of dogs with presumptive idiopathic epilepsy show hippocampal asymmetry: a volumetric comparison with non-epileptic dogs using MRI. *Front Vet Sci*. 2017; 4:183.
9. Czerwik A, Płonek M, Podgórski P, Wrzosek M. Comparison of electroencephalographic findings with hippocampal magnetic resonance imaging volumetry in dogs with idiopathic epilepsy. *J Vet Intern Med*. 2018; 32(6):2037–44.
10. Kuwabara T, Hasegawa D, Kobayashi M et al. Clinical magnetic resonance volumetry of the hippocampus in 58 epileptic dogs. *Vet Radiol Ultrasound*. 2010; 51(5):485–490.
11. Milne ME, Anderson GA, Chow KE et al. Description of technique and lower reference limit for magnetic resonance imaging of hippocampal volumetry in dogs. *Am J Vet Res*. 2013; 74(2):224–231.
12. Johnson PJ, Luh W, Rivard BC et al. Stereotactic cortical atlas of the domestic canine brain. *Sci Rep*. 2020; 10(1):4781.
13. Frank L, Lüpke M, Kostic D et al. Grey matter volume in healthy and epileptic beagles using voxel-based morphometry – a pilot study. *BMC Vet Res*. 2018; 14(1):50.
14. Milne ME, Steward C, Firestone SM, O'Brien TJ, Moffat BA. Development of representative magnetic resonance imaging–based atlases of the canine brain and evaluation of three methods for atlas-based segmentation. *Am J Vet Res*. 2016; 77(4):395–403.
15. Stolzberg D, Wong C, Butler BE, Lomber SG. Catlas: An magnetic resonance imaging-based three-dimensional cortical atlas and tissue probability maps for the domestic cat (Felis catus). *J Comp Neurol*. 2017; 525(15):3190–3206.
16. Hamamoto Y, Hasegawa D, Yu Y et al. Statistical structural analysis of familial spontaneous epileptic cats using voxel-based morphometry. *Front Vet Sci*. 2018; 5:1–9.
17. Rusbridge C, Long S, Jovanovik J et al. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol. *BMC Vet Res*. 2015;11(1):194.
18. De Risio L, Bhatti S, Muñana K et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015; 11(1):148.
19. Glushakov A V., Glushakova OY, Doré S et al. Animal models of posttraumatic seizures and epilepsy. *Methods Mol Biol*. 2016; 1462:481–519.
20. Nagendran A, McConnell JF, De Risio L et al. Peri-ictal magnetic resonance imaging characteristics in dogs with suspected idiopathic epilepsy. *J Vet Intern Med*. 2021; 35(2):1008–1017.
21. Mellema LM, Koblik PD, Kortz GD et al. Reversible magnetic resonance imaging abnormalities in dogs following seizures. *Vet Radiol Ultrasound*. 1999; 40(6):588–595.
22. Viitmaa R, Cizinauskas S, Bergamasco LA et al. Magnetic resonance imaging findings in Finnish Spitz dogs with focal epilepsy. *J Vet Intern Med*. 2006; 20(2):305–310.
23. Hasegawa D, Orima H, Fujita M et al. Complex partial status epilepticus induced by a microinjection of kainic acid into unilateral amygdala in dogs and its brain damage. *Brain Res*. 2002; 955(1–2):174–182.

24. Hasegawa D, Nakamura S, Fujita M et al. A dog showing Klüver-Bucy syndrome-like behavior and bilateral limbic necrosis after status epilepticus. *Vet Neurol Neurosurg*. 2005; 7:1–14.
25. Mariani CL, Platt SR, Newell SM et al. Magnetic resonance imaging of cerebral cortical necrosis (polioencephalomalacia) in a dog. *Vet Radiol Ultrasound*. 2001; 42(6):524–531.
26. Malmgren K, Thom M. Hippocampal sclerosis-Origins and imaging. *Epilepsia*. 2012; 53(SUPPL. 4):19–33.
27. Lorincz BA, Anson A, Csébi P et al. Novel approach to magnetic resonance imaging of epileptic dogs — T2 relaxometry of the brain with emphasised hippocampus. *Acta Vet Hung*. 2017; 65(2):185–197.
28. Wagner E, Rosati M, Molin J et al. Hippocampal sclerosis in feline epilepsy. *Brain Pathol*. 2014; 24:607–619.
29. Klang A, Högler S, Nedorost N et al. Hippocampal necrosis and sclerosis in cats: A retrospective study of 35 cases. *Acta Vet Hung*. 2018; 66(2):269–280.
30. Classen AC, Kneissl S, Lang et al. Magnetic resonance features of the feline hippocampus in epileptic and non-epileptic cats: a blinded, retrospective, multi-observer study. *BMC Vet Res*. 2016; 12(1):165.
31. Raimondi F, Shihab N, Gutierrez-Quintana R et al. Magnetic resonance imaging findings in epileptic cats with a normal interictal neurological examination: 188 cases. *Vet Rec*. 2017; 180(25):610.
32. Hasegawa D, Orima H, Fujita M et al. Diffusion-weighted imaging in kainic acid-induced complex partial status epilepticus in dogs. *Brain Res*. 2003; 983(1–2):115–127.
33. Hartmann A, Söffler C, Failing K et al. Diffusion-weighted magnetic resonance imaging of the normal canine brain. *Vet Radiol Ultrasound*. 2014; 55(6):592–598.
34. Hartmann A, Sager S, Failing K et al. Diffusion-weighted imaging of the brains of dogs with idiopathic epilepsy. *BMC Vet Res*. 2017;13(1):338.
35. Hamamoto Y, Hasegawa D, Mizoguchi S et al. Changes in the interictal and early postictal diffusion and perfusion magnetic resonance parameters in familial spontaneous epileptic cats. *Epilepsy Res.* 2017; 133:176–182.
36. MacLellan MJ, Ober CP, Feeney DA, Jessen CR. Diffusion-weighted magnetic resonance imaging of the brain of neurologically normal dogs. *Am J Vet Res*. 2017; 78(5):601–608.
37. Hartmann A, von Klopmann C, Lautenschläger IE et al. Quantitative analysis of brain perfusion parameters in dogs with idiopathic epilepsy by use of magnetic resonance imaging. *Am J Vet Res*. 2018; 79(4):433–442.
38. Alisauskaite N, Wang-Leandro A, Dennler M et al. Conventional and functional magnetic resonance imaging features of late subacute cortical laminar necrosis in a dog. *J Vet Intern Med*. 2019; 33(4):1759–1765.
39. Olszewska A, Schmidt MJ, Failing K et al. Interictal single-voxel proton magnetic resonance spectroscopy of the temporal lobe in dogs with idiopathic epilepsy. *Front Vet Sci*. 2020; 7:644.
40. Kowalczyk MA, Omidvarnia A, Abbott DF et al. Clinical benefit of presurgical EEG-fMRI in difficult-to-localize focal epilepsy: A single-institution retrospective review. *Epilepsia*. 2020; 61(1):49–60.
41. Beckmann KM, Wang-Leandro A, Dennler M et al. Resting state networks of the canine brain under sevoflurane anaesthesia. *PLoS One*. 2020; 15(4):e0231955.
42. Kyathanahally SP, Jia H, Pustovyy OM et al. Anterior–posterior dissociation of the default mode network in dogs. *Brain Struct Funct*. 2015; 220(2):1063–1076.

43. Gonen OM, Kwan P, O'Brien TJ et al. Resting-state functional MRI of the default mode network in epilepsy. *Epilepsy Behav*. 2020; 111:107308.
44. Jokinen TS, Haaparanta-Solin M, Viitmaa R et al. FDG-PET In healthy and epileptic Lagotto Romagnolo dogs and changes in brain glucose uptake with age. *Vet Radiol Ultrasound*. 2014; 55(3):331–341.
45. Viitmaa R, Haaparanta-Solin M, Snellman M et al. Cerebral glucose utilization measured with high resolution positron emission tomography in epileptic Finnish Spitz dogs and healthy dogs. *Vet Radiol Ultrasound*. 2014; 55(4):453–461.
46. Martlé V, Peremans K, Audenaert K et al. Regional brain perfusion in epileptic dogs evaluated by technetium-99m-Ethyl cysteinate dimer spect. *Vet Radiol Ultrasound*. 2009; 50(6):655–659.
47. Huaijantug S, Theeraphun W, Suwanna N et al. Localization of cerebral hypoperfusion in dogs with refractory and non-refractory epilepsy using [99mtc] ethyl cysteinate dimer and single photon emission computed tomography. *J Vet Med Sci*. 2020; 82(5):553–558.
48. Hasegawa D, Tamura S, Nakamoto Y et al. Magnetic resonance findings of the corpus callosum in canine and feline lysosomal storage diseases. *PLoS One*. 2013; 8(12):e83455.
49. Wakshlag JJ, De Lahunta A, Robinson T et al. Subacute necrotising encephalopathy in an Alaskan husky. *J Small Anim Pract*. 1999; 40(12):585–589.
50. Abramson C, Platt S, Garosi L, Penderis J. L-2-hydroxyglutaric aciduria in Staffordshire bull terriers. *Vet Rec*. 2003; 153(3):95–96.
51. Yu Y, Hasegawa D, Chambers JK et al. Magnetic resonance imaging and histopathologic findings from a standard Poodle with neonatal encephalopathy with seizures. *Front Vet Sci*. 2020; 7:578936.
52. Hasegawa D, Yayoshi N, Fujita Y et al. Measurement of interthalamic adhesion thickness as a criteria for brain atrophy in dogs with and without cognitive dysfunction (dementia). *Vet Radiol Ultrasound*. 2005; 46(6):452–457.
53. Kerwin SC, Levine JM, Budke CM et al. Putative cerebral microbleeds in dogs undergoing magnetic resonance imaging of the head: a retrospective study of demographics, clinical associations, and relationship to case outcome. *J Vet Intern Med*. 2017; 31(4):1140–1148.
54. Alisauskaite N, Beckmann K, Dennler M, Zölch N. Brain proton magnetic resonance spectroscopy findings in a Beagle dog with genetically confirmed Lafora disease. *J Vet Intern Med*. 2020; 34(4):1594–1598.
55. Barkovich AJ, Guerrini R, Kuzniecky RI et al. A developmental and genetic classification for malformations of cortical development: Update 2012. *Brain*. 2012; 135(5):1348–1369.
56. Lazzerini K, Gutierrez-Quintana R, José-López R et al. Clinical features, imaging characteristics, and long-term outcome of dogs with cranial meningocele or meningoencephalocele. *J Vet Intern Med*. 2017; 31(2):505–512.
57. Hall R, Labruyere J, Volk H, Cardy TJ. Estimation of the prevalence of idiopathic epilepsy and structural epilepsy in a general population of 900 dogs undergoing MRI for epileptic seizures. *Vet Rec*. 2020; 187(10):e89.
58. Bentley RT. Magnetic resonance imaging diagnosis of brain tumors in dogs. *Vet J*. 2015; 205(2):204–216.
59. Bentley RT, Ober CP, Anderson KL et al. Canine intracranial gliomas: Relationship between magnetic resonance imaging criteria and tumor type and grade. *Vet J*. 2013; 198(2):463–471.
60. Young BD, Levine JM, Porter BF et al. Magnetic resonance imaging features of intracranial astrocytomas and oligodendrogliomas in dogs. *Vet Radiol Ultrasound*. 2011; 52(2):132–141.

61. Pakozdy A., Patzl M, Zimmermann L et al. LGI proteins and epilepsy in human and animals. *J Vet Intern Med*. 2015; 29(4):997–1005.
62. Hasegawa D, Ohnishi Y, Koyama E et al. Deleted in colorectal cancer (netrin-1 receptor) antibodies and limbic encephalitis in a cat with hippocampal necrosis. *J Vet Intern Med*. 2019; 33(3):1440–1445.
63. Steinmetz S, Tipold A, Löscher W. Epilepsy after head injury in dogs: A natural model of posttraumatic epilepsy. *Epilepsia*. 2013; 54(4):580–588.
64. Beltran E, Platt SR, Mcconnell JF et al. Prognostic value of early magnetic resonance imaging in dogs after traumatic brain injury: 50 cases. *J Vet Intern Med*. 2014; 28(4):1256–1262.
65. Caine A, Brash R, De Risio L et al. MRI in 30 cats with traumatic brain injury. *J Feline Med Surg*. 2019; 21(12):1111–1119.
66. Garosi L, Mcconnell JF, Platt SR et al. Clinical and topographic magnetic resonance characteristics of suspected brain infarction in 40 dogs. *J Vet Intern Med*. 2006; 20(2):311–321.
67. Arnold SA, Platt SR, Gendron KP, West FD. Imaging ischemic and hemorrhagic disease of the brain in dogs. *Front Vet Sci*. 2020; 7:279.
68. Dewey CW, Rishniw M, Johnson PJ et al. Interthalamic adhesion size in aging dogs with presumptive spontaneous brain microhemorrhages: A comparative retrospective MRI study of dogs with and without evidence of canine cognitive dysfunction. *PeerJ*. 2020; 8:e9012.

Electroencephalography 07

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There are many methods of measuring brain function including positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG).[1] Out of all these modalities, there is only one bedside test capable of monitoring brain function in real time: electroencephalography (EEG). It provides minimally invasive insight into brain activity with reasonable spatial and temporal resolution. The downside, however, is that the EEG learning curve is considered fairly steep for both key knowledge areas pertinent to clinical veterinary practice: the recording technique and interpretation.

Why record an EEG?

Electroencephalography is the only diagnostic test that can answer the often-challenging clinical question, "is it an epileptic seizure?". This is highlighted in the 2015 International Veterinary Epilepsy Task Force consensus proposal regarding the diagnosis of epilepsy. Only the highest confidence in the diagnosis, tier III, can be achieved with EEG confirmation of ictal or interictal abnormalities[2] (see Chapter 1, Box 1.4). Even when it comes to assessing an episode via video recording, agreement between veterinarians as to the nature of an episode is low, except in the case of a generalized tonic-clonic seizure.[3] Electroencephalography distinguishes between the clinical diagnosis of epilepsy and other episodic or transient paroxysmal disorders.[4] It provides diagnostic refinement when epileptic seizures have similar physical or behavioral manifestations, like absence and focal seizures sometimes do.[5–8] In this way, EEG becomes an essential part of the definition of electroclinical syndromes.[7,9] These syndromes are defined by a typical age of onset, specific EEG characteristics, seizure

semiology (the physical manifestations) and other features such as genetic testing, all of which form a distinctive, recognizable clinical disorder. Electroencephalography is useful in the veterinary intensive care unit where it distinguishes between coma and nonconvulsive seizures and optimizes patient management for status epilepticus cases.[10–15] Finally, EEG is an integral part of presurgical evaluation for epilepsy in dogs and cats, admittedly a currently rare procedure.[1]

Electroencephalography is a key component of polysomnography, used to study and diagnose sleep-related disorders. In dogs this would include rapid eye movement (REM) sleep behavior disorder.[16–20] Conversely, EEG-detectable alterations to sleep patterns can be manifestations or comorbidities of neurological disorders, as well as cognitive, behavioral or social dysfunction, or physiological aging.[21–25]

Another major indication for EEG use in species other than dogs and cats is documentation of brain function. This documentation can be for determination of brain death.[26–28] More commonly, it is used to control drug administration to maintain specific depths of anesthesia in people, both for surgery and in the intensive care unit (ICU).[29–32] This function incorporates EEG data into proprietary algorithms developed by various medical monitor venders to create visual displays on anesthesia or ICU monitoring equipment.[32] These specialized monitors have been explored in veterinary medicine and more particularly in canine anesthesia to test the antinociceptive, sedative, and anesthetic effects of various pharmaceuticals.[33–39] More recently, assessment of such proprietary algorithms for monitoring of canine brain function in the ICU has begun by looking for correlations with the Modified Glasgow Coma Scale.[40]

A final consideration for recording EEG data is to gain experience and knowledge. There are yet to be standards for EEG in any veterinary species comparable to those agreed for people. The historical veterinary EEG literature needs to be updated using current technology and information. Fortunately, much-needed knowledge about the various uses and limitations of EEG continues to be acquired by the many veterinary EEG research groups globally, including to support antiseizure and other drug development.[41] Future uses might include wearable or implantable EEG devices for seizure detection and forecasting; these may revolutionize personalized therapeutic approaches and caregiver quality of life.[42–46]

HOW DOES EEG WORK?

Physiological basis

Electroencephalography works for two main reasons.[47] First, the brain is an electrically active organ. Second, these electrical fields conduct through the volume of the brain, skull, and head. These concepts have been developed since they were discovered in the late 19th century.[47] The basic physiological principle for EEG is similar to that of other electrodiagnostic tests, that is, recording the electrical activity of the target organ. In the brain, the significant electrical generators of the EEG signal are the pyramidal neurons of the cortex in layers III, V, and VI. These pyramidal neurons have their long axis oriented perpendicular to the surface of the cortex, with their dendrites more superficially located.[48] Incoming volleys of action potentials create excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs, respectively) in the dendritic trees of these neurons. These potentials, and their associated changes in the local extracellular fluid ion concentrations, result in the formation of a dipole along the long axis of the neurons, generating an electrical field.[49,50] Excitatory postsynaptic potentials create a dipole with the negative pole towards the cortical surface. This field is propagated through the tissues of the head by volume conduction (and capacitance) to where it is sensed by measurement devices, i.e., the electrodes.[50,51]

The electrical field generated by a single neuron dipole is insufficiently large for detection other than by an immediately adjacent electrode. A huge population of neurons needs to form dipoles simultaneously in order for their field to be detected at the scalp.[49] The recorded electrical activity arises from a depth of approximately 5 mm and a surface diameter of 1–2 cm.[50] This is the concept underlying the different forms of EEG that could be performed. Intracranial EEG involves electrodes either placed within the brain parenchyma to record the focal activity of deep structures or on the cortical surface to delineate the epileptogenic zone.[1,45] The proximity of these intracranial electrodes to the electrical sources allows high spatial resolution but placement requires a surgical approach and depends on the individual patient's case circumstances. Typically, intracranial EEG depends on initial source localization by scalp EEG. Scalp EEG is the clinical diagnostic workhorse, ideal for routine clinical use as it is minimally invasive.[50]

Fortunately for scalp EEG, the mass formation of postsynaptic potentials in a large population of neurons happens through the temporal coordination of the neural processes underlying cortical functions such as behavior, perception, cognition and memory. This coordination results in synchronized neuronal activity detectable by scalp EEG as rhythmic oscillations.[52] This neuronal activity is well visualized when presented as a plot of voltage differences between two scalp electrode recording sites over time,[53] hence the term *electro* (electrical) *encephalo* (brain) *gram* (picture). These oscillations are associated with brain state changes such as the stages of sleep and waking. The converse of synchronized activity is referred to as *blocking*, where there is an attenuation and replacement of synchronized waves with a lower amplitude, higher frequency signal.[52,53]

Frequency and amplitude

Two parameters, frequency and amplitude, are the main descriptors of these oscillations;[50] other features to note include the topographical field, gradient across the field, or any associated time lag. Frequency is measured in cycles per second, with Hertz (Hz) as the unit. Amplitude is measured in microVolts (μV); it varies between a few to several hundred μV, and is usually below 100 μV in dogs.[50] Various factors affect the amplitude measured at the scalp, including:

- The voltage of the cortical source
- The cortical area involved
- The depth of the source
- The intervening tissues
- The synchronicity of the source neurons[54]

The clinically relevant cortical-origin waveforms on the scalp EEG generally fall within the frequency range of 1–70 Hz.[55] Note that this range overlaps with that of other physiological electrical signals. The EEG range is broken by convention into frequency bands or bins that are associated with specific mentation states, with the gamma band being subsumed into the beta band by many clinical electroencephalographers (see Table 7.1).[53,56]

Amplitude is magnified on the screen using sensitivity settings in units of μV/mm.[55] Amplification, gain and sensitivity are practically synonymous. The scale has the opposite effect on what is seen, where a large number means a low sensitivity setting and a small number means a

high sensitivity setting. Recordings are typically made and viewed with an initial sensitivity setting between 5 to 10 μV/mm.[55] Sensitivity can be adjusted as necessary during review to "zoom in" to inspect detail.

TABLE 7.1. Frequency band groupings over the EEG bandwidth, with associated mentation states. The gamma band is often subsumed into the beta band in clinical EEG discussion.

Frequency (Hz)	Band name	Mentation state
0.5 to <4	delta	sleep
4 to 7	theta	sleep
8 to 13	alpha	wake
>13 to 30	beta	wake
>30 to 80	gamma	wake

Solid angle theorem

Scalp EEG does have limitations. As discussed above, it does not measure the activity of a single neuron, but instead the summated PSPs of thousands of neurons. In addition, localization of the signal source is complicated. An electrode will "see" the sum of nearby dipoles' fields, that is, the greater the active area "seen" by the electrode, the larger the detected signal, a concept governed by the solid angle theorem.[49] This is affected by timing–the more synchronous the creation of dipoles, the stronger the field, and thus the stronger the EEG signal. Further, adjacent opposite dipoles will cancel each other out. Radial dipoles, perpendicular to the surface of the scalp, make a better EEG signal than tangential dipoles parallel to the scalp surface.[57] As a visual analogy for the solid angle theorem, look at a nearby plate on a table. The surface of the plate represents the active area of cortex, a region of synchronous negative dipoles, known as a **dipole layer**. Your eye is the electrode. The plate's apparent size is its solid angle. If you are standing over the table looking straight down at the plate, it will have a large apparent size (solid angle), representing a strong signal, whereas if the plate is at the far end of the table, it will have a smaller apparent size (solid angle), resulting in a weaker signal. The closer the plate is to your eye, the larger its apparent size (solid angle) and therefore the stronger the signal. The plate (signal source) itself has not changed, but the location of your eye (the detector) has, and this is what affects the detected signal. The converse is also true–consider the dipole layer at various locations in the cortex–the

solid angle formed at the top of a gyrus would be very different from one formed on a sulcal wall as detected by a stationary electrode. It follows, then, that the more electrodes that are used, the more accurate the map of the scalp field potential.[58] Human EEG standards recommend at least 21 electrodes placed to record a minimum of 16 channels,[58] although this may be difficult for veterinary patients with small skulls.

Differential amplification

All these analog biosignals are then digitized by the recording apparatus of the EEG machine. This digitization affects the signal that is eventually seen. As the EEG is a plot of the voltage difference over time between two points on the scalp, the recording itself should be made with a single reference electrode that is not part of the topographical electrode placement protocol[58] (see also *Electrode arrays* section); this allows post-hoc reformatting of the data for the optimal display of activity (see the later comments on montages). As the cortical signal is relatively weak compared to the ambient electrical noise, electroencephalography machines use differential amplifiers, which measure the difference between two voltage signals (from the electrode of interest and the reference electrode) and magnify the output signal through multiplication by a constant (Fig. 7.1). The sensitivity setting (mentioned earlier) controls the dynamic range of the amplifier. Differential amplifiers have the helpful ability of minimizing artifactual electrical potentials common to the two inputs; this is known as **common mode rejection**.[53] Such common artifacts may include noise from the recording environment, e.g., fields generated by lights or wiring. However, the risk is that common cortical signals will also be reduced.[55] Impedance (which is usually equal to electrode resistance, i.e, the resistance to the flow of electric current between the electrode and the tissue) affects common mode rejection—ideally, the impedance value should be kept uniform across electrodes and below 5–10 kΩ according to human EEG standards.[58,59] By international convention, in EEG, when input 1 is more negative than input 2, the resulting waveform shows an upward deflection.[53] Similarly, wiring of inputs to these differential amplifiers is responsible for the phase reversal visual feature on bipolar montages (see later comments on montages). Note that a consequence of differential amplification is that no channel displays the cortical signal at a single electrode location alone–what is displayed is always the difference between two electrode channels.[55]

Sampling frequency

There is one final effect of digitization on the EEG biosignal that should be mentioned: the sampling frequency. The discrete-time digitization of a continuous-time analog signal involves noting the data values at a certain rate over time. A sampling frequency that is too low will misrepresent the original analog signal, a concept described by the Nyquist theorem.[53] In order to faithfully reproduce the analog biosignal the sampling frequency must be at least twice the highest frequency of interest.[53] Even this minimum merely preserves the frequency content of the data—reasonable reproduction of waveforms may require sampling at five times the highest frequency of interest.[53] As mentioned before, scalp EEG signals range up to around 70 Hz, so the sampling frequency typically ranges between 250–500 Hz.[53,59] Without this, a distortion of the signal is introduced in the recording, called an **aliasing error**.[53]

HOW TO RECORD EEG?

Recordings are most likely to be made in a veterinary clinic under veterinary supervision, because reports of home recordings are rare.[60] The awake recording technique allows EEGs to be recorded in dogs while at home with their family, in a similar way to 24-hour Holter monitoring in cardiology patients. An ambulatory EEG machine of the type used for pediatric human outpatients would be needed, ideally with integrated videosynchrony.[61] Figure 7.2 shows a dog wearing a wireless EEG system.

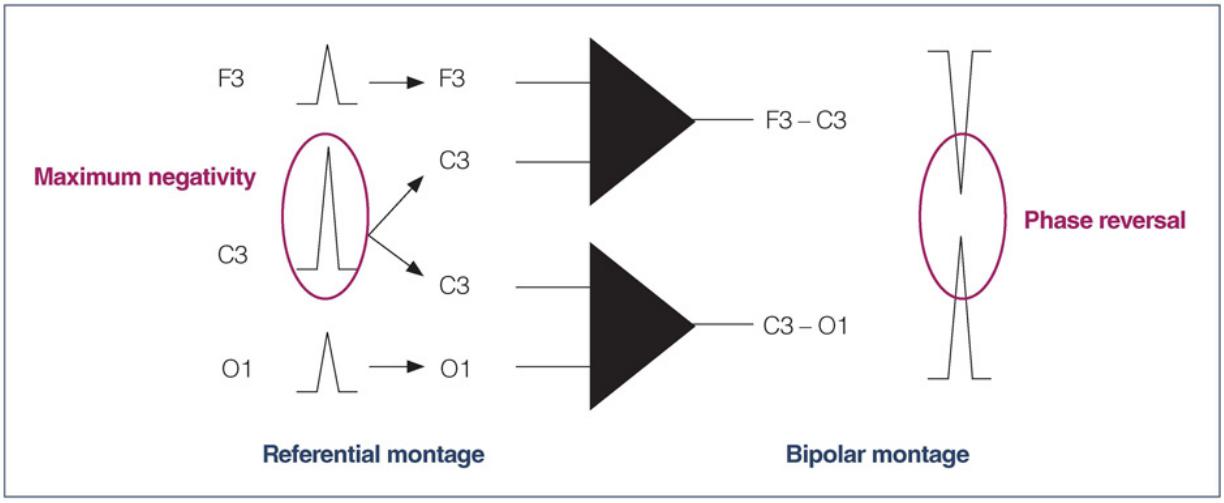


FIGURE 7.1. Diagram illustrating several keys principles in EEG. Differential amplifiers are represented by the black triangles. Each amplifier takes two electrode inputs, top: F3 and C3, bottom: C3 and O1, and outputs the result of subtracting input 2 from input 1. When these signals are displayed on a screen, they are arranged in a montage. Left: referential montage; each channel is the difference between the named electrode and a reference electrode. On a referential montage, the electrode closest to the cortical signal will have the maximum negative amplitude, referred to as *maximum negativity*. Right: the same signals as seen on a bipolar montage where adjacent electrodes are subtracted from their neighbors. The sharing of an electrode by adjacent channels results in an instrumental phase reversal. The polarity convention means that negative is up.



FIGURE 7.2. A Border Collie wearing a wireless EEG system. The white self-adhesive bandage covers zinc oxide fabric tape securing subdermal wireless electrodes on the scalp. The braided electrode leads are secured with a tension loop to a self-adhesive bandage collar (not visible due to the long fur) and then proceed to the transmission box on the dog's back. The grey and black fabric jacket has a large pocket to hold the transmission box (with extra self-adhesive bandage to keep it from slipping).

Electrode arrays

The first step of EEG is instrumentation. This involves applying electrodes to the scalp and wiring up the connection to the EEG machine. Several questions arise regarding the location and number of electrodes. There are no validated standard electrode placement protocols for dogs or cats.[1,2,62]

One major benefit of a validated standard is to be able to compare recordings between patients and clinics.

In people, electrodes are positioned using the international 10–20 standard.[63–65] This involves measuring between palpable bony landmarks of the skull and placing electrodes at defined points that are 10% or 20% of the distance. The positions are named, e.g., F3, Cz, or O2. A similar nomenclature for these electrodes is generally followed in veterinary electrode arrays, with odd numbers for the left side, even numbers for the right side, and z indicating midline.[1,4,66] The initial capital letter designates the cerebral region over which the electrode is believed to be placed, e.g., F for frontal, C for central, or O for occipital. The largest electrode arrays in veterinary use typically place around 13–15 electrodes plus ground and reference.[1,4,66] Figure 7.3 illustrates one array schematic (a, b) and how it looks on a dog (c). The original electrode arrays were two plus ground and reference.[67,68] Some veterinary electroencephalographers continue to use an older, smaller five-channel (plus ground and reference) protocol.[69] Associated with this, an older nomenclature also exists in the veterinary literature: exemplar electrodes are RF and LO, where right and left are designated R and L respectively, with F or O indicating frontal versus occipital respectively. In this protocol, V may be used to indicate the vertex electrode, equivalent to Cz.

As discussed earlier, the more electrodes that are used, the more accuracy in the definition of the region of cerebral activity.[58] To demonstrate the cortical origin of a potential, it is ideal to be able to show that it is detectable by electrodes throughout its field, with an appropriate gradient where the signal has lower amplitude the further the electrode is from the epicenter. On large enough heads, there may be a detectable time lag, with the peak appearing later at more distant electrodes. On a limited electrode protocol, e.g., five electrodes at RF, LF, RO, LO, and V, it may be hard to distinguish sleep transients from interictal discharges as only coarse spatial resolution of the signal is available. A limited electrode protocol may not be a problem if the EEG is being performed as part of a sleep study rather than for epileptic seizure diagnosis.[70] Finally, a limited electrode protocol severely restricts the possibility of post-hoc reformatting of the data to help with interpretation. The benefit of a limited electrode protocol is its speed of instrumentation.

Electrode types

Having decided the number and location of electrodes to place, the next step is how to attach them to the patient. This will depend on the type of electrode chosen. Electrodes comprise a metal contact surface connected to a terminal end (to plug into the machine) by means of an insulated wire. There are two types of electrodes in common veterinary usage:

- Skin surface electrodes
- Needle or subdermal wire electrodes[71]

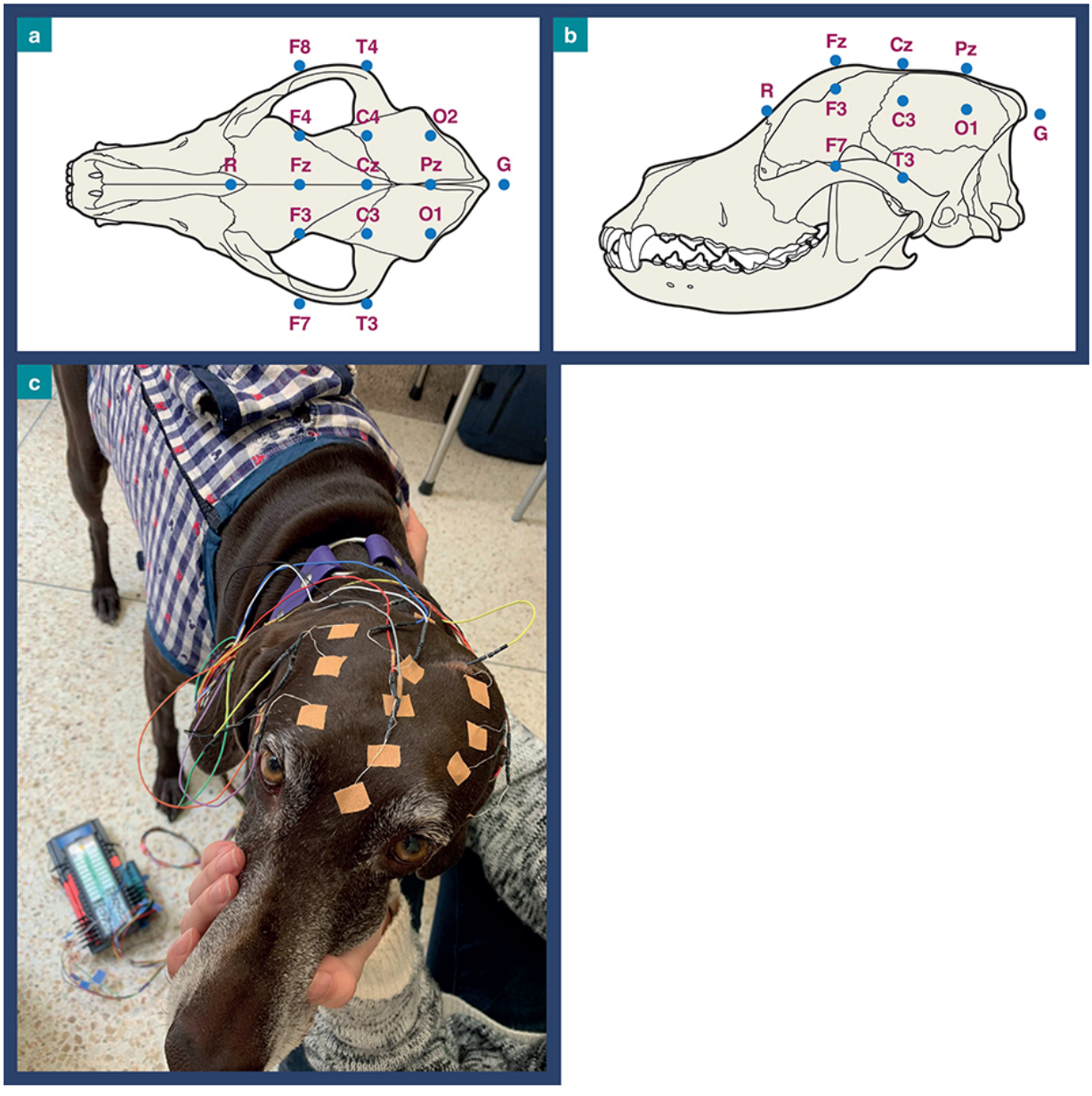


FIGURE 7.3. An electrode array in common use. a) Electrode positioning, dorsal view of the skull. b) Electrode positioning, lateral view of the skull. Adapted from James FMK et al. (2017).[4] c) A 6-year-old, FS, German Shorthaired Pointer having subdermal wire electrodes placed for unsedated EEG. Each electrode is fixed in place with a square of zinc oxide adhesive tape.

Skin surface electrodes are noninvasive and are attached or glued to bare (shaved) skin, requiring electrode paste or gel as an intermediary conductor. These may be familiar as alligator clips, electrocardiogram (ECG) sticker electrodes, or the less common metallic shallow cups with a hole for refilling the conducting gel. Surface disk electrodes are the ones routinely used in people.[59] Their benefits include rapid non-invasive attachment and removal. Concerns with this type of electrode include the need for periodic conducting gel maintenance, local electromyogram (EMG) artifact, loss of contact, and movement artifact.[72,73] Further, these electrodes may not be compatible with advanced imaging modalities, creating both computed tomography (CT) and magnetic resonance imaging (MRI) artifacts.[74]

Needle or subdermal wire electrodes are common minimally invasive electrodes, the latter being inserted under the skin using a hypodermic needle vehicle (see Figs. 7.2 and 7.3), whereas the former combines both insertion and electrode functions in one needle tip. Both types should be taped to the skin at the insertion point to keep them in place. Needle electrodes are the most common EEG electrode in veterinary use.[71] Benefits include the convenience of rapid, easy application without skin or fur preparation and a reduced likelihood of movement or slippage. The neuroimaging incompatibilities they suffer are similar to those of surface electrodes[74] and they are not recommended in people.[58] Subdermal wire electrodes have the specific benefit of imaging compatibility, but they are easily dislodged without fixation and may cause local bleeding in up to 40% of placements in humans.[75]

Clinical comparison of gold cup with needle and subdermal wire electrodes found that all three had comparable function over an 8-hour recording day in dogs.[76] All of these electrode types benefit from additional fixation using adhesive tape or an adhesive bandage. Two particularly effective adhesive materials are the transparent adhesive waterproof film dressings used for surgery sites and zinc oxide fabric tapes (see Figs. 7.2 and 7.3). It is helpful to affix each electrode with adhesive tape upon placement to prevent them from dislodging while the others are attached.

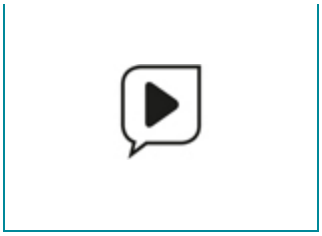
However, before committing to whole-head sticky bandages, please remember to check the electrode impedances; this is a function offered on the EEG machine software control panel. An extremely high impedance (>20 kΩ) on a single channel means that the electrode, its attachment to the patient, and its connection to the machine need to be checked for integrity; it may need to be replaced entirely. Extremely high impedances across all channels mean that the reference and ground electrodes need checking. Check the impedances again after the wrapping is finished, then again intermittently through the recording and finally at completion. This is one way to ensure the electrodes are still functioning under the layers of wrapping.

Instrumentation

Generally, instrumentation is faster in an anesthetized or sedated patient as they are less wriggly, but it is possible to set up about 1 in 5 dogs with only physical restraint and positive reinforcement[4] (see Video 7.1). Using anesthesia or sedation for instrumentation does not appear to reduce the likelihood of diagnostic success.[77] Once electrodes are in place, extra protection for the electrodes and leads may be applied using self-adhesive bandages and Elizabethan collars as needed. Sometimes less is more, but try to avoid stray wires dangling near the ears as these are often a trigger for scratching. Do not forget to check electrode impedances. The cable should be secured to self-adhesive bandage around the neck with a tension loop; avoid attaching it to the collar or harness to minimize unwanted tension on the electrode leads while on leashed walks (see Fig. 7.2).

The instrumentation of a 3-year-old Boxer sped up to three times normal speed. There is no sedation, only light physical restraint and praise. Subdermal wire electrodes are placed, followed immediately by little squares of white tape placed over the insertion point. Once all the electrodes are placed, they are plugged into extension leads which themselves are plugged into the wireless EEG transmitter box. A pause is taken to check electrode impedances, then further strips of white tape are placed over the scalp. The electrode leads are gathered into a "ponytail" with self-adhesive bandage strips and secured to a self-adhesive bandage collar in a tension loop. As there was no fitted body harness or jacket available, a self-adhesive harness is created on the spot and the transmitter box is secured between the shoulder blades. This remained functional until the recording was discontinued 5.5 hours later.

Video 7.1.



Electroencephalography machines can be wireless or wired. The benefit of wireless recording is that the patient can behave freely and naturally, with flexibility as to location and environment. This can also be achieved to a degree with wired machines using meters-long cables but brings with it the risk of entanglement as can occur with intravenous lines. Some wireless machines can livestream the data to a base station display. This function can be useful for patients in the ICU where the base station can be set up at the nurse's station or in the neurology offices, or for fieldwork where events of interest occur during certain trigger activities. Another useful function is remote access over the internet, which means that questions or concerns raised by the ICU can be viewed by a veterinarian from home while on call.

Patient restraint

While EEG recording has historically been performed with patients maintained under a light plane of general anesthesia or sedation, it is also possible to successfully record completely awake patients.[4,67,76] Awake recording can be helpful to capture behavioral events of interest as the absence of abnormalities on an EEG recording does not rule out either epileptic seizures or behavioral events. Awake recording also offers the opportunity to present triggers, if they exist for the patient. Conversely, recording under sedation or anesthesia definitely reduces the physiological artifacts that are encountered during awake recording, particularly when muscle paralysis is induced.[78]

Activation techniques

Presentation of patient-specific triggers is a form of a technique known as **activation**. Other methods of activation are more general. For people, they include spontaneous sleep, withdrawal of antiseizure drugs (ASDs), hyperventilation, and intermittent photic stimulation (IPS).[79] Activation techniques are used to increase the likelihood of the EEG's diagnostic

success, either to enhance physiological waveforms or provoke epileptogenic paroxysmal discharges.[53]

For people, sleep deprivation is helpful for diagnosis of idiopathic generalized epilepsies but not focal epilepsies.[80] Sleep deprivation involves allowing half the time of a normal sleep pattern[59] which, in addition to sleeping out-of-cycle during the EEG, enhances sleep instability causing interictal epileptogenic discharges.[81–84] How sleep deprivation might affect the EEG of dogs and cats, species with sleep patterns quite different from those of people, is yet to be described. Whereas sleep may be induced by prior sleep-deprivation for people,[80] induction of spontaneous sleep during awake recordings in dogs may be achieved by having the handler's attention focused on their smartphone or similar. An out-of-the-way quiet room or run helps, as does lowering the lights and providing a comfortable resting place for the dog. Cats are aided by a hiding place, so plan ahead with furnishing of the recording location and video camera placement.

Some drugs can have activating effects on the EEG of dogs, e.g., phenothiazines.[71,76] Withdrawal of ASDs is only rarely performed in veterinary medicine.[85] Hyperventilation can only be performed in veterinary EEG when recording with control of the airway under general anesthesia.[78,86,87] For performing IPS in humans, the recommendation is that the subjects are awake, because sleeping individuals or those with eyes closed may be less photic-sensitive.[88] An abnormal response to both hyperventilation and IPS is an epileptogenic paroxysmal discharge; such discharges are described later. Induction of a photoparoxysmal response in people with photosensitive generalized epilepsies means that the IPS results in an epileptogenic pattern on the EEG that eventually precipitates an epileptic seizure (absence, myoclonic, or tonic-clonic).[89] In the veterinary literature, IPS is used with either general anesthesia or sedation for patient restraint.[78,86,87,90] The role of IPS in the diagnosis of small animal epilepsy syndromes has not been methodically studied, so specific photosensitive epilepsy syndromes have not been identified yet beyond the juvenile myoclonic epilepsy in the Rhodesian Ridgeback.[90]

Collection of other data

Polygraphy involves the recording of other biosignals such as ECG, electrooculography (EOG), and EMG. Recording these signals is useful for two reasons. First, they help to identify physiological artifacts on the EEG.

Second, they give information about behavioral states, particularly during sleep studies. Thus, it is advantageous, if possible, to record other biosignals simultaneous with the EEG. An example of ECG artifact on the EEG is presented in Figure 7.4.

Simultaneous video recording during the EEG brings further advantages in terms of confirming episodes of interest, characterizing the physical manifestations of an episode, or correlating behavior states with the EEG data.[4,5,61,91–93] For adult humans, the diagnostic yield of video-EEG can be 66–69%.[94] In pediatrics, there is a similar diagnostic yield of up to 70%.[91,95] Video-EEG performed in unsedated dogs has a comparable diagnostic yield of 72%.[4]

Not all EEG systems and software packages have the built-in ability to capture and review synchronized video. If video-EEG is not available with the system at hand, video is still extremely useful particularly if the recording has a timestamp to aid manual synchronization. Consider that a brief video recording using a cell phone camera can help to clarify the order of events when evaluating semiology. If in doubt about the location of the onset of any physical manifestations, focus the camera on the face. If doing a sleep study, e.g., to diagnose sleep-related disorders, try to get the whole body in the camera's view. To confirm the video-synchronization, it is advised to generate a video-EEG artifact in every record, e.g., disconnect/reconnect a lead while video recording.

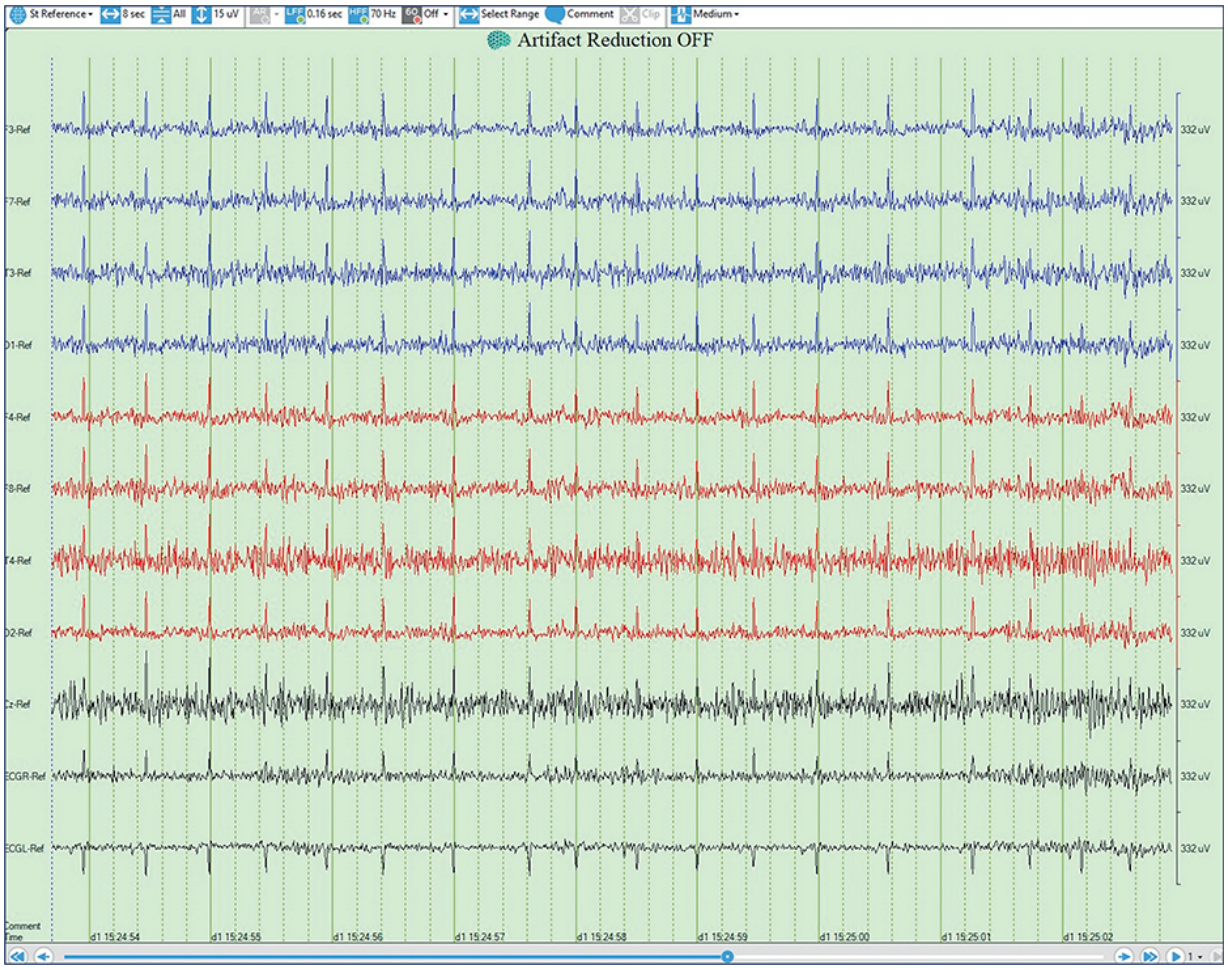


FIGURE 7.4. Electrocardiographic (ECG) artifacts contaminating all channels of a referential montage in an EEG recording of a dog. The last two channels were specifically recorded ECG channels. The QRS complex manifests as a negative transient of very short duration on the ECGR-Ref channel at the same time as a positive transient of identical duration on the ECGL-Ref channel. The sharp, short duration negative transient is picked up in all the channels of the montage. There is also muscle (electromyographic) artifact, worse on the T4-Ref and Cz-Rec channels. This is a limited 9-electrode array where C3/4, Fz and Pz have not been recorded due to the size of the patient's head. Left side of the head channels are colored blue; right side of the head channels are colored red; midline channels are black. Left y-axis: channels. Right y-axis: 332 µV per marker. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 8 seconds per page, sensitivity: 15 µV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF): 70 Hz, and notch filter: off.

Other recording considerations

If recording awake, try to ensure the recording includes all the stages of wakefulness, drowsiness, and sleep prior to attempting activation techniques. This is useful particularly if the triggers involve chasing balls or playing tug, for example, as the equipment may come loose. An optimal

length of recording under general anesthesia or sedation has yet to be determined in veterinary epileptology. In awake recordings, it appears that 95% of dogs will present at least one abnormality within 4.5 hours.[77]

As with any medical procedure, the recording should note patient details, signalment, date and time. This is usually captured by the machine's acquisition software during set-up as veterinary clinics will likely be using machines designed for human medicine. Please also note the drugs that the patient received prior to and during the recording: both those used for anesthesia and sedation as well as chronic medications. This will help the reviewer to determine whether the drugs influence the findings.

Finally, if a handler is present during the recording, use them. Most machines will allow comments and patient-derived event markers to be made during the recording. These can be created by either special buttons or specific keystrokes. These markers and comments by witnesses to the events of interest can help speed up the review process as they can be jumped to like digital bookmarks within the record. Video-recording the triggering of an event marker is also a way to routinely confirm the synchronization of the video and EEG recordings on your system.

HOW TO INTERPRET EEG?

Review software for interpretation may or may not be bundled with machine's acquisition software. There are a variety of independent review software programs available, which range from freeware tools through to medical-grade programs that can access recordings from multiple machine manufacturers. There is a universal EEG data file format that can be exported across platforms, the European Data Format (EDF). While some comments and variables such as electrode impedance values may not transfer nicely, the basic signal is usually accessible. The review software generally opens into a workspace that displays the recordings for the veterinarian's choice of qualitative or quantitative review.

Quantitative review

Quantitative review involves the application of mathematics to the EEG data, evaluating and analyzing portions of the recording. This pulls out

trends in variables such as frequency-specific power, derived via Fourier transform, or interhemispheric coherence. This type of EEG analysis, known as **spectral analysis**, is most commonly used in research or anesthesia and ICU settings.[36,96] Electroencephalogram review software will usually have some basic quantitative review tools available, with some platforms offering more options than others.

Quantitative variables that are most frequently derived from the power spectrum include the spectral edge frequency (F95), median frequency F50, and total power. A fast Fourier transform is usually used to transfer the data from the time domain to the frequency domain. This breaks down the signal into its component frequencies and their power, i.e., how much they contribute to the signal in the period examined, resulting in a power spectrum for that epoch.[97] Another similar technique presents the evolution of this data over time, plotted as a heat map or spectrogram,[97] which is a nice visualization of trends in the EEG. Finally, wavelet analysis is helpful to identify brief signals or those with sudden onset/offset; these include artifacts, spikes, and sharp waves.[97]

Qualitative (visual) review

Qualitative or visual review involves inspection of the plots of the differences in electrical potentials over time for specific electrode pairs. While this is typically done by an expert reviewer, proprietary algorithms exist to remove artifacts and identify epileptogenic patterns. These algorithms have not yet been validated for use in veterinary epilepsy.

Proprietary algorithms bundled with some software options include spike or seizure detectors. These are used in human epileptology to flag events for the epileptologist to review. In this way, they may help to reduce the amount of time needed to review a recording by highlighting areas of interest. These algorithms have yet to be validated in small animals.

Montages

When displayed on a screen, the arrangement of the derivations, or channels, of the electrode pairs is called the montage.[50,53,98] There are two types of montage: **referential** and **bipolar** (see Fig. 7.1). Both types of montages are used when visually analyzing an EEG as the two views of the same data help to construct a three-dimensional mental image of the cortical potential, similar to taking two-view radiographs of the vertebral column to

assess for luxation. Video 7.2 shows how an event with a large amplitude and short duration may be more visually arresting on a bipolar, rather than referential, montage.

Custom referential or bipolar montages, constructed on the fly in the review software, can be helpful to focus on abnormalities of interest. **Paired-channel montages (**e.g., F3-Ref, F4-Ref, C3-Ref, C4-Ref, and so on) help highlight hemispheric symmetry; however, this distorts anatomical organization. **Paired-group montages** group channels from homologous brain areas, e.g., left and right frontal are placed together, giving a fair sense of symmetry with some distortion of the anatomy. Unpaired montages where electrodes are placed in anatomical neighboring sequences, e.g., from front to back, left to right, or circumferentially, offer the least anatomical distortion but the worst visual display for picking up hemispheric asymmetry. Fortunately, post-hoc re-montaging is a simple process with digital EEG machines and review software. The visual difference between paired (Fig. 7.5) and unpaired (Fig. 7.6) montages is striking–these figures use eye movements to emphasize the effects of the different channel groupings.

Referential montages

Referential montages come in several forms, either computed or real. The **common average referential montage** computes an average potential using some or all of the electrodes in the array. This average potential is then used as a reference electrode. A more complex version is the **Laplacian montage**, where the reference for each electrode is the weighted average of neighboring electrodes. This montage emphasizes regions of local voltage peaks while de-emphasizing widely distributed activity. The simplest is the **common reference montage** in which each of the channels has the same reference electrode. Ideally, this electrode is placed on an electrically inactive site on the body to minimize any risk of detecting the same cortical signal as the other electrode it is being compared to.[50] On a referential montage, epileptogenic patterns present as negative, upward deflections, following the polarity convention.[53] The maximum negativity indicates the electrode closest to the source of the potential. The benefits of a referential montage beyond the unambiguous determination of field polarity include the minimal distortion of the EEG pattern and the clear characterization of widespread or complex fields. However, because there is

no electrically neutral point on the body, there is no single reference electrode that will be optimal for all recording situations. For example, if a reference is placed over the cortical source, that signal would be detected by the reference as well as adjacent electrodes in the field, meaning that the signal would be minimized by the differential amplifier on a referential montage.[50] These limitations, known as **active reference** or **nonzero reference**, are somewhat mitigated by the ability to re-montage post-hoc in digital recordings. As the best way to reduce these unwanted effects is at the point of recording, an observant electroencephalographer should re-reference (switch to a new reference electrode position) during the recording as needed to generate the best recording.

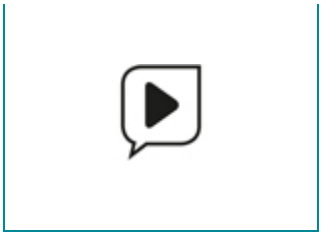
Switching between referential and bipolar montages on EEG review software in a recording from a 4-year-old mixed breed dog. The background (in agreement with synchronized video) was consistent with drowsiness (low frequency, high voltage). Between time points d1 22:38:33 and 22:38:34, there are three spikes of variable amplitude with the last being the largest, with maximal negativity and phase reversal centered on C3. F8 also has spikes with maximum negativity in the second half of the epoch, but these are less visible as phase reversals on the bipolar montage as the paired F8 channels are not adjacent. Channels on the left side of the head are colored blue; channels on the right side of the head are colored red; midline channels are black. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Referential 13-channel montage: right y-axis: 116 µV per marker; timebase: 5 seconds per page, sensitivity: 7 µV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF); 70 Hz, and notch filter: off. Bipolar combined longitudinal (top half) and transverse (lower half) montage: right y-axis: 88.6 µV per marker; timebase: 5 seconds per page, sensitivity: 7 µV, low frequency filter (LFF) time constant: 0.1 s, high frequency filter (HFF); 70 Hz, and notch filter: off.

Video 7.2.



Adding color to a referential montage allows immediate recognition of the anatomical location of channels, distinguishing between left (blue) and right (red) hemispheres and midline (black). This epoch is identical to that in Video 7.2. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Referential 13-channel montage: right y-axis: 116 µV per marker; timebase: 5 seconds per page, sensitivity: 7 µV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF); 70 Hz, and notch filter: off.

Video 7.3.



Bipolar montages

Bipolar montages, on the other hand, do not have an electrode that is common to all channels. This has the benefit of minimizing the effect of a reference electrode contaminated by artifact. Typically, bipolar channels are linked such that adjacent channels from electrodes along the same line (or chain) have an electrode in common.[50] In this way, the reference electrode in one channel becomes the exploring electrode in the next channel. These chains of electrodes are then usually organized on the display in an anatomical fashion, e.g., rostral to caudal (longitudinal, sometimes referred to as a "double banana" montage), transverse, or circumferential. Such an anatomical organization preserves the spatial relationship between electrodes in the plane of the chain, so a longitudinal bipolar montage presents a sagittal view, for example. The bipolar montage shown in Video 7.2 is a combination of longitudinal (top half) and transverse (lower half). A bipolar montage is useful as the two channels derived from the electrode closest to the source of the epileptogenic potential present a visually arresting feature known as **instrumental phase reversal**[50] (see Video 7.2). Caution should be employed when comparing source electrodes between recordings as existing veterinary electrode arrays still require confirmation of their accuracy and precision.[99] Another limitation of the bipolar montage is the "end of chain" phenomenon, occurring as a result of the montage's construction. As the eye-catching phase reversal feature is dependent on two adjacent channels having an electrode in common, it will not occur for the last channel in a chain where instead a maximal amplitude will occur. The solution is to work with multiple bipolar montages during review in order not to overlook any peak voltages occurring at the end of a chain.



FIGURE 7.5. An epoch from an EEG of a dog showing how the pairing of channels highlights the equal and opposite amplitudes of eye movement artifacts. Left side of the head channels are colored blue; right side of the head channels are colored red; midline channels are black. Referential 11-channel montage. Left y-axis: channels. The right y-axis gives amplitude values (μV) for each channel measured at the blue solid vertical line (arrowhead) at the leftmost side of the epoch. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 10 seconds per page, sensitivity: 10 μV, low frequency filter (LFF) time constant: 0.016 s, high frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

Filters, sensitivity, time scale

Having chosen the initial montage for the software workspace, the next step is to doublecheck the filter, sensitivity, and time scale settings. Filters can be applied to the raw EEG data to improve visualization. For example, a notch filter set at 50 or 60 Hz removes mains artifacts from the displayed signals. This is demonstrated in Video 7.4. Similarly, a high-pass filter allows frequencies higher than its set point to be seen (also known as a **low-frequency filter** as it filters out low frequencies). Conversely, a low-pass filter removes frequencies higher than its set point while passing through low frequencies to be seen (also known as a **high-frequency filter**). Typically, these are initially set for a typical EEG bandwidth between 1 and 70 Hz and can be adjusted as necessary. Likewise, an initial sensitivity setting of 7 μV/mm is a good place to start.

Turning on and off the (60 Hz) notch filter over an epoch contaminated with mains artifacts. Notice how the sharpest peaks become more rounded when this filter is applied. However, without the filter in place, all channels appear uniformly fuzzy due to the high frequency constant amplitude artifact. A limited referential 5-channel montage is shown solely to demonstrate this artifact.

Video 7.4.

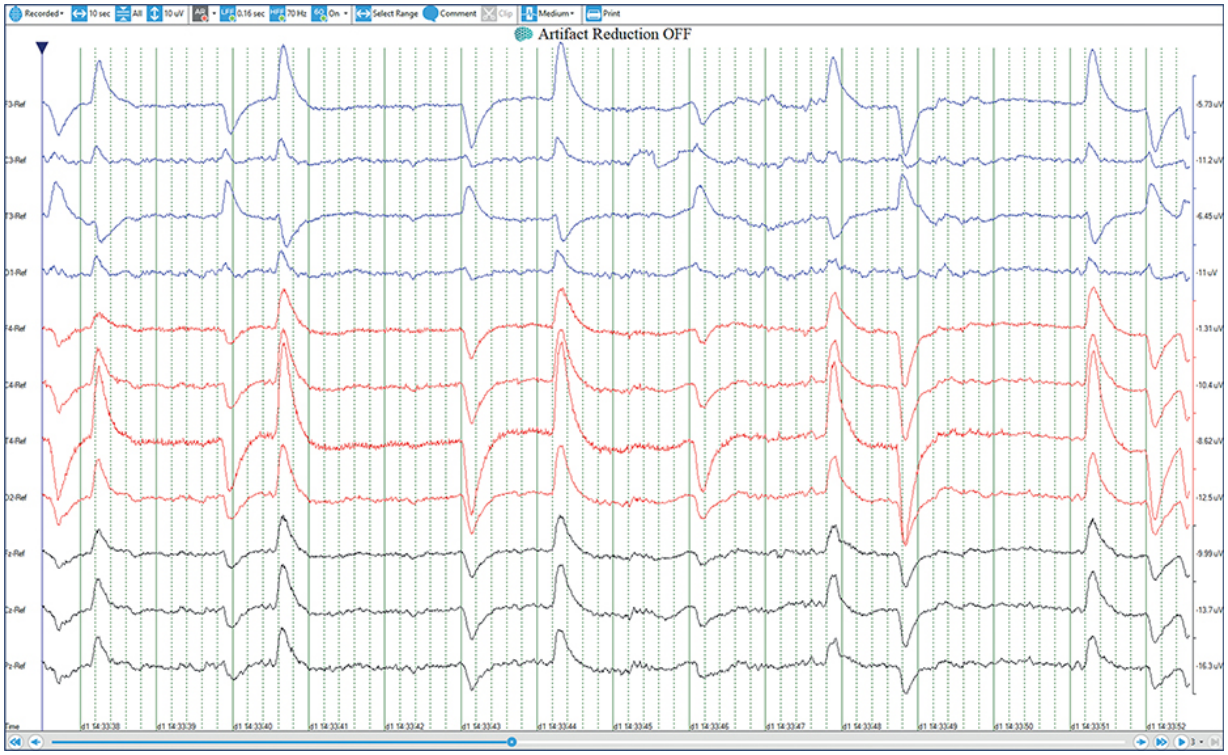


FIGURE 7.6. An epoch from an EEG of a dog showing how the grouping of channels highlights the regional differences in what is detected regarding eye movements. Left side of the head channels are colored blue; right side of the head channels are colored red; midline channels are black. Referential 11-channel montage. Left y-axis: channels. The right y-axis gives amplitude values (μV) for each channel measured at the blue solid vertical line (arrowhead) at the leftmost side of the epoch. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 10 seconds per page, sensitivity: 10 μV, low frequency filter (LFF) time constant: 0.016 s, high frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

Filters have several uses beyond removing mains artifacts. Lowering the high-frequency filter helps to minimize muscle artifacts. The cost of this is

a rounding of epileptogenic potentials such as spike or sharp waves (discussed later), which is also a consequence of using the notch filter. Additionally, muscle artifacts may more easily be confused for spikes or sharp waves or beta activity. Raising the low-frequency filter may be helpful to unmask patterns "hidden" by large slow waves, but also reduces the amplitude of any abnormal delta band activity. There are other limitations to the filters. The available filter frequencies listed in the software are predetermined by the manufacturers. Further, these filters do not cleanly cut the frequency spectrum at the listed Hz with a square edge. Instead, their effect on the frequency spectrum has an exponential drop off.[97] These filters are named for their cutoff, the frequency at which they will create a 30% reduction in the amplitude. As an example, a high frequency filter of 35 Hz will reduce amplitudes at 35 Hz by 30%. Faster activity will be much more reduced or eliminated and slower activity will be slightly reduced or unaffected. Filters may also be named based on their time constant, an expression of the decay (or rise) of the frequency-response curve. The time constant is inversely proportional to their cutoff frequency related via the formula:

Time constant = $1/(2\pi \times$ cutoff frequency$)$.[53]

Thus, a low-frequency filter time constant of 0.16 s is equivalent to a low-frequency filter cutoff of 1 Hz. Review software may offer one or the other variable for manipulation of filter settings.

The time setting controls the x-axis display, the amount of time shown on your screen. There are usually solid vertical lines indicating 1-second divisions, with sometimes smaller breakdowns indicated, e.g., 200 ms markers. Setting time to minutes will give an overall impression of activity and mentation state but will be too coarse to identify cortical level events. Setting the time to single seconds can pixelate the data and smoothen cortical events but will identify lag between events of interest. An initial time setting of 8–10 seconds on the screen is reasonable, zooming in or out as necessary for detailed examination or context respectively. "Paper speed" allows control of the x-axis for playback, with manufacturers offering several paper speeds within the software, in units of mm/s. Slow motion playback is good for picking up the order of events of interest, whereas fast-forward gives a sense of the behavioral context.

Keep in mind that remontaging or adjusting the filters or other variables in the review software does not change the data. It changes only the way the data is displayed on the screen. Put another way, playing with these variables can only go so far to fix a recording made with a contaminated reference electrode. The best way to eliminate an artifact is to fix it at the source during the recording process.

Artifacts

Artifacts can be divided into two categories, physiological and nonphysiological.[97] Nonphysiological artifacts arise out of the environment, e.g., mains artifact, or from the instrumentation, e.g., electrode pop artifacts. Physiological artifacts derive from other sources of electrical activity in the body, including the heart, eyes and muscles, and whole-body movements such as scratching, panting, and licking. Automated artifact detectors provided within review software can help to highlight epochs of interest, but caution must still be used as they are not yet 100% accurate across species.[100] Therefore, visual inspection of the original recording is still recommended.

In the head, two major sources of artifacts are the eyes and the tongue. Each organ forms a very large dipole, orders of magnitude larger than cortical-origin dipoles. The eyes have the positive dipole tip at the cornea and the tongue has the negative dipole tip at the tongue tip. Eye movements can generate quite recognizable movement artifacts on the EEG, especially so when the eye movements are horizontal. If there are electrodes on the zygomatic arch adjacent to the lateral canthi, then a horizontal eye movement will direct the dipole tips towards one electrode and equally away from the other. These two electrodes will therefore display equal and opposite deflections, perfectly out of phase. Figures 7.5 and 7.6 show these deflections when viewed on differently organized montages (see *Montages* section).

Electrocardiographic artifacts are best identified by comparing EEG waveforms of interest against a simultaneous ECG recording (see Fig. 7.4). Electromyographic artifacts overlap the EEG bandwidth at the high frequency end and can be intermittent or continuous. While topical lidocaine cream does not appear to reduce this type of artifact, subcutaneous or intramuscular injection of lidocaine can be effective to reduce EMG signals if recording awake. Again, recording with sedation or

general anesthesia can help to reduce large movement artifacts that present as transient high-amplitude activity. However, the movements generated by epileptic seizure activity do not necessarily obscure the EEG recording of the cortical onset as the motor events lag the cortical events by up to 50 ms.[101,102]

Normal EEG findings

In addition to recognizing artifacts, the patient's age, sex, and vigilance state must be taken into account before identifying EEG abnormalities. This is because these patient-dependent variables can affect the background activity and the presence of transient waveforms. The background is the EEG activity against which patterns are distinguished. The background is typically described by its amplitude and dominant frequency; this is related to the mentation state (see Table 7.1). The waveforms that appear against the background are referred to as **transients** or **paroxysms**, with the latter term being generally used to refer to epileptogenic and seizure patterns.

Most age effects happen early in life. The EEG background changes in a predictable fashion from birth through adulthood. Recognizing these changes will be helpful for reviewing EEGs from very young animals. Dogs achieve mature EEG patterns by 1 year of age.[68,103–105] Initially, the amplitude increases until 7 weeks old, then decreases thereafter. Background frequencies increase steadily throughout. Sleep patterns emerge by two weeks and appear adult around 16 weeks of age. The EEG in cats shows a similar evolution, with awake kittens showing periods of very low amplitude that resolve by 4 weeks of age.[103,106] The background amplitude peak is reached around 6 to 8 weeks, then decreases to adult levels by 6 months. Background frequencies level out around 5 months of age. Sleep patterns and transients are apparent from 4 weeks onwards.

Transients

Examples of vigilance state-dependent transients include the alpha rhythm, sleep spindles, vertex waves, and K complexes.[53] An alpha rhythm occurs during relaxed wakefulness, generally with maximum amplitude over the occipital region. This 8–13 Hz rhythm is best seen with the eyes closed as it is blocked or attenuated by visual attention (Fig. 7.7). The sleep state hosts the other three transients mentioned.

Sleep is categorized into rapid eye movement (REM) and non-REM phases. The consensus for people is that non-REM sleep can be further broken down into three stages: N1, N2, and N3.[107,108] In nonhuman sleep research, there is a looser classification of sleep with generally two stages of non-REM sleep identified: drowsiness and slow-wave sleep that do not necessarily correspond directly to the human sleep stages.[17,70,109] While wakefulness is characterized on EEG with a high-frequency, low-voltage or amplitude (HFLV) background, drowsiness in dogs has fewer eye movements with a background that is low-frequency, high voltage (LFHV), with decreased but not absent muscle tone. These dogs are recumbent but easily rousable, and their eyes may be partially or completely closed. Slow-wave sleep has a predominantly delta background while the dogs are harder to rouse. Canine REM sleep is very similar to that of humans—the dog remains recumbent, but there is a return of HFLV background activity, against which rapid eye movements occur while there is generalized atonia. Video 7.5 illustrates a case of REM behavior disorder (RBD) in a 1-year-old Golden Retriever with a history of violent sleep movement since adoption. The REM sleep at the start of the epoch is characterized by eye movements against a HFLV background with no muscle artifacts. However, midway through the sequence of eye movements, the pelvic limbs suddenly kick out along with subsequent appearance of muscle (EMG) artifacts. The coincident onset of movements within REM sleep characterizes RBD.[19,20]

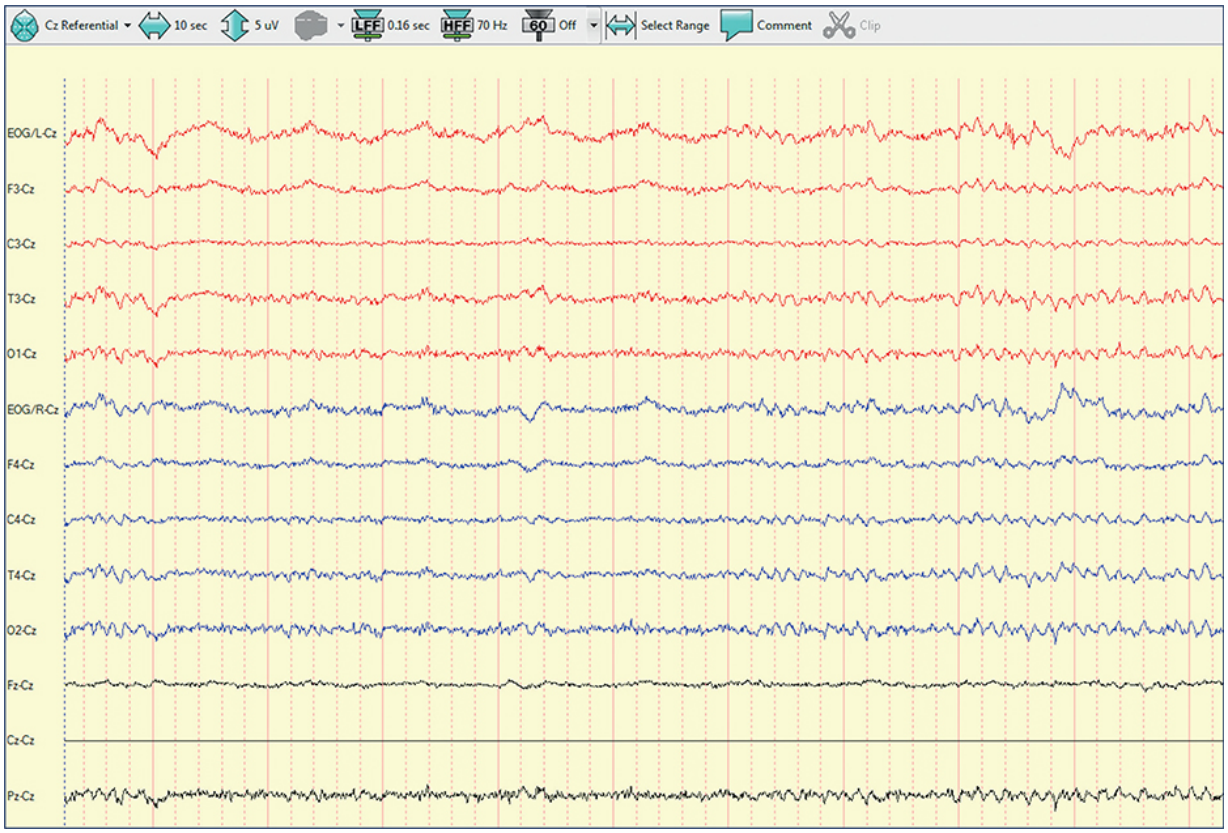


FIGURE 7.7. Alpha rhythm seen during an unsedated EEG recording of a 2-year-old Rhodesian Ridgeback (predominantly in the second half of the epoch). During this 8 Hz pattern, the dog was sitting sternal with their eyes closed. Cz referential 13-channel montage. EOG/L = F7. EOG/R = F8. Channels on the left side of the head are colored red. Channels on the right side of the head are colored blue. Midline channels are black. Left y-axis: channels. Amplitude values (μV) display for each channel has been turned off. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 10 seconds per page, sensitivity: 5 μV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF); 70 Hz, and notch filter: off.

Amidst the drowsiness/sleep background in a dog, **vertex waves** may be seen (stage N1 in humans). Also known as **V waves** or **vertex sharp transients**, they are either spontaneous or elicited by a sensory stimulus with highest amplitude usually over the vertex, hence their name. They are bilateral synchronous sharply contoured negative waves lasting less than 0.5 s in duration. **K complexes** are similar to V waves but longer (>0.5 s) and are followed by a large positive component making them bi- or triphasic. They have their maximum amplitude on central channels and are often associated with sleep spindles, with both of these transients occurring during human N2 sleep. **Sleep spindles** are a group of rhythmic symmetrical waves at a frequency of 9–16 Hz, a range that can be referred

to as the sigma band overlapping the alpha band. They are called spindles because they wax and wane, forming a spindle shape on the channel. Spindle duration in humans is typically ≥0.5 s. As with the other sleep transients, the maximal amplitude is over the central (vertex) region. Spindles are an example of a burst, a group of waves with at least four phases lasting longer than 0.5 s. All three sleep transients are illustrated in Figure 7.8. Spindle frequency and bursts per minute (density) appear to be affected by the dog's age and sex, with intact older females showing the highest density of high frequency spindles.[24] Further, low-frequency spindle density declines with age in both humans and dogs in correlation with age-related cognitive decline.[25]

EEG recording of a rapid-eye-movement (REM) behavior disorder in a 1-year-old Golden Retriever with a history of violent sleep movement since adoption. The REM sleep at the start of the epoch is characterized by eye movements against a high frequency, low voltage background with no muscle artifacts. Midway through the sequence of eye movements, the pelvic limbs suddenly kick out along with subsequent appearance of muscle (electromyographic) artifacts. Referential 13-channel montage with electrocardiogram. Channels on the left side of the head are colored blue; channels on the right side of the head are colored red; midline channels are black. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Right y-axis: amplitude values (μV) for each channel measured at their intersection with the moving vertical line; timebase: 10 seconds per page, sensitivity: 7 μV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF); 70 Hz, and notch filter: 60 Hz.

Video 7.5.



Abnormal EEG findings

Once adequate knowledge of normal background, transients, and artifacts is acquired, the next step is to be able to identify of abnormal EEG findings. These are clinically classified as either nonspecific or specific abnormalities. Nonspecific EEG abnormalities include **slowing of the background activity** not consistent with the behavioral state, often in the delta bands. If this is localized and continuous, consider a focal brain lesion. Localized intermittent focal slowing (delta) can be seen in epilepsy. Diffuse slowing is associated with encephalopathies of various causes or induced by

sedative medications. Metabolic encephalopathies can also present triphasic waves difficult to distinguish from epileptogenic spikes (discussed later). **Triphasic waves** are sharply contoured with a negative-positive-negative polarity seen in patients with altered levels of consciousness (not in the awake state). A classic example in which triphasic waves can be seen is hepatic encephalopathy. Triphasic waves are distinguished from the typical spike-wave epileptogenic pattern by their frequency; triphasics are rarely faster than 2.5 Hz.[55] To distinguish them from atypical spike-wave complexes, consider that triphasic waves rarely show stereotypical evolution over time as the epileptogenic spike-wave trains will do.[55]

Periodic discharges (PDs) are nonspecific relatively uniform waveforms that recur at nearly regular intervals.[55] They are usually described by their distribution—general, lateralized, or bilateral independent —and are not necessarily specific to seizures. For example, PDs can be seen with brain injury resulting from trauma, hemorrhage, ischemia, encephalitis, during or after status epilepticus, metabolic encephalopathy, and hypothermia. They do not provide any prognostic information but tend to be associated with acuity of the brain injury.

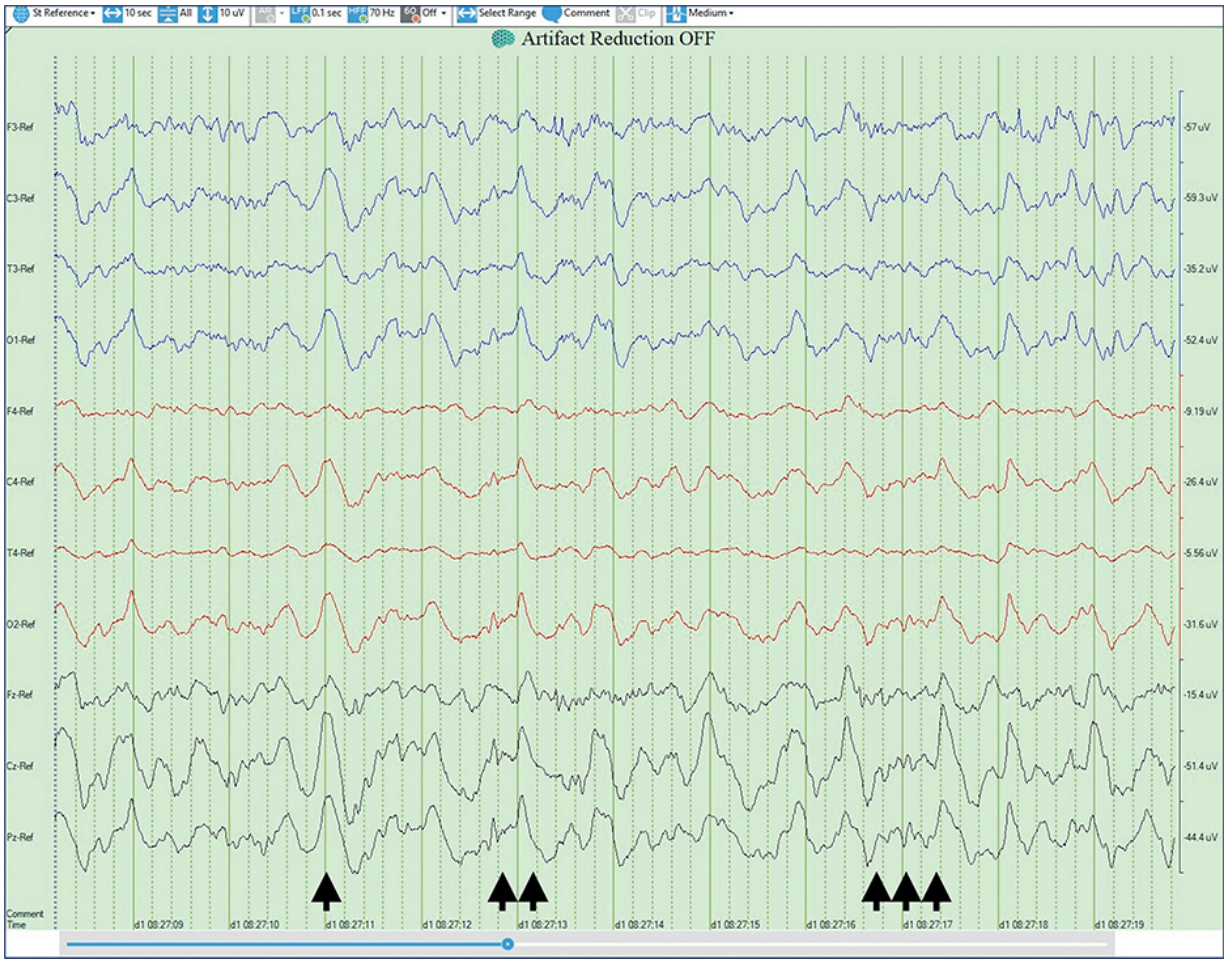


FIGURE 7.8. An epoch of an EEG from a 5-month-old German Shepherd dog having received dexmedetomidine for instrumentation, taken prior to reversal with atipamezole. The background is entirely slow wave sleep, with almost constant K complexes (single arrow, d1 08:27:11), V waves (double arrow, d1 08:27:13), and spindles (triple arrow, d1 08:27:17), all of which have maximum negativity over the vertex (Cz). Channels on the left side of the head are colored blue. Channels on the right side of the head are colored red. Midline channels are black. Left y-axis: channels. The right y-axis gives amplitude values (μV) for each channel measured at the blue dotted vertical line at the leftmost side of the epoch. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 10 seconds per page, sensitivity: 10 μV, low frequency filter (LFF) time constant: 0.016 s, high frequency filter (HFF); 70 Hz, and notch filter: 60 Hz.

Specific EEG abnormalities are those that are epileptogenic and paroxysmal, evolving from their sudden onset, rapidly attaining a maximum, and ending equally suddenly. They may be ictal or interictal. There are three basic elements: spikes, sharp waves, and spike- (or sharp-)-and-slow-wave complexes. All these can occur singly or in paroxysmal groups. **Spikes** or **sharp waves** are almost always negative and are distinguished by their duration, with spikes lasting 20 to 70 ms and sharp

waves lasting 70 to 200 ms.[53] The following negative slow wave represents hyperpolarization (GABA-b mediated currents).[110] When these occur singly or in small groups with no apparent clinical manifestations, these can be considered interictal epileptiform discharges (IEDs). However, they should be consistent and seen persistently. In people, focal IEDs are more associated with temporal or frontal lobe epilepsies rather than parietal or occipital epilepsies. See Videos 7.2 and 7.3 for examples of bilateral independent spikes as focal IEDs. Generalized IEDs are usually spike-waves, polyspike-waves, or polyspike discharges. Approximately 50% of people with new onset seizures will show IEDs,[111] but so will between 1–13% of normal individuals (higher in those nonepileptics with a first-degree relative with generalized epilepsy). This kind of information regarding IEDs in the epilepsies of small animals generally remains to be described, with the exception of familial spontaneous epilepsy in Shetland Sheepdogs[112] and cats in Japan[113] and a handful of dogs with continuous intracranial EEG.[43–45,114]

Clinical ictal epileptiform discharges, on the other hand, are accompanied by a clinical manifestation, the seizure. These discharges have a spatiotemporal evolution[53] that is artificially divided into an opening phase (~1 s), then a stabilization phase (subsequent 3 s) when it is easiest to determine the waveform and frequency, after which the frequency will often slow and morphology will change, and a terminal phase (final 3 s) to end.[115] The opening phase may be asymmetrical and asynchronous with spike-wave frequencies that are faster or more irregular than the stabilization phase. The terminal phase is either characterized by an abrupt end or brief rhythmic or irregular slow waves or, sometimes, focal or fragmentary spikes. Figure 7.9 illustrates the evolution of a generalized clonic seizure in a dog.

The most difficult seizures to identify clinically are nonmotor focal or absence seizures. Generalized spike-wave patterns at 3–5 Hz are seen in typical absence, myoclonic absence, absence with eyelid myoclonus and other generalized seizures in humans.[89] The human absence seizures are easily provoked by drowsiness, hyperventilation and IPS.[116] Interictal epileptiform discharges are also spike-wave trains but are usually shorter and may be fragmentary; if longer than 6 s, they are thought to alter awareness.[116] The absence seizures observed in dogs also have a frequency range of 3–5 Hz and may or may not be accompanied by myoclonus that

can be quite subtle; behavioral arrest alone is sometimes challenging to appreciate.[5,8,90] Human atypical absence seizures are associated with a slower spike-wave discharge.[116] Videos 7.6–7.8 show the EEG of absence seizures in dogs recorded without sedation or any other medications. In Video 7.6, a 12-year-old Cavalier King Charles Spaniel with hypoglycemia manifests behavioral arrest as a pause in eye movements during approximately 12 s, with a generalized 3-Hz, irregular spike-wave pattern. For comparison, Video 7.7 shows a 6-year-old Powderpuff Chinese Crested dog with low-amplitude, vertical "yes" myoclonic movements of the head, which are timelocked to the approximately 6- s train of generalized 4 to 5-Hz spike-waves. Muscle (EMG) artifacts are also particularly evident on the central and posterior midline channels. Video 7.8 shows a 5-month-old mixed breed dog manifesting rapid eye blinks, head bobbing, and episodic incoordination or inability to stand. Two episodes of 3–4 Hz spike-wave complexes lasting approximately 2 s each are seen in this epoch. The dog is in sternal recumbency, having just rested its chin on its left thoracic limb. During the first episode, the left thoracic limb paw slips laterally out from under its chin. During the second episode, the nose can be seen jerking rhythmically in time with the spike-wave complexes. For Videos 7.6–7.8, while muscle and movement artifacts are observed, they do not interfere with the ability to make a diagnosis.

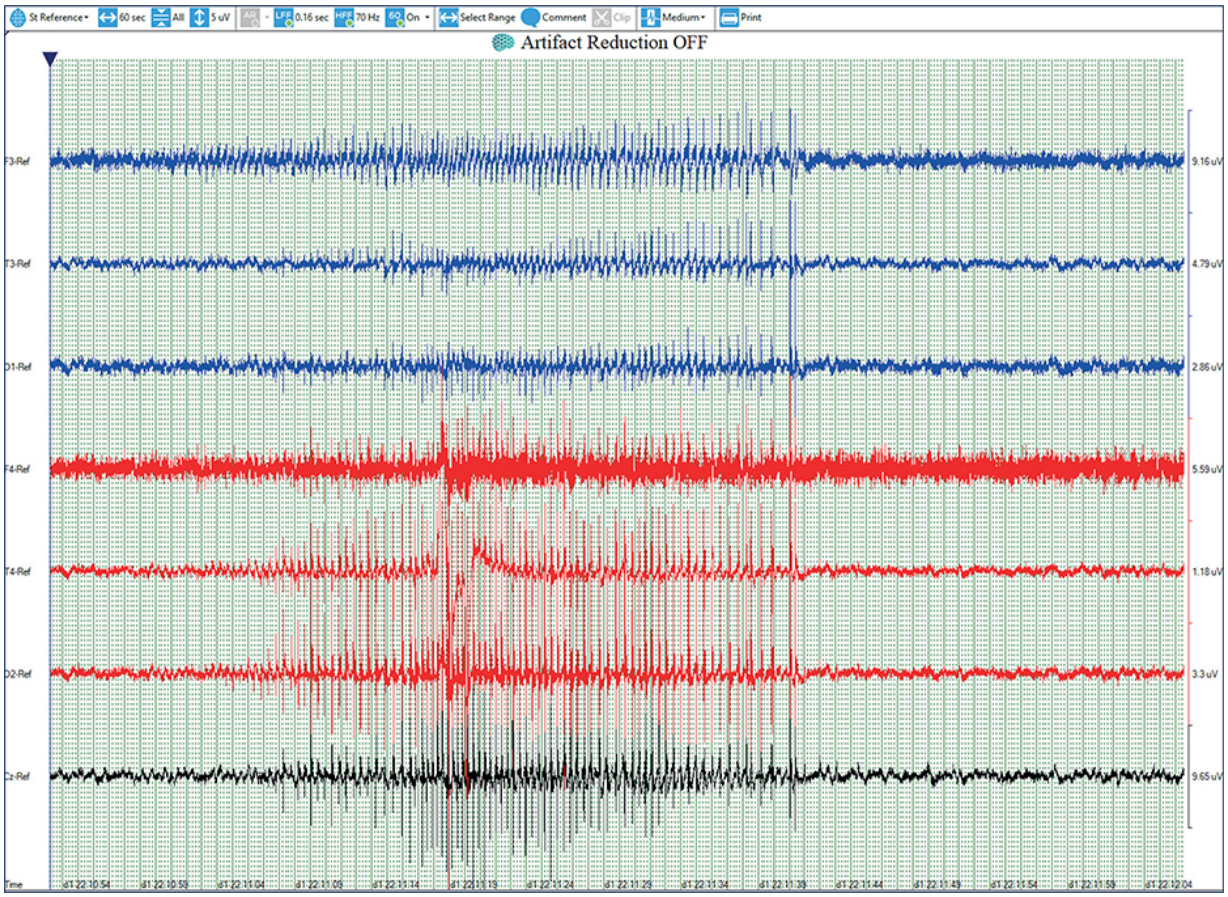


FIGURE 7.9. The evolution of a generalized clonic seizure in a 6-year-old Dachshund with hepatic encephalopathy (same dog as in Video 7.9, but different seizure), illustrated by adjusting the timebase setting in the EEG review software. There are more muscle artifacts on F4-Ref than on any other channel. Referential 7-channel montage. Channels on the left side of the head are colored blue; channels on the right side of the head are colored red; midline channels are black. Left y-axis: channels. The right y-axis gives amplitude values (μV) for each channel measured at the blue solid vertical line (arrowhead) at the leftmost side of the epoch. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 60 seconds per page, sensitivity: 5 μV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF); 70 Hz, and notch filter: 60 Hz.

The other generalized ictal patterns encountered in dogs and cats are **polyspike** or **polyspike-and-slow-wave complexes**. Figure 7.10 shows a polyspike pattern in nonconvulsive status epilepticus recorded from an 8-year-old Labrador Retriever with imaging and cerebrospinal fluid findings consistent with meningoencephalitis of unknown etiology. The polyspike frequency ranged from 7–15 Hz during the status, with evolution of morphology and amplitude also seen. During this period, the dog was recumbent and nonresponsive.

EEG recording of an absence seizure in a 12-year-old Cavalier King Charles Spaniel with hypoglycemia. Eye movements seen prior to the event cease during the period of behavioral arrest coincident with the 3-Hz spike-wave pattern. Referential 13-channel montage. Channels on the left side of the head are colored blue; channels on the right side of the head are colored red; midline channels are black. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Right y-axis: amplitude values (μV) for each channel measured at their intersection with the moving vertical line. Timebase: 10 seconds per page, sensitivity: 7 μV, low-frequency filter (LFF) time constant: 0.16 s, high-frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

Video 7.6.



EEG recording of an absence seizure with "yes" myoclonus of the head in a 1-year-old Powderpuff Chinese Crested dog. The myoclonus is timelocked to the 4–5 Hz spike-wave train. EMG artifact is also visible on Cz and Pz channels. Referential 11-channel montage. Channels on the left side of the head channels are colored blue; channels on the right side of the head are colored red; midline channels are black. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Right y-axis: amplitude values (μV) for each channel measured at their intersection with the moving vertical line. Timebase: 8 seconds per page, sensitivity: 7 μV, low-frequency filter (LFF) time constant: 0.16 s, high-frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

Video 7.7.



EEG recorded from a 5-month-old mixed breed dog whose episodes are rapid eye blinks, head bobbing, and episodic incoordination or inability to stand. The epoch captures two episodes of 3–4 Hz spike-wave complexes lasting approximately 2 s each. With the first episode, the left thoracic limb paw slips laterally. The second episode is accompanied by subtle jerking of the nose, timelocked to the spike-wave complexes. Referential 11-channel montage. Channels on the left side of the head are colored blue; channels on the right side of the head are colored red; midline channels are black. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Right y-axis: amplitude values (μV) for each channel measured at their intersection with the moving vertical line. Timebase: 8 seconds per page, sensitivity: 7 μV, low-frequency filter (LFF) time constant: 0.16 s, high-frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

Video 7.8.

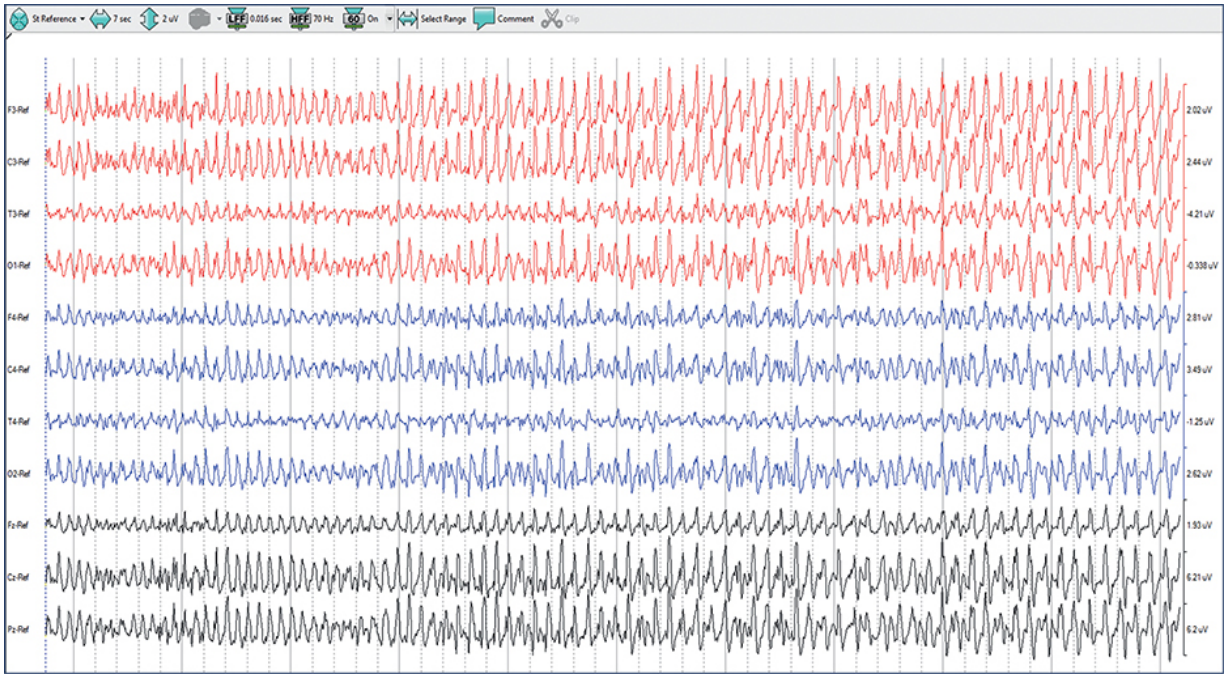


FIGURE 7.10. EEG recording of a polyspike pattern in nonconvulsive status epilepticus recorded from an 8-year-old Labrador Retriever (same dog as in Fig 7.11) with imaging and cerebrospinal fluid findings consistent with meningoencephalitis of unknown etiology. The polyspike frequency, morphology, and amplitude all evolve during this epoch while the dog remained recumbent and nonresponsive. Referential 10-channel montage. Channels on the left side of the head channels are colored red; channels on the right side of the head are colored blue; midline channels are black. Left y-axis: channels. The right y-axis gives amplitude values (μV) for each channel measured at the blue dotted vertical line at the leftmost side of the epoch. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 7 seconds per page, sensitivity: 2 μV, low-frequency filter (LFF) time constant: 0.016 s, high-frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

Polyspike-and-slow-waves are commonly seen in myoclonic epilepsy (where myoclonus is the initial clinical manifestation), and more rarely in focal epilepsy. They are often activated by IPS. The complex is comprised of a slow wave subsequent to a series of repetitive spikes. These can occur in combination, as with generalized tonic-clonic seizures where a

generalized polyspike pattern of increasing frequency (tonic phase) precedes a generalized spike-wave pattern (clonic phase). Postictal suppression (period of markedly decreased amplitude) often follows. Video 7.9 shows a generalized clonic seizure in a 6-year-old Dachshund with hepatic encephalopathy. The epoch is captured after recovery from general anesthesia, the EEG being recorded without further sedatives or anesthetics. There are two technical items to note in this record. First, the timescale has been increased to display 15 seconds per page in order to show the evolution of the waveforms. Second, a limited 9-channel electrode array (and, therefore, montage) was used due to the size of the patient's head, but this was still sufficient to see the field and gradient of the onset as the electrodes that were withheld were on the midline and central regions. The seizure lasts approximately 3.5 minutes, with the rhythmic polyspike discharge preceding visible clonus by several seconds. Towards the middle of the seizure, the morphology evolves into spike-wave complexes. The terminal phase is marked by greater irregularity of the complexes and their periodicity.

The ictal EEG of focal seizures shows a range of patterns and spatiotemporal evolution similar to the pattern of generalized seizures.[89] Initial rhythms increase in amplitude while slowing in frequency. Subclinical focal seizures do not have any overt physical or behavioral manifestation. Focal seizures in humans can have completely normal scalp EEGs due to the limited spatial distribution of the region of onset.[89] When focal ictal discharges are recorded, they may be poorly lateralized or localized, have minimal amplitude, or may show focal rhythmic activity over the lobe of onset; this all depends on the spatial distribution of the propagated seizure. In these instances, too, the motor activity artifact can obscure the cortical signal. The focal seizures that evolve to be bilateral tonic-clonic may also be difficult to differentiate from true generalized tonic-clonic seizures even with video-EEG depending on whether the focal signal is detectable at the scalp. In these instances, focal IEDs may be more helpful than ictal discharges for determining the region of onset (see Videos 7.2 and 7.3).

EEG recording of a generalized clonic seizure in a 6-year-old Dachshund with hepatic encephalopathy (same dog as in Fig. 7.9 but different seizure). During the 3.5-minute seizure, the frequency, morphology, and amplitude of the complexes are seen to evolve. The physical manifestations are initially myoclonic jerks of the head timelocked to the complexes, with later

tonicity of the thoracic limbs appearing around the same time as the polyspikes evolve to polyspike-slow-waves. Referential 9-channel montage. Channels on the left side of the head channels are colored blue; channels on the right side of the head channels are colored red; midline channels are black. Left y-axis: channels. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Right y-axis: amplitude values (μV) for each channel measured at their intersection with the moving vertical line; timebase: 15 seconds per page, sensitivity: 7 μV, low frequency filter (LFF) time constant: 0.16 s, high frequency filter (HFF); 70 Hz, and notch filter: 60 Hz. Video courtesy of Dr. V. Sammut.

Video 7.9.



In coma, the abnormal EEG patterns are marked by their invariability and lack of reactivity, in line with the physical state of the unresponsive patient. Changes in the background frequency in response to sensory stimuli indicate relative cortical integrity, which might be viewed favorably. These background patterns are named after the predominant frequency, e.g., alpha coma or theta coma, and correlate to the depth of coma, from obtundation through somnolence to coma.[117] Periodic discharges and triphasic waves, mentioned earlier in this section, may also be seen since coma may be a presentation of these diseases.

Burst suppression is an ambiguous pattern comprised of bursts of spikes, polyspikes, or sharp waves, with very low-amplitude intervening epochs that represent more than 50% of the recording.[53] While this pattern can be seen in the deepest stages of coma caused by severe diffuse encephalopathies, it can also be achieved by pharmaceuticals, e.g., during propofol anesthesia or anesthetic doses of barbiturates. The indices used in anesthetic and ICU monitors of brain function mentioned earlier are calculated using the relative durations of the bursts and intervals of suppression. Figure 7.11 shows burst suppression in an 8-year-old Labrador Retriever after the animal had received 20 mg/kg of phenobarbital intravenously to treat status epilepticus. The right y-axis gives the amplitude values for each channel, measured at the leftmost side of the epoch.

Finally, **electrocerebral inactivity** (ECI) is defined as an EEG with amplitudes <2 µV. The EEG may be referred to as "isoelectric" or "flat", using older terminology.[26,53] In lay terms, this is often equated with "brain death". Electrocerebral inactivity indicates the absence, over the entire head, of any identifiable electrical activity of cortical origin.[53] This could be spontaneous or induced by pharmacological agents. Committing to a diagnosis of ECI should include distinguishing it from low-voltage EEG by adjusting the sensitivity to 2 µV/mm maximum, placing sufficient electrodes on the head for generalized coverage, recording for a sufficient period of time to ensure that the pattern is invariable (even to intense sensory stimuli), and ruling out artifactual causes of the absent electrical activity.[26] If in doubt, try recording again the next day.

HOW TO REPORT EEG?

The basic requirements for any veterinary medical procedural report should be followed. These include providing patient information such as signalment, prior medications, and reason for requesting the EEG. In addition to past medical history and diagnostic testing, the EEG request should ideally include a description of any events of interest and any video recordings of them so that the reviewer can match them to events on the EEG.

The report itself should have a standard format including a factual description of the recording and a clinical interpretation of the findings. The clinical interpretation, in addition to summarizing the findings, must take into account the clinical question for which the EEG was requested. Jargon should be avoided in the interpretation, so that it is understandable to any veterinary team member not specialized in EEG.

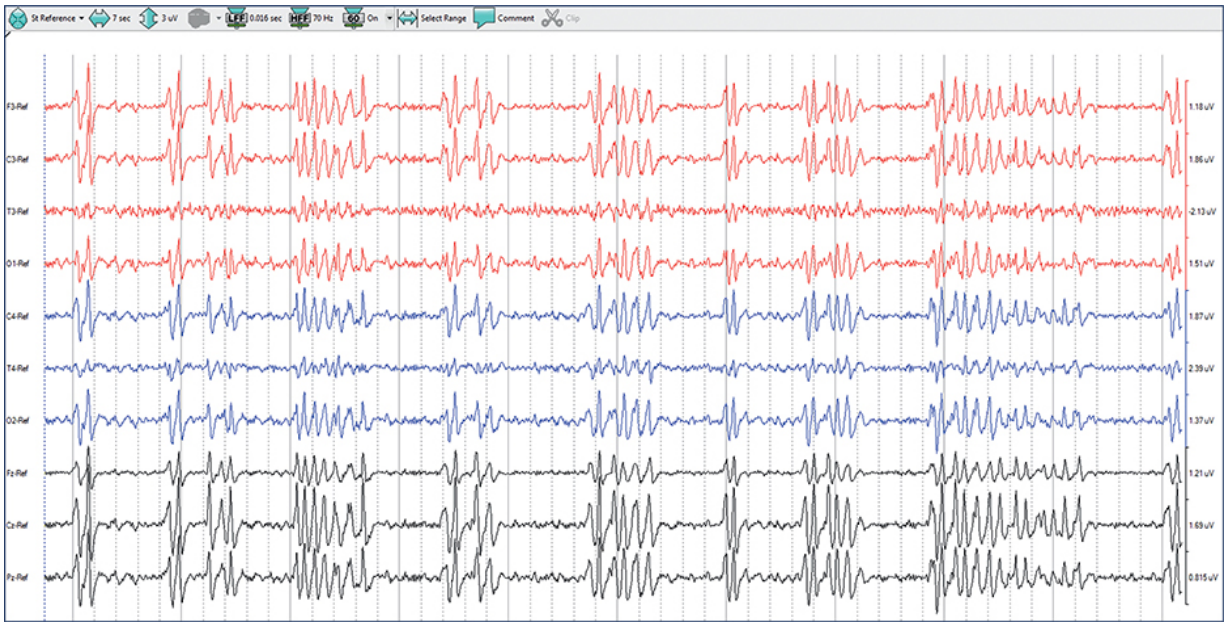


FIGURE 7.11. EEG recorded from an 8-year-old Labrador Retriever (same case as in Fig. 7.10) after the animal had received 20 mg/kg of phenobarbital intravenously to treat status epilepticus, showing the resulting burst suppression. Referential 10-channel montage. Channels on the left side of the head are colored red; channels on the right side of the head are colored blue; midline channels are black. Left y-axis: channels. The right y-axis gives amplitude values (μV) for each channel measured at the blue dotted vertical line at the leftmost side of the epoch. Horizontal axis: time in seconds; solid verticals mark seconds and dotted verticals mark 200 ms. Timebase: 7 seconds per page, sensitivity: 3 μV, low frequency filter (LFF) time constant: 0.016 s, high frequency filter (HFF): 70 Hz, and notch filter: 60 Hz.

The factual description should be precise in terms of frequency, amplitude, waveform, localization, quantity, and variability of EEG phenomena.[53,59] Representative images (e.g., screen captures) should not go amiss. Ideally, the description should be such that there is no need to open the recording again.

The main consideration when discussing the clinical significance of the results is that a normal EEG does not rule out epilepsy. In people, sensitivity is 50% at the first recording rising to 80% when a second recording is made.[118] Also, the electrographic correlates of focal seizures can be so limited in onset and spread that they are missed by scalp EEG.[89] Conversely, the percentage of normal dogs and cats that have EEG abnormalities is unknown, so it is necessary to curb enthusiasm and avoid overinterpretation of the EEG. For example, one should be cautious diagnosing epilepsy based on the finding of only one waveform suspicious for an IED in an otherwise normal EEG recording. It is important to

correlate the EEG findings with the whole clinical picture; this is the attending veterinarian's responsibility. Admittedly, veterinary epileptology has yet to match specific ASDs with specific seizure types or epilepsy syndromes as has been done to a great extent for people. While waiting for this to be achieved, it would be reasonable to consider the repeat EEG as a gold standard for objective confirmation of a change in the severity or frequency of ictal and interictal events.

WHERE TO LEARN MORE ON EEG?

There are a number of international societies that publish standards and protocols related to EEG. Most standards are aimed at recording in people. Veterinary clinical standards are focused on by the International Veterinary Epilepsy Task Force (IVETF) and the American College of Veterinary Internal Medicine.[2,62,119–124] There is one standard for recording in animals published by the International League Against Epilepsy (ILAE), with a focus on the typical animal models used for laboratory-based epilepsy research.[97] The ILAE provides comprehensive updates and glossaries based on the current understanding built by global research into epilepsy.[7,53] The International Federation for Clinical Neurophysiology (IFCN) has a slightly broader scope including other neurodiagnostic tests.[65,125]

The ILAE is an umbrella organization with local chapters and conferences by geographical area across the planet. The corresponding organization in the United States of America is the American Epilepsy Society (AES), which holds an annual conference with a more-than-clinical focus. The American Clinical Neurophysiology Society (ACNS) publishes useful guidelines covering minimum technical requirements.[26,58,64,98,126–132] In Canada, the Canadian Society for Clinical Neurophysiology (CSCN) reviews standards and terminology, while also certifying physicians in EEG.[59,88] Other global society websites or publications hosting useful information include the American Society of Electroneurodiagnostic Technologists (ASET), the American Academy of Neurology (AAN), the National Association of Epilepsy Centers (NAEC), the Canadian Association of Electroneurophysiology Technologists (CAET), and the National Institute for Health and Care Excellence (NICE).

Further online resources include the Cochrane databases and the National Center for Biotechnology Information (NCBI) Bookshelf. The Veterinary Information Network (VIN) hosts veterinary conference proceedings and the few issues of the defunct journal *Veterinary Neurology and Neurosurgery*.

TAKE-HOME MESSAGES

- ✔ Electroencephalography monitors brain function in real time, and can help to answer the following questions that are relevant in different clinical scenarios (such as investigation of seizure disorders [1, 2], assessment of treatment efficacy in nonconvulsive status epilepticus [3] and brain death determination [4]):
  1. Is this transient event an epileptic seizure?
  2. Is this continuous mentation change an epileptic seizure?
  3. Are the antiseizure drugs working?
  4. Is there brain function?
- ✔ The montage is the arrangement of derivations or channels of electrode pairs as displayed on a screen to provide lateralizing and localizing information. Referential and bipolar montages are different views of the same event from various angles, like orthogonal radiographs.
- ✔ You can construct montages on the fly to improve your view of an event.
- ✔ Using sedation or general anesthesia for instrumentation will not interfere with the success of the subsequent recording.
- ✔ Simultaneous video recording with the EEG should be performed if possible, to provide confirmation of the episodes of interest, characterize the physical manifestations of an episode, and correlate behavior states with the EEG data.
- ✔ If recording unsynchronized video, e.g., cell phone camera, use a visual marker or time stamp on the video recording to help with video synchronization post-hoc.

- ✔ The clinician should be aware of common artifacts that occur on EEG, including eye and tongue movement artifact, electromyography artifact due to movement of other muscles, and electrocardiography artifact.
- ✔ Training and experience are required to accurately identify and interpret EEG abnormalities.
  - ✔ Nonspecific abnormalities include slowing of background activity that can be seen with various encephalopathies and sedative medications, and periodic discharges seen with brain injury.
  - ✔ Specific EEG abnormalities are epileptogenic, and include spikes, sharp waves, and spike- (or sharp-) and-slow-wave complexes, either singly or in groups.
- ✔ Software spike and seizure detectors flag epochs of interest but their sensitivity and specificity are still unknown.
- ✔ A normal interictal EEG does not rule out epilepsy
- ✔ Ninety-five percent of dogs presenting for transient events will present at least one EEG abnormality within a 4.5-hour recording.
- ✔ Do not overinterpret! The percentage of normal dogs and cats with EEG abnormalities is unknown.

REFERENCES

1. Hasegawa D. Diagnostic techniques to detect the epileptogenic zone: Pathophysiological and presurgical analysis of epilepsy in dogs and cats. *Vet J*. 2016; 215:64–75.
2. De Risio L, Bhatti S, Muñana KR et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. BioMed Central; 2015; 11(1):148.
3. Packer RMA, Berendt M, Bhatti S et al. Inter-observer agreement of canine and feline paroxysmal event semiology and classification by veterinary neurology specialists and non-specialists. *BMC Vet Res*. BioMed Central Ltd; 2015; 11(1):39.
4. James FMK, Cortez MA, Monteith G et al. Diagnostic utility of wireless video-electroencephalography in unsedated dogs. *J Vet Intern Med*. 2017; 31(5):1469–1476.
5. Poma R, Ochi A, Cortez MA. Absence seizures with myoclonic features in a juvenile Chihuahua dog. *Epileptic Disord*. 2010; 12(2):138–141.

6. Britton JW, Frey LC, Hopp JL et al. (authors), St Louis EK, Frey LC (eds.). *Electroencephalography: An Introductory Text and Atlas of Normal and Abnormal Findings in Adults, Children, and Infants*. Chicago: American Epilepsy Society; 2016.
7. Fisher RS, Cross JH, French JA et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE commission for classification and terminology. *Epilepsia*. 2017; 58(4):522–530.
8. Wielaender F, James FMK, Cortez MA et al. Absence seizures as a feature of juvenile myoclonic epilepsy in Rhodesian Ridgeback dogs. *J Vet Intern Med*. 2018; 32(1):428–432.
9. Berg AT, Berkovic SF, Brodie MJ et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. 2010; 51(4):676–85.
10. Serrano S, Hughes D, Chandler KE. Use of ketamine for the management of refractory status epilepticus in a dog. *J Vet Intern Med*. 2006; 20(1):194–197.
11. Raith K, Steinberg TA, Fischer A. Continuous electroencephalographic monitoring of status epilepticus in dogs and cats: 10 patients (2004-2005). *J Vet Emerg Crit Care*. 2010; 20(4):446–455.
12. Cuff DE, Bush WW, Stecker MM, Williams DC. Use of continuous electroencephalography for diagnosis and monitoring of treatment of nonconvulsive status epilepticus in a cat. *J Am Vet Med Assoc*. 2014; 244(6):708–714.
13. Blades Golubovic S, Rossmeisl JH Jr. Status epilepticus in dogs and cats, part 1: etiopathogenesis, epidemiology, and diagnosis. *J Vet Emerg Crit Care*. 2017; 27(3):278–287.
14. Blades Golubovic S, Rossmeisl JH Jr. Status epilepticus in dogs and cats, part 2: treatment, monitoring, and prognosis. *J Vet Emerg Crit Care*. 2017; 27(3):288–300.
15. Granum LK, Bush WW, Williams DC et al. Prevalence of electrographic seizure in dogs and cats undergoing electroencephalography and clinical characteristics and outcome for dogs and cats with and without electrographic seizure: 104 cases (2009-2015). *J Am Vet Med Assoc*. 2019; 254(8):967–973.
16. Hendricks JC, Morrison AR, Farnbach GL et al. A disorder of rapid eye movement sleep in a cat. J Am Vet Med Assoc. *J Am Vet Med Assoc*. 1981; 178(1):55–57.
17. Hendricks JC, Morrison AR. Normal and abnormal sleep in mammals. *J Am Vet Med Assoc*. 1981; 178(2):121–126.
18. Hendricks JC, Lager A, O'Brien DP, Morrison AR. Movement disorders during sleep in cats and dogs. *J Am Vet Med Assoc*. 1989; 194(5):686–689.
19. Bush WW, Barr CS, Stecker MM et al. Diagnosis of rapid eye movement sleep disorder with electroencephalography and treatment with tricyclic antidepressants in a dog. *J Am Anim Hosp Assoc*. 2004; 40(6):495–500.
20. Schubert TA, Chidester RM, Chrisman CL. Clinical characteristics, management and long-term outcome of suspected rapid eye movement sleep behaviour disorder in 14 dogs. *J Small Anim Pract*. 2011 Feb; 52(2):93–100.
21. Iotchev IB, Kis A, Bódizs R et al. EEG transients in the sigma range during non-REM sleep predict learning in dogs. *Sci Rep*. 2017; 7(1):12936.
22. Iotchev IB, Kis A, Bódizs R et al. Author correction: EEG transients in the sigma range during non-REM sleep predict learning in dogs. *Sci Rep*. Nature Publishing Group; 2018; 8(1):6138–6143.
23. Bódizs R, Kis A, Gácsi M, Topál J. Sleep in the dog: comparative, behavioral and translational relevance. *Curr Opin Behav Sci.* 2020; 33:25–33.

24. Iotchev IB, Kis A, Turcsán B et al. Age-related differences and sexual dimorphism in canine sleep spindles. *Sci Rep*. Nature Publishing Group; 2019 Jul 12; 9(1):10092.
25. Iotchev IB, Szabó D, Kis A, Kubinyi E. Possible association between spindle frequency and reversal-learning in aged family dogs. *Sci Rep*. Nature Publishing Group; 2020 Apr 16; 10(1):6505–6511.
26. Stecker MM, Sabau D, Sullivan L et al. American Clinical Neurophysiology Society Guideline 6: Minimum Technical Standards for EEG Recording in Suspected Cerebral Death. *J Clin Neurophysiol*. 2016; 33(4):324–327.
27. Hernandez E, James FMK, Torrey S et al. Electroencephalographic, physiologic and behavioural responses during cervical dislocation euthanasia in turkeys. *BMC Vet Res*. 2019; 15(1):132.
28. Hernandez E, James FMK, Torrey S et al. Evaluation of brain death in laying hens during on-farm killing by cervical dislocation methods or pentobarbital sodium injection. *Front Vet Sci*. 2019; 6:1–16.
29. Bauerle K, Greim C-A, Schroth M et al. Prediction of depth of sedation and anaesthesia by the Narcotrend EEG monitor. *Br J Anaesth*. 2004; 92(6):841–845.
30. Kreuer S, Wilhelm W, Grundmann U et al. Narcotrend index versus bispectral index as electroencephalogram measures of anesthetic drug effect during propofol anesthesia. *Anesth Analg*. 2004; 98(3):692–697.
31. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev*. 2014 Jun 17; 2014(6):CD003843.
32. Hajat Z, Ahmad N, Andrzejowski J. The role and limitations of EEG-based depth of anaesthesia monitoring in theatres and intensive care. *Anaesthesia*. 2017 Jan 2; 72(Suppl. 1):38–47.
33. Greene SA, Benson GJ, Tranquilli WJ. Comparison of surface and subdermal electrodes for monitoring bispectral index in anesthetized dogs. *Vet Anaesth Analg*. 2001; 28(2):98.
34. Lopes PCF, Nunes N, Paula DP et al. Bispectral index in dogs at three intravenous infusion rates of propofol. *Vet Anaesth Analg*. 2008; 35(3):228–231.
35. Morgaz J, Granados MM, Domínguez JM et al. Relationship of bispectral index to hemodynamic variables and alveolar concentration multiples of sevoflurane in puppies. *Res Vet Sci*. 2009; 86(3):508–513.
36. Bleijenberg EH, van Oostrom H, Akkerdaas LC et al. Bispectral index and the clinically evaluated anaesthetic depth in dogs. *Vet Anaesth Analg*. 2011; 38(6):536–543.
37. Youngblood BL, Ueyama Y, Muir WW et al. A new method for determining levels of sedation in dogs: A pilot study with propofol and a novel neuroactive steroid anesthetic. *J Neurosci Methods*. 2018; 305:82–88.
38. Hernandez-Avalos I, Mota-Rojas D, Mora-Medina P et al. Review of different methods used for clinical recognition and assessment of pain in dogs and cats. *Int J Vet Sci Med*. 2019; 7(1):43–54.
39. Koyama C, Haruna T, Hagihira S, Yamashita K. New criteria of burst suppression on electroencephalogram in dogs anesthetized with sevoflurane. *Res Vet Sci*. 2019 Apr; 123:171–177.
40. Saenubol P, Akatvipat A, Pleumsamran A, Chankrachang S. Correlation between bispectral index value and modified Glasgow Coma Scale score in dogs with altered level of consciousness. *J Vet Emerg Crit Care*. 2021; 31(1):52–58.

41. Bassett L, Troncy E, Pouliot M et al. Telemetry video-electroencephalography (EEG) in rats, dogs and non-human primates: methods in follow-up safety pharmacology seizure liability assessments. *J Pharmacol Toxicol Methods*. 2014; 70(3):230–240.
42. Davis KA, Sturges BK, Vite CH et al. A novel implanted device to wirelessly record and analyze continuous intracranial canine EEG. *Epilepsy Res*. 2011; 96(1–2):116–122.
43. Coles LD, Patterson ENE, Sheffield WD et al. Feasibility study of a caregiver seizure alert system in canine epilepsy. *Epilepsy Res*. 2013; 106(3):456–460.
44. Howbert JJ, Patterson ENE, Stead SM et al. Forecasting seizures in dogs with naturally occurring epilepsy. *PLoS ONE*. 2014; 9(1):e81920.
45. Brinkmann BH, Patterson ENE, Vite CH et al. Forecasting seizures using intracranial eeg measures and svm in naturally occurring canine epilepsy. *PLoS One*. 2015; 10(8):e0133900.
46. Brinkmann BH, Wagenaar J, Abbot D et al. Crowdsourcing reproducible seizure forecasting in human and canine epilepsy. *Brain*. 2016; 139(Pt 6):1713–1722.
47. Caton R. The Electric Currents of the Brain. *BMJ*. 1875; 2(765):278.
48. Skerritt GC. *King's Applied Anatomy of the Central Nervous System of Domestic Mammals*, 2nd ed. John Wiley & Sons; 2018.
49. Gloor P. Neuronal generators and the problem of localization in electroencephalography: application of volume conductor theory to electroencephalography. *J Clin Neurophysiol*. 1985; 2(4):327–54.
50. Holliday TA, Williams DC. Clinical Electroencephalography in Dogs. *Vet Neurol Neurosurg J*. 1999; 1(1):1–38.
51. Holliday TA. Volume conduction principles in clinical neurophysiology: how to tell up from down and read those squiggly lines. *Vet Neurol Neurosurg J*. 2003; 5(1):37.
52. Steriade M, Gloor P, Llinás RR et al. Report of IFCN committee on basic mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalogr Clin Neurophysiol*. 1990; 76(6):481–508.
53. Kane N, Acharya J, Benickzy S et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. *Clin Neurophysiol Pract*. 2017; 2:170–85.
54. Alarcon G, Guy CN, Binnie CD et al. Intracerebral propagation of interictal activity in partial epilepsy: implications for source localisation. *J Neurol Neurosurg Psychiatr*. 1994; 57(4):435–49.
55. Stern JM. *Atlas of EEG Patterns*. Lippincott Williams & Wilkins; 2013.
56. Kane N, Acharya J, Beniczky S et al. Corrigendum to "A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017" [Clin. Neurophysiol. Practice 2 (2017) 170–185]. *Clin Neurophysiol Pract.* 2019; 4:133.
57. Olejniczak P. Neurophysiologic basis of EEG. *J Clin Neurophysiol*. 2006; 23(3):186–189.
58. Sinha SR, Sullivan L, Sabau D et al. American Clinical Neurophysiology Society Guideline 1: Minimum technical requirements for performing clinical electroencephalography. *J Clin Neurophysiol*. 2016; 33(4):303–307.
59. Dash D, Dash C, Primrose S et al. Update on minimal standards for electroencephalography in canada: a review by the Canadian Society of Clinical Neurophysiologists. *Can J Neurol Sci*. 2017; 44(6):631–642.

60. JAMES FMK, VURIK K, GAITERO L et al. Environment in canine ambulatory electroencephalography. *J Vet Intern Med*. 2016; 30(6):1938.
61. BRUNNHUBER F, AMIN D, NGUYEN Y et al. Development, evaluation and implementation of video-EEG telemetry at home. *Seizure*. 2014; 23(5):338–343.
62. BERENDT M, FARQUHAR RG, MANDIGERS PJJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11(1):182.
63. JASPER HH. The ten twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol*. 1957; 10:371–375.
64. ACHARYA JN, HANI A, CHEEK J et al. American Clinical Neurophysiology Society guideline 2: Guidelines for standard electrode position nomenclature. *J Clin Neurophysiol*. 2016; 33(4):308–311.
65. SEECK M, KOESSLER L, BAST T et al. The standardized EEG electrode array of the IFCN. *Clinical Neurophysiology*. 2017; 128(10):2070–2077.
66. PELLEGRINO F, SICA R. Canine electroencephalographic recording technique: findings in normal and epileptic dogs. *Clin Neurophysiol*. 2004; 115(2):477–487.
67. CROFT PG. The EEG as an aid to diagnosis of nervous diseases in the dog and cat. *J Small Anim Pract*. 1962; 3(4):205–213.
68. FOX MW. Postnatal development of the EEG in the dog. I. Introduction and EEG techniques. *J Small Anim Pract*. 1967; 8(2):71–76.
69. REDDING RW, KNECHT CE. *Atlas of electroencephalography in the dog and cat*. Praeger; 1984.
70. KIS A, SZAKADÁT S, KOVÁCS E et al. Development of a non-invasive polysomnography technique for dogs (Canis familiaris). *Physiol Behav*. 2014; 130:149–156.
71. STEISS JE. A survey of current techniques in veterinary electrodiagnostics: EEG, spinal evoked and brainstem auditory evoked potential recording. *Vet Res Commun*. 1988; 12(4-5):281–288.
72. KLEMM WR. Technical aspects of electroencephalography in animal research. *Am J Vet Res*. 1965; 26(115):1237–1248.
73. YOUNG GB, IVES JR, CHAPMAN MG, MIRSATTARI SM. A comparison of subdermal wire electrodes with collodion-applied disk electrodes in long-term EEG recordings in ICU. *Clin Neurophysiol*. 2006; 117(6):1376–1379.
74. MIRSATTARI SM, IVES JR, BIHARI F et al. Real-time display of artifact-free electroencephalography during functional magnetic resonance imaging and magnetic resonance spectroscopy in an animal model of epilepsy. *Magn Reson Med*. 2005; 53(2):456–464.
75. IVES JR. New chronic EEG electrode for critical/intensive care unit monitoring. *J Clin Neurophysiol*. 2005; 22(2):119–123.
76. JAMES FMK, ALLEN DG, BERSENAS AME et al. Investigation of the use of three electroencephalographic electrodes for long-term electroencephalographic recording in awake and sedated dogs. *Am J Vet Res*. 2011; 72(3):384–390.
77. PARMENTIER T, MONTEITH G, CORTEZ MA et al. Effect of prior general anesthesia or sedation and antiseizure drugs on the diagnostic utility of wireless video electroencephalography in dogs. *J Vet Intern Med*. 2020; 34(5):1967–1974.
78. BRAUER C, KÄSTNER SBR, SCHENK HC et al. Electroencephalographic recordings in dogs: prevention of muscle artifacts and evaluation of two activation techniques in healthy individuals. *Res Vet Sci*. 2011; 90(2):306–311.

79. MENDEZ OE, BRENNER RP. Increasing the yield of EEG. *J Clin Neurophysiol*. 2006; 23(4):282–293.
80. RENZEL R, BAUMANN CR, PORYAZOVA R. EEG after sleep deprivation is a sensitive tool in the first diagnosis of idiopathic generalized but not focal epilepsy. *Clin Neurophysiol*. 2016; 127(1):209–213.
81. GIORGI FS, MAESTRI M, GUIDA M et al. Controversial issues on EEG after sleep deprivation for the diagnosis of epilepsy. *Epilepsy Res Treat*. 2013; 2013:614685.
82. GIORGI FS, PERINI D, MAESTRI M et al. Usefulness of a simple sleep-deprived EEG protocol for epilepsy diagnosis in de novo subjects. *Clin Neurophysiol*. 2013; 124(11):2101–2107.
83. GIORGI FS, GUIDA M, CACIAGLI L et al. What is the role for EEG after sleep deprivation in the diagnosis of epilepsy? Issues, controversies, and future directions. *Neurosci Behav Rev*. 2014; 47:533–548.
84. GIORGI FS, MAESTRI M, GUIDA M et al. Cyclic alternating pattern and interictal epileptiform discharges during morning sleep after sleep deprivation in temporal lobe epilepsy. *Epilepsy Behav*. 2017; 73:131–136.
85. UTSUGI S, SAITO M, SATO T, KUNIMI M. Relationship between interictal epileptiform discharges under medetomidine sedation and clinical seizures in canine idiopathic epilepsy. *Vet Rec*. 2020; 187(2): 67.
86. BRAUER C, KÄSTNER SBR, KULKA AM, TIPOLD A. Activation procedures in the electroencephalograms of healthy and epileptic cats under propofol anaesthesia. *Vet Rec*. 2012; 170(14):360.
87. BRAUER C, KÄSTNER SBR, ROHN K et al. Electroencephalographic recordings in dogs suffering from idiopathic and symptomatic epilepsy: diagnostic value of interictal short time EEG protocols supplemented by two activation techniques. *Vet J*. 2012; 193(1):185–192.
88. TASK FORCE OF THE CANADIAN SOCIETY OF CLINICAL NEUROPHYSIOLOGISTS. Guidelines for visual-sensitive EEG testing. *Can J Neurol Sci*. 2014; 35(2):133–135.
89. RUBBOLI G, SILIPO S, GARDELLA E, TASSINARI CA. Ictal EEG. In: PANAYIOTOPOULOS CP (ed.). *Atlas of Epilepsies*.London: Springer; 2010. pp. 713–722.
90. WIELAENDER F, SARVIAHO R, JAMES FMK et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. *Proc Natl Acad Sci USA*. 2017; 114(10):2669–2674.
91. ALIX JJP, KANDLER RH, MORDEKAR SR. The value of long term EEG monitoring in children: a comparison of ambulatory EEG and video telemetry. *Seizure*. 2014; 23(8):662–665.
92. LAWLEY A, EVANS S, MANFREDONIA F, CAVANNA AE. The role of outpatient ambulatory electroencephalography in the diagnosis and management of adults with epilepsy or nonepileptic attack disorder: A systematic literature review. *Epilepsy Behav*. 2015; 53:26–30.
93. LAWLEY A, MANFREDONIA F, CAVANNA AE. Video-ambulatory EEG in a secondary care center: A retrospective evaluation of utility in the diagnosis of epileptic and nonepileptic seizures. *Epilepsy Behav*. 2016; 57(Pt A):137–140.
94. THEITLER J, DASSA D, GANDELMAN-MARTON R. The yield of non-elective inpatient video-EEG monitoring in adults. *Neurol Sci*. 2017; 38(6):961–965.
95. WATEMBERG N, TZIPERMAN B, DABBY R et al. Adding video recording increases the diagnostic yield of routine electroencephalograms in children with frequent paroxysmal events. *Epilepsia*. 2005; 46(5):716–719.
96. MUSTEATA M, BORCEA DG, STEFANESCU R et al. Influence of stainless needle electrodes and silver disk electrodes over the interhemispheric cerebral coherence value in vigil dogs. *Sensors*

(Basel). 2018; 18(11):3990.

97. Moyer JT, Gnatkovsky V, Ono T et al. Standards for data acquisition and software-based analysis of in vivo electroencephalography recordings from animals. A TASK1-WG5 report of the AES/ILAE Translational Task Force of the ILAE. *Epilepsia*. 2017; 58 Suppl 4:53–67.
98. Acharya JN, Hani AJ, Thirumala PD, Tsuchida TN. American Clinical Neurophysiology Society Guideline 3: A proposal for standard montages to be used in clinical EEG. *J Clin Neurophysiol*. 2016; 33(4):312–316.
99. Poma R, Frey S, Barnard L et al. Subdermal EEG electrode placement in the dog using neuronavigation. *American Epilepsy Society Annual Meeting Abstracts*. 2010.
100. Levitt J, Nitenson A, Koyama S et al. Automated detection of electroencephalography artifacts in human, rodent and canine subjects using machine learning. *J Neurosci Methods*. 2018; 307:53–59.
101. Gross J, Tass PA, Salenius S et al. Cortico-muscular synchronization during isometric muscle contraction in humans as revealed by magnetoencephalography. *J Physiol (Lond)*. 2000; 527 Pt 3(3):623–631.
102. Tassinari CA, Cantalupo G, Rubboli G. Polygraphic recording of epileptic seizures. In: Panayiotopoulos CP (ed.). *Atlas of Epilepsies*. London: Springer; 2010. pp. 723–740.
103. Petersen J, Diperri R, Himwich WA. The comparative development of the eeg in rabbit, cat and dog. *Electroencephalogr Clin Neurophysiol*. 1964;17:557–563.
104. Fox MW. Postnatal development of the EEG in the dog. II. Development of electrocortical activity. *J Small Anim Pract*. 1967; 8(2):77–107.
105. Fox MW. Postnatal development of the EEG in the dog. III. Summary and discussion of development of canine EEG. *J Small Anim Pract*. 1967; 8(2):109–112.
106. Lewis MJ, Williams DC, Vite CH. Evaluation of the electroencephalogram in young cats. *Am J Vet Res*. 2011; 72(3):391–397.
107. Silber MH, Ancoli-Israel S, Bonnet MH et al. The visual scoring of sleep in adults. *J Clin Sleep Med*. 2007; 3(2):121–131.
108. Grigg-Damberger MM. The AASM Scoring Manual four years later. *J Clin Sleep Med*. 2012; 8(3):323–332.
109. Williams DC, Aleman M, Holliday TA et al. Qualitative and quantitative characteristics of the electroencephalogram in normal horses during spontaneous drowsiness and sleep. *J Vet Intern Med*. 2008; 22(3):630–638.
110. Destexhe A. Spike-and-wave oscillations based on the properties of GABAB receptors. *J Neurosci*. 1998; 18(21):9099–9111.
111. Wirrell EC. Prognostic significance of interictal epileptiform discharges in newly diagnosed seizure disorders. *J Clin Neurophysiol*. 2010; 27(4):239–48.
112. Hasegawa D, Fujita M, Nakamura S et al. Electrocorticographic and histological findings in a Shetland sheepdog with intractable epilepsy. *J Vet Med Sci*. 2002;64(3):277–279.
113. Kuwabara T, Hasegawa D, Ogawa F et al. A familial spontaneous epileptic feline strain: A novel model of idiopathic/genetic epilepsy. *Epilepsy Res*. 2010; 92(1):85–88.
114. Ung H, Davis KA, Wulsin D et al. Temporal behavior of seizures and interictal bursts in prolonged intracranial recordings from epileptic canines. *Epilepsia*. 2016; 57(12):1949–1957.
115. Panayiotopoulos CP. *The Epilepsies*, 2nd ed. Springer. 2012.
116. Camfield CS, Camfield PR. Absence Seizures. In: Panayiotopoulos CP (ed.). *Atlas of Epilepsies*. London: Springer; 2010. pp. 379–383.

117. Trinka E, Cock H, Hesdorffer D et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on classification of status epilepticus. *Epilepsia*. 2015; 56(10):1515–1523.

118. Smith SJM. EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatr*. 2005; 76(suppl 2):ii2–ii7.

119. Bhatti SFM, De Risio L, Muñana KR et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015; 11(1):176.

120. Potschka H, Fischer A, Löscher W et al. International Veterinary Epilepsy Task Force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. *BMC Vet Res*. 2015; 11(1):177.

121. Rusbridge C, Long SN, Jovanovik J et al. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol. *BMC Vet Res*. 2015; 11(1):194.

122. Matiasek K, Pumarola I Batlle M, Rosati M et al. International Veterinary Epilepsy Task Force recommendations for systematic sampling and processing of brains from epileptic dogs and cats. *BMC Vet Res*. 2015; 11(1):216.

123. Hülsmeyer V-I, Fischer A, Mandigers PJJ et al. International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. *BMC Vet Res*. 2015; 11(1):175.

124. Podell MA, Volk HA, Berendt M et al. 2015 ACVIM small animal consensus statement on seizure management in dogs. *J Vet Intern Med*. 2016; 30(2):477–490.

125. Tankisi H, Burke D, Cui L et al. Standards of instrumentation of EMG. *Clin Neurophysiol*. 2020; 131(1):243–258.

126. Tsuchida TN, Wusthoff CJ, Shellhaas RA et al. American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. *J Clin Neurophysiol*. 2013; 30(2):161–173.

127. Kuratani J, Pearl PL, Sullivan LR et al. American Clinical Neurophysiology Society guideline 5: Minimum technical standards for pediatric electroencephalography. *Neurodiagn J*. 2016; 56(4):266–75.

128. Hirsch LJ, LaRoche SM, Gaspard N et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. *J Clin Neurophysiol*. 2013; 30(1):1–27.

129. Tatum WO, Olga S, Ochoa JG et al. American Clinical Neurophysiology Society guideline 7: Guidelines for EEG reporting. *J Clin Neurophysiol*. 2016; 33(4):328–332.

130. Halford JJ, Sabau D, Drislane FW et al. American Clinical Neurophysiology Society guideline 4: Recording clinical EEG on digital media. *J Clin Neurophysiol*. 2016; 33(4):317–319.

131. Herman ST, Abend NS, Bleck TP et al. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. *J Clin Neurophysiol.* 2015 Apr; 32(2):87–95.

132. Herman ST, Abend NS, Bleck TP et al. Consensus statement on continuous EEG in critically ill adults and children, part II: personnel, technical specifications, and clinical practice. *J Clin Neurophysiol*. 2015 Apr; 32(2):96–108.

Fundamental Principles of Pharmacokinetics for Antiseizure Drugs

08

Mark G. Papich

Two disciplines of pharmacology are **pharmacodynamics** and **pharmacokinetics**:

- **Pharmacodynamics** is the study of the effects of drugs, drug concentration–effect relationships, and mechanism of action.
- **Pharmacokinetics** (PK) is the study of the time course of change in the concentration of drugs in tissues of animals. It includes an understanding of the absorption, distribution, biotransformation (metabolism) and excretion of drugs.

It is important to understand how PK affects drug therapy when deciding on a patient's treatment. The affinity of a drug for receptors, its cellular effect, and the susceptibility of pathogenic organisms to it do not vary appreciably between patients, between healthy animals and ill animals, or between animals with variations in physiological parameters (or at least these effects are poorly quantified or understood in animals.) However, PK parameters can change dramatically from one patient to another. Therefore, an understanding of PK becomes more important for bench-to-bedside transfer of drug therapy and design of drug regimens in clinical patients. An understanding of **clinical pharmacokinetics** is important for formulating dosage regimens in animals. These principles will benefit patients who may handle drugs differently than healthy adult animals that are used in preclinical experiments.

In veterinary medicine, controlled clinical trials are often not performed before drugs are administered to patients. Many drugs—especially those used in small and exotic animals—are used extralabel (also referred to as "off-label"). Dose titrations are rarely performed unless a drug is intended to be approved by regulatory authorities for use in the target animal species (TAS) by a drug sponsor. When a drug is used extralabel, which is the situation for many of the antiseizure drugs (ASDs) used in animals, studies in the TAS may not be available. Therefore, an important use of PK principles in veterinary medicine is to extrapolate drug use in one species to another (for example, from humans to animals).

IMPORTANT DEFINITIONS

To derive and adjust dosages of ASDs in animals, one must understand the basic elements of PK. There are four important components that contribute to determining the clinical dose of a medication for animals. The following basic terms (with abbreviations) should be understood; **systemic availability** (F), **clearance** (Cl), **volume of distribution** (V_D or VD) and **elimination half-life** ($t_{½}$) (Box 8.1). Each item will be discussed in the sections to follow.

PRINCIPLES OF DRUG DISPOSITION IN ANIMALS

Drugs administered to animals are described as if they circulate through various "compartments" in the body. These are arbitrary compartments, and do not reflect anatomic body sites. It is simply a useful method to describe how a drug behaves in the body. After a drug is administered, it can circulate extensively and evenly into all body sites, which can be described as "one compartment", or it may distribute to some tissues more than others (e.g., plasma vs muscle vs fat vs other organs). In this latter case, drug

distribution may be described using a multicompartment model (two-compartment, three-compartment, etc.)

BOX 8.1. Important pharmacokinetic definitions.

- **Systemic availability** (F) defines how much of the drug is absorbed into the systemic circulation. This defines the dosage adjustment necessary for oral, subcutaneous (SC), intramuscular (IM) or other nonintravenous (IV) administration. For an IV dose, F = 1.0 (100% absorption). For other routes it may be much less than 1.
- **Clearance** (Cl) defines the ability of the body to eliminate the drug (e.g., "high clearance drug", "low clearance drug"). Two important organs of clearance are the kidney (Cl_R) and liver (Cl_H). The clearance is measured as the volume of blood (or plasma) cleared of the drug over time.
- **Volume of distribution** (V_D, or VD) defines the extent to which a drug distributes in the body. The determinants of V_D are lipophilicity, protein binding, molecular size, and other drug factors. It may also be influenced by patient characteristics such as obesity, fluid shifts, muscle mass, and age, among other things. The V_D helps determine how much of the administered dose is in the plasma circulation, which is often defined as the maximum plasma concentration (C_{max}), average concentration (C_{ave}), or minimum concentration (C_{min}).
- **Elimination half-life** ($t_{½}$) is the time that it takes for half of the drug to be eliminated. Or, more properly stated, it is the time that it takes for the drug concentration to decline by one half (drug concentrations in plasma can decline without elimination from the body). The $t_{½}$ will be used to define the dosing interval and duration of effect.

One-compartment model

A one-compartment model (Fig. 8.1) assumes that there is instantaneous distribution of a drug to tissues after drug administration. In this model, the whole body behaves as a homogeneous unit and it is assumed that the drug distributes to all areas of the body at equal rates.

The equation used to describe a one-compartment model is:

$$C(t) = C_0 \times e^{-kt}$$

where C is the plasma concentration of the drug in the body at time t, C_0 is the initial plasma concentration immediately after dosing (i.e., t = 0), and e is the base of the natural logarithm (e = 2.718). It is important to recognize that it is an exponential function. That is, the elimination rate (described by k) is exponential (Fig. 8.2). The relationship shown by the formula above is important for designing dosage regimens and predicting drug disposition. If we know the initial concentration and the elimination rate, we can predict

the drug concentration at any time *t*. As seen in Figure 8.2, which depicts a one-compartment model, the decline in plasma concentration is exponential when plotted on a linear axis. When transferred to a logarithmic scale (or alternatively, the concentrations could be converted to a log scale and plotted on a linear axis), the curve becomes linear.

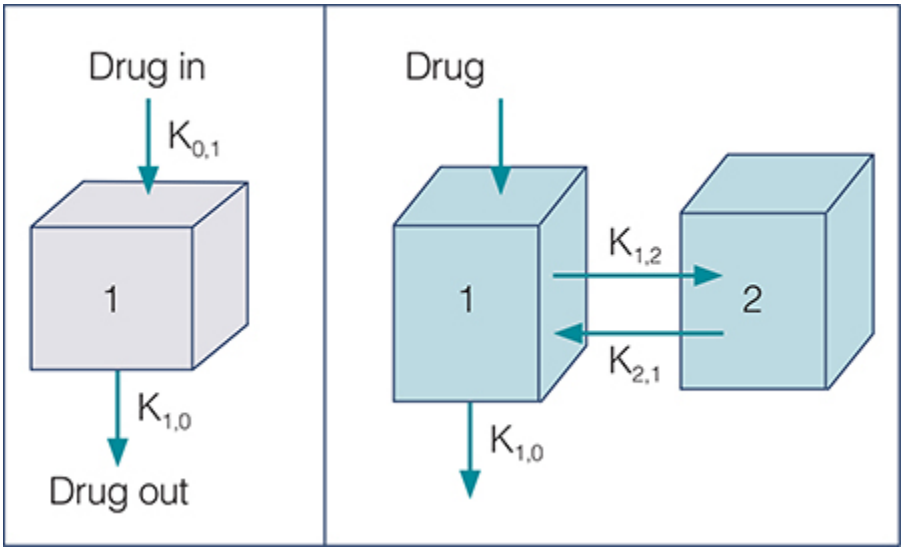


FIGURE 8.1. Pharmacokinetic models. One-compartment simple model on the left, and a more common, two-compartment model on the right. Rates (K) describe the rate of drug movement from one compartment to another, with "0" representing outside of the body (e.g., $K_{0,1}$ is the rate of drug into the body; $K_{1,0}$ is elimination out of the body).

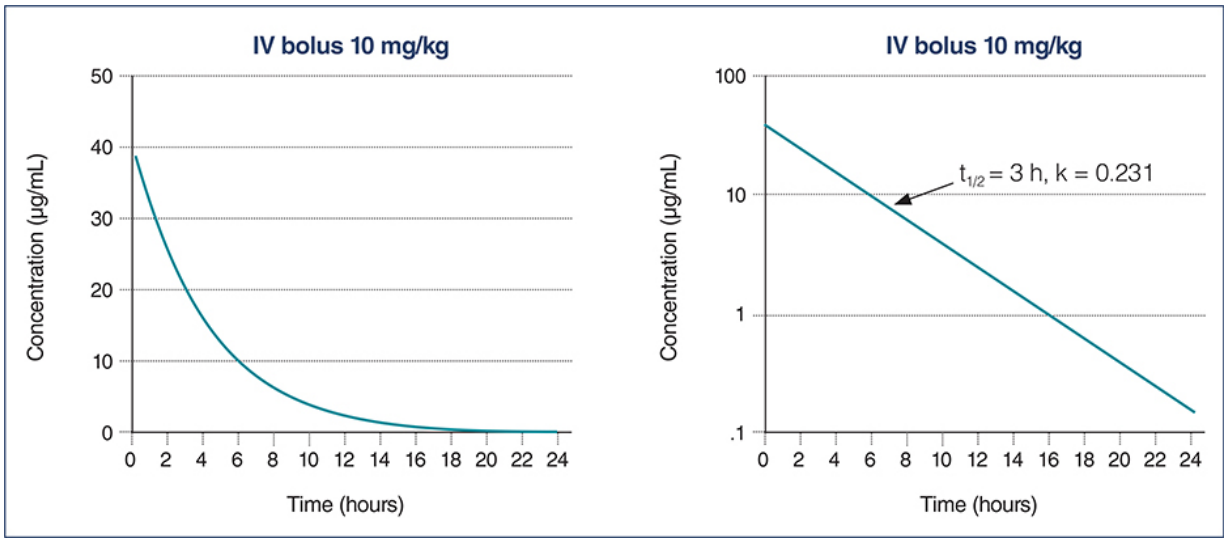


FIGURE 8.2. Typical graphs for a one-compartment model with first-order elimination. A linear scale is used on the left and a logarithmic scale on the right. Note that when plotted on a linear axis,

the curve is exponential. When the same data are transferred to a logarithmic scale (right), it becomes a straight line. Semilogarithmic plots are common in pharmacokinetic analysis.

Two-compartment model

A two-compartment model recognizes that there is a noticeable distribution phase after the drug is administered (see Fig. 8.1, right panel). In this model the drug requires time for equilibration between plasma and tissue concentrations, shown as $K_{1,2}$ and $K_{2,1}$ in Figure 8.1, where K is the rate of drug movement between compartments. In a two-compartment model the drug first distributes rapidly throughout the **first compartment (central compartment)** and as equilibrium occurs, the drug distributes to the **second compartment (peripheral compartment)**.

In the two-compartment model shown in Figure 8.1, Compartment 1 best represents the circulating blood and highly perfused organs (e.g., bone marrow, liver, and kidneys). Compartment 2 probably best represents the less highly perfused tissues (e.g., muscle, fat, and bone).

Note: The compartments are not intended to represent a specific anatomical space. Attempts to equate the various compartments with anatomical spaces usually result in erroneous assumptions. These compartments are merely "black boxes" that provide a method for mathematically analyzing the distribution and elimination of a drug in the body.

In a two-compartment model, the decline in plasma concentration (Fig. 8.3) shows a biexponential decline when plotted on a semilogarithmic axis: an initial steep slope, followed by a shallower slope. During the distribution phase (the initial steep portion of the curve characterized by the Greek letter alpha, α), only a small fraction of the drug is eliminated from the body, but some elimination is always occurring. The largest change in the concentration of the drug in plasma during the distribution phase (α phase) reflects movement of the drug *within* the body, rather than loss *from* the body.

Once distribution to tissues is complete, equilibrium occurs and the slope of the curve becomes less steep, as seen in Figure 8.3. This portion of the curve represents the *elimination* portion of the curve (characterized by the Greek letter beta, β). The elimination phase is the irreversible removal of the drug from the body, which means that the drug is excreted from the

body or metabolized to a different compound. The equation for a two-compartment model is as follows:

$$C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

where *C* is the plasma concentration of drug in the body at time *t*, *e* is the base of the natural logarithm (e = 2.718) as previously defined, *A* is the intercept of the distribution phase of the curve, α is the distribution rate constant, *B* is the intercept of the elimination portion of the curve, and β is the elimination rate constant. Resolving a curve into its two components can be done using a technique called "curve stripping" (Fig. 8.3) or computer programs capable of performing nonlinear regression analysis. This type of analysis is usually beyond what is required of most veterinarians, but it is important for investigators attempting to understand the PK of the drug. Most practical dosing regimens used in veterinary medicine use simple one-compartment PK models. Multicompartment PK models are more appropriate as a research tool.

Beyond one- and two-compartment models are more complex models with three or more compartments. Analysis of these complex models is beyond the scope of this chapter, but these techniques can be helpful for research.

Modeling for oral, subcutaneous, or intramuscular administration

After non-IV administration (oral, SC, IM, or transdermal) a "distribution phase" of the curve may not be seen. Why is that? Distribution still occurs, but the rate of absorption is slower than the rate of distribution. Thus, the distribution is "hidden" in the plasma concentration profile. The appearance of plasma drug concentrations on a curve will always show the slowest rate (Figs 8.4 and 8.5). Non-IV administration can also be modeled with PK equations, with the rate constants as shown in Figure 8.4. The absorption rate is depicted as $K_{0,1}$ and the elimination rate as $K_{1,0}$.

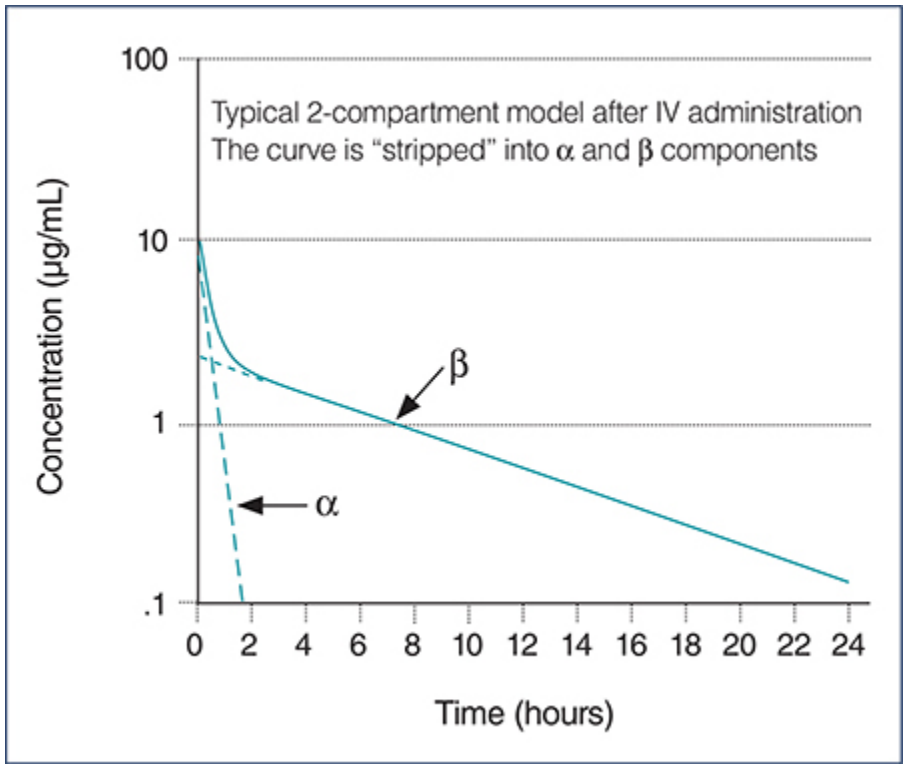


FIGURE 8.3. Two-compartment disposition of a drug plotted on a semilogarithmic axis. The α phase is the rapid distribution phase of decline in plasma drug concentrations and the β phase represents elimination from the body.

DRUG ELIMINATION (ELIMINATION HALF-LIFE, $T_{1/2}$)

What determines the half-life?

First-order elimination means that drugs are eliminated at a constant rate (while zero order would imply that drug elimination is by a constant amount instead of a constant rate). This can also be interpreted to mean that a constant fraction of the drug is eliminated during each period of time (e.g., per hour, or per minute). For a drug that undergoes first-order elimination (most drugs obey this principle), if the slope of the elimination curve (and the value of k) is known, the $t_{1/2}$ can be calculated by $t_{1/2} = 0.693/k$ (because the natural logarithm [Ln] of one-half is 0.693). The $t_{1/2}$ provides important information regarding the properties of the drug. The $t_{1/2}$

is probably the parameter most often used by clinicians when evaluating the PK features of a drug. It is useful clinically because it provides an indication of how often a drug should be administered to patients and how long a PK or toxic effect of a drug will persist. Since the $t_{1/2}$ indicates how long a drug remains in the body, one can show that at 1 $t_{1/2}$, the plasma concentration has decreased by 50%, at 2 $t_{1/2}$, the plasma concentration has decreased to 25% of the original concentration, and so on (Fig. 8.6).

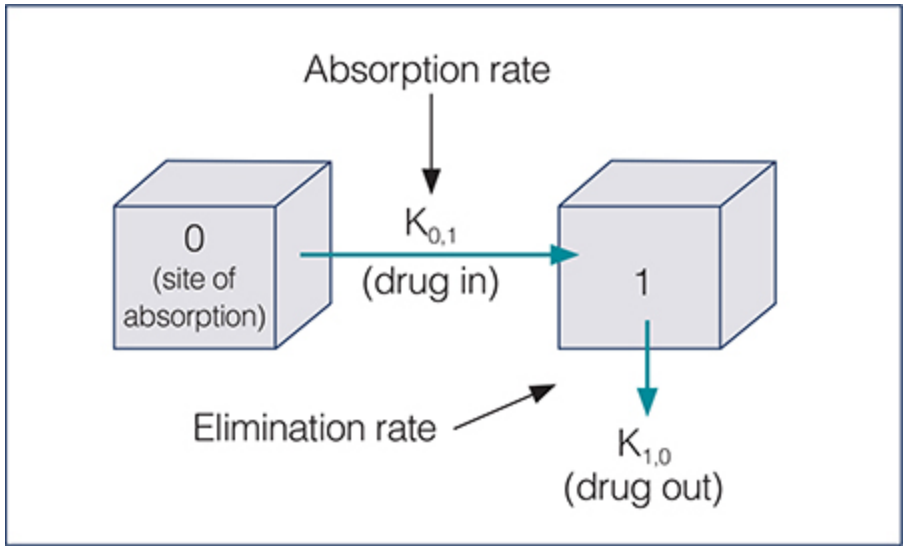


FIGURE 8.4. Compartment model with a non-IV dose component, showing the absorption rate into the main compartment.

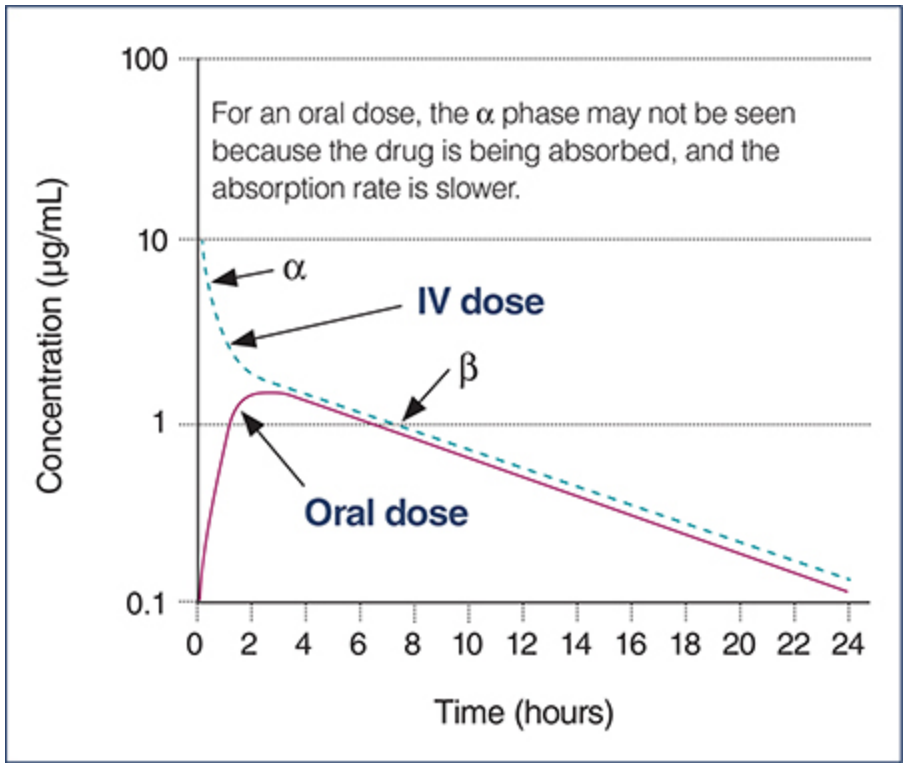


FIGURE 8.5. Oral dose plasma concentration from the model shown in Figure 8.4. In this figure, the dashed line is not seen when plasma concentrations are measured. The oral absorption rate is slower than distribution, so you only see the solid line when concentrations are plotted.

From the example in Figure 8.6, you can observe that approximately 90% of a drug will be eliminated from the body in 3.3 $t_{1/2}$; and 99% of a drug dose will be eliminated in 7 $t_{1/2}$. These concepts are depicted graphically in the figure. This assumption applies regardless of the length of the $t_{1/2}$.

Time to reach steady state

If multiple doses of a drug are administered, a **steady-state** or plateau plasma concentration is the point at which the amount of drug eliminated during a dosing interval is equal to the amount that goes in (i.e., dose). In other words, the rate in is equal to the rate out. The time necessary to achieve steady state is related to the $t_{1/2}$.

If a drug is administered with multiple doses, or as a constant rate infusion (CRI), it will take 3.3 $t_{1/2}$ for a drug to reach 90% of its steady-state plasma concentration, 5 $t_{1/2}$ for 95%, and 7 $t_{1/2}$ for a drug to reach 99% of its

steady state. This principle applies regardless of the dose administered and the $t_{1/2}$ of the drug. The same rule applies for constant rate infusions. This principle is shown in Figure 8.7, for a drug that has a $t_{1/2}$ of 48 hours and is administered every 12 hours. To avoid the time lag to steady state, a loading dose (D_L) may be administered. A loading dose is a large initial dose designed to instantaneously produce plasma drug concentrations at the desired steady-state level (see examples below).

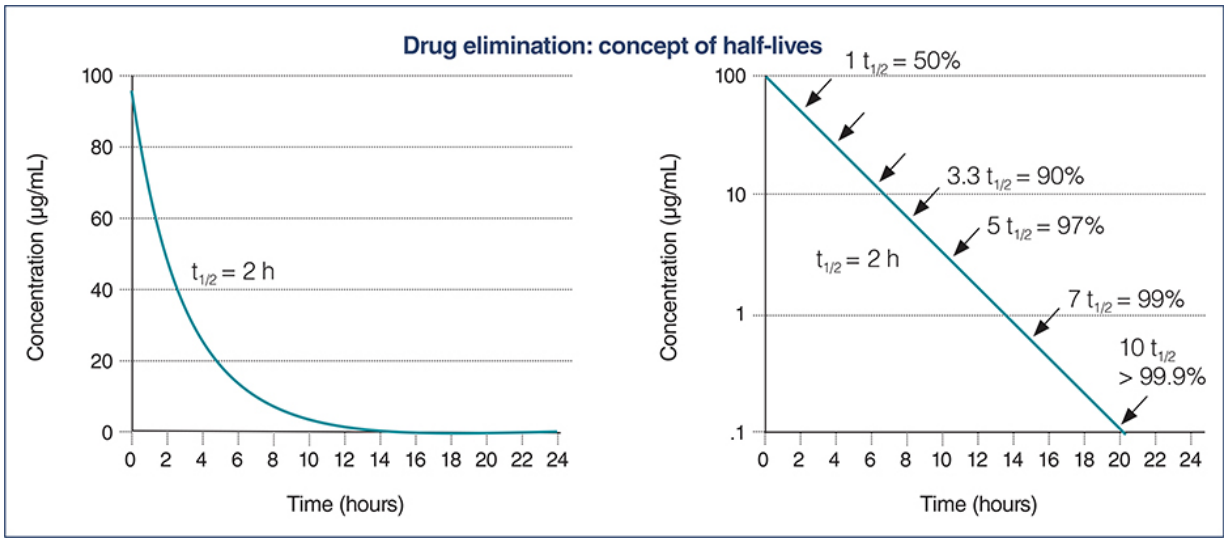


FIGURE 8.6. The concept of half-lives ($t_{1/2}$). The plot on the left is on a linear axis for a drug with a $t_{1/2}$ of 2 hours. The plot on the right is the data depicted on a logarithmic axis, showing the percent decline in drug concentration with each $t_{1/2}$.

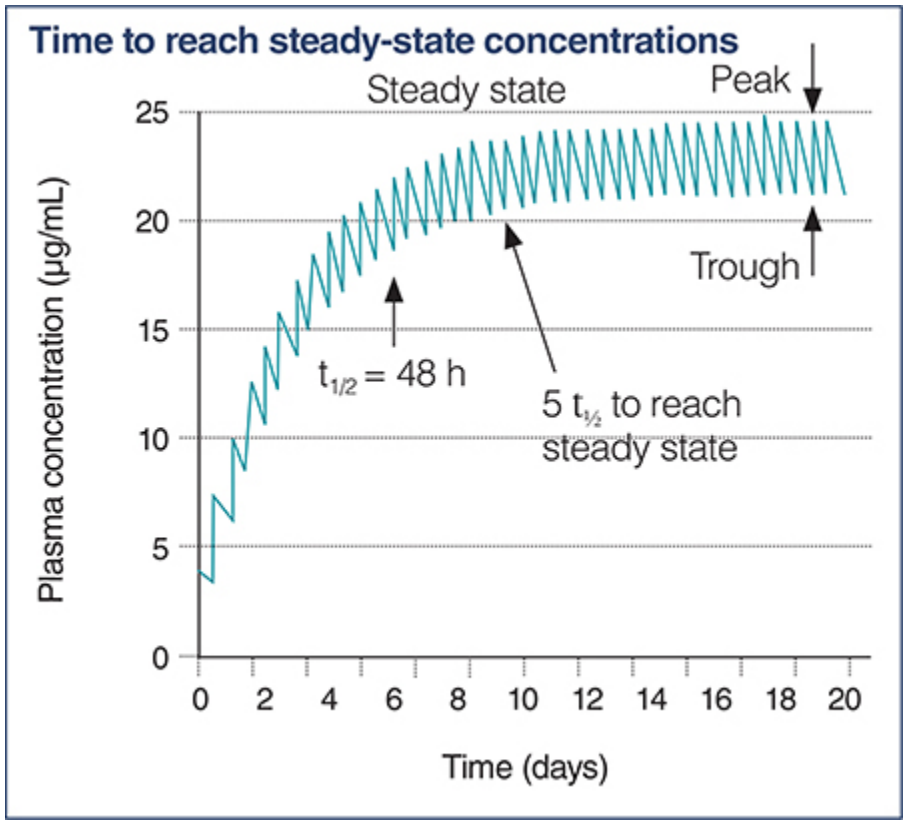


FIGURE 8.7. Time to reach steady state ($t_{½}$, half-life). The time to reach steady state is approximately 5 $t_{½}$ for a drug administered with multiple doses at regular intervals.

Implications for antiseizure drugs

After multiple doses, the concentration at steady state will increase to a level that is higher than the initial concentration. As shown in Figure 8.7, it will take approximately 5 $t_{½}$ to attain steady-state concentrations (actually 97% of steady-state concentrations). Steady state will therefore be attained quickly if a drug with a short $t_{½}$ is administered as a constant rate infusion (CRI), for example. This was demonstrated with midazolam. It has a $t_{½}$ in dogs of approximately 1 hour[1] and will reach steady-state concentrations quickly during a CRI. With an initial CRI dose of 0.25 mg/kg/hour (average dose), 60% (64/106) of dogs that presented with cluster seizures or status epilepticus had seizure control and did not require an increase.[2] In the other dogs, the CRI rate was increased, and a new steady-state was quickly attained to control seizures in most (77%, or 82/106) of the dogs.

For an ASD such as levetiracetam, the $t_{½}$ in dogs is 3–4 hours for the immediate-release tablet. Therefore, after just one day of dosing, steady-

state concentrations should be attained. A loading dose is probably unnecessary in this instance. For drug such as phenobarbital, the $t_{½}$ is approximately 40–50 hours in dogs and cats. Therefore, several days of dosing are needed before steady state is attained. For a patient that needs immediate therapeutic drug concentrations to manage seizures, a loading dose of 15–24 mg/kg (divided in multiple administrations over 24–48 hours) has been administered. Phenobarbital has an additional characteristic of increased Cl with multiple doses. Therefore, there are other factors to be considered with multiple doses. This issue is discussed later in the *Clearance* section, and in Figure 8.9.

Bromide (usually administered as potassium bromide) is the extreme example. Bromide has a $t_{½}$ in dogs that has ranged from 15–46 days. Time to reach steady state may be too long for managing of an epileptic. In these cases, high loading doses (600 mg/kg divided over 3–6 days) have been used to overcome this delay to reach steady state.

DRUG DISTRIBUTION (VOLUME OF DISTRIBUTION)

The **volume of distribution** (V_D) is a proportionality constant relating the plasma drug concentration to the amount of drug administered (dose). Since the V_D does not relate to a precise physiological volume or space, the term **apparent volume of distribution** is used (although this adjective is often omitted when writing; it is usually implied). For a simple one-compartment model, the formula for calculating the V_D is:

$$V_D = \text{Dose} / C_0$$

The dose is usually known, and C_0 is the initial concentration at time = 0, which can be extrapolated from the plasma concentration versus time graph (y-axis intercept). The V_D is usually expressed in relation to the animal's weight, e.g., L/kg or mL/kg.

What determines drug distribution?

Although we cannot always relate the V_D to a physiological space, to some extent, the V_D is an indication of a drug's ability to cross biological membranes and accumulate in tissues outside the vascular compartment. A highly lipophilic (fat-soluble) drug will diffuse across membranes more easily throughout the body than a polar, hydrophilic drug. For lipophilic drugs, this is reflected by a high V_D. Conversely, a polar, hydrophilic drug may be restricted in its distribution to the extracellular water and will exhibit a low V_D. A highly protein-bound drug in plasma, with relatively less tissue binding, tends to be confined to the plasma compartment and shows a low V_D.

Because ASDs are required to cross the blood–brain barrier (BBB) to produce a therapeutic effect, it is not surprising that their volumes of distribution are large (greater than 1 L/kg).

Mechanisms of drug transport across membranes

How do drugs move across membranes? Antiseizure drugs must cross the BBB and enter the central nervous system (CNS) to produce a therapeutic effect. Drugs move across membranes in the body by four basic mechanisms, and variations of each type (Fig. 8.8).

- Passive transport includes:
  1. Passive diffusion of the drug along a concentration gradient (from high concentration to low concentration).
  2. Paracellular transport, which also takes place along a concentration gradient, for drug molecules small enough to pass between cells.
- The other mechanisms are active transport mechanisms requiring energy (e.g., ATP), and they are characterized as:
  1. Facilitated diffusion with transport against a concentration gradient.
  2. Active transport requiring transporters, such as the p-glycoprotein (P-gp), organic anion-transporter polypeptide (OATP), and many others.

Antiseizure drugs obey these properties. Most of these agents are sufficiently lipophilic that they can enter the brain by passive diffusion, but some are substrates for transporters.

Effects of transporters

Some drugs, including ASDs, depend on active transport (Fig. 8.8). For example, gabapentin and pregabalin must utilize mechanisms of active transport to enter the brain. Because gabapentin and pregabalin are γ-amino acids, they utilize the large amino acid transporters to cross the BBB.

Transporters such as P-gp can transport drugs *out* of the CNS. This can potentially play an important role in the management of epilepsy. Overexpression of P-gp in epileptic patients can lead to drug resistance. This has been shown in rats and people.[3] However, this does not appear to be responsible for ASD refractoriness in dogs. A study in dogs concluded that at clinically relevant doses, ASDs were weak substrates (diazepam, gabapentin, lamotrigine, levetiracetam, and phenobarbital) or were not substrates (carbamazepine, felbamate, phenytoin, topirimate, and zonisamide) for canine P-gp. Therefore, it seems unlikely that efficacy of these ASDs is affected by P-gp expression at the BBB in dogs.[4]

Lipid solubility

The degree of lipid solubility (lipophilicity) is one of the properties that determines how readily a drug will cross the BBB and produce antiseizure effects. Highly lipophilic drugs diffuse easily across almost all tissue membranes. The ease of penetration can be quantitatively expressed as the **permeability constant**. As expected, ASDs have high permeability constants. For example, the benzodiazepines diazepam and midazolam both have high LogP values, near 3 or higher (LogP is a partition coefficient that measures the extent of lipid solubility). This explains why animals can respond quickly to these agents during treatment of status epilepticus. Barbiturates (e.g., phenobarbital), on the other hand, have lower LogP values (for example, phenobarbital has a LogP of 1.4 according to Drug Bank—https://go.drugbank.com/drugs). The slower rate of diffusion across the BBB produces a delay to achieve effectiveness after administration compared to benzodiazepines.

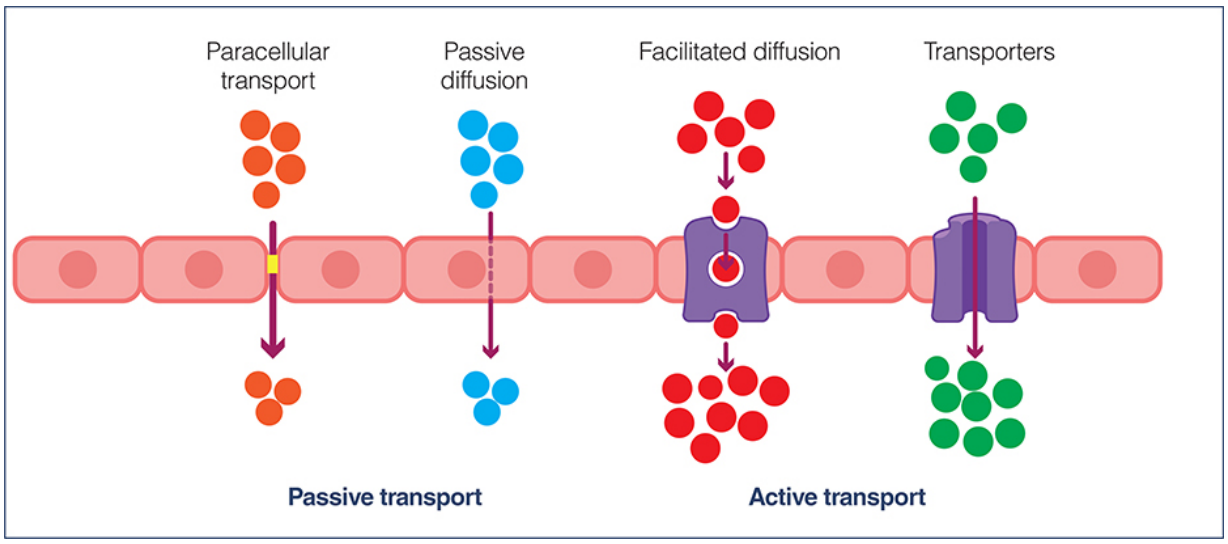


FIGURE 8.8. Mechanisms of drug transport across membranes into tissues.

Lipophilicity is also affected by the pH-partition hypothesis. Most drugs administered exist either as weak acids or weak bases. A drug's lipophilicity depends on the degree of **ionization**. An ionized (polar) drug is hydrophilic and poorly lipid soluble. An unionized (nonpolar) drug, on the other hand, is lipophilic and can cross biological membranes more easily. The degree of ionization for a drug that is a weak acid or a weak base depends on the pKa of the drug and the pH of the surrounding fluids, according to the Henderson–Hasselbalch equation. If we take the example of diazepam, which is a weak base with a pKa of approximately 3, and apply the principles of the Henderson–Hasselbalch equation, at a pH of 7.4 (physiological), the ratio of the unionized to ionized fraction of the drug is over 10,000:1. This explains why diazepam rapidly distributes to the CNS for an immediate response to control seizures after IV injection.

DRUG CLEARANCE

Drug Cl measures the ability of an organ system (e.g., liver, kidney) to remove a drug. Clearance is defined as the rate of drug elimination from the body by all routes, expressed as the volume of plasma (or serum) completely cleared of the drug by all elimination processes. Total systemic

Cl is the sum of all the processes: hepatic (subscript H), renal (subscript R), and other routes:

$$Cl_S = Cl_H + Cl_R + Cl_{OTHER\ ROUTES}$$

Clearance is abbreviated as Cl or Cl_S (systemic Cl). Clearance is usually expressed in units such as volume per weight and time, such as mL/kg/min or L/kg/h. The more efficient an animal is at eliminating a particular drug, the higher the Cl value.

Mathematically, Cl is related to both the V_D and the $t_{½}$. Clearance and V_D are independent parameters. The $t_{½}$ is a dependent parameter and influenced by both Cl and V_D. The relationship between Cl, V_D, and $t_{½}$ is shown in the equation below. In this equation, Ln 0.5 is the natural logarithm of ½. If Cl declines, (due to organ failure, for example), and V_D is unchanged, $t_{½}$ increases. If V_D is kept constant, high Cl corresponds to a short $t_{½}$. Factors that affect the V_D (body fluid shifts for example) can also affect the $t_{½}$ if Cl is unchanged.

$$T_{1/2} = \frac{\text{Ln } 0.5 \cdot V_D}{Cl}$$

Organ clearance

The concept of Cl can be appreciated by considering the intrinsic Cl ability of specific organs (e.g., liver, kidney). An understanding of individual organ Cl allows us to appreciate alterations that may occur in animals with impaired organ function (e.g., hepatic failure, renal insufficiency). This approach also allows us to consider influences of blood flow on high clearance drugs versus low clearance drugs.

Most ASDs undergo metabolism and the liver is the primary route of drug Cl, followed by elimination of an inactive metabolite. Drugs cleared by the liver can be characterized as “high clearance” or “low clearance” drugs. High clearance drugs obey this equation for organ Cl (subscript H designates hepatic parameters):

$$\mathbf{Cl_H = Q_H \cdot ER_H}$$

The ER_H is the hepatic extraction ratio. This is a ratio without units that defines the ability of the liver to extract a drug. The extraction ratio is calculated by comparing the drug concentration in the blood that is presented to an organ (arterial concentration) to the drug concentration in the blood that leaves the organ (venous concentration). The parameter Q in the equation is blood flow.

For drugs with a high hepatic extraction ratio (e.g., ER >0.8), the equation $Cl_H = Q_H \cdot ER_H$ simply reduces to $Cl_H = Q_H$, indicating that Cl directly depends on hepatic blood blow. These drugs are called **high clearance drugs**. Diazepam is one of the ASDs that fits this definition for dogs. Other drugs that are not ASDs belonging to the high clearance drug category are lidocaine and opiates. The Cl of these drugs is highly influenced by changes in hepatic blood flow. These drugs are considered to be **flow limited** with respect to their Cl, which means that this parameter is influenced more by organ blood flow than by protein binding, intrinsic Cl of the liver, or changes in drug metabolizing enzymes (related to their induction or inhibition). For a high clearance drug such as diazepam, changes in hepatic blood flow (e.g., portosystemic shunt) can have a profound effect on Cl. When a high clearance drug is administered by the oral route, after absorption across the intestinal mucosa, there is a large **first-pass effect** (e.g., most of the drug is cleared in one pass through the liver).

For drugs with a low hepatic extraction ratio (i.e., ER ≤0.2), Cl is small and the equation that defines it is:

$$\mathbf{Cl_H = Cl_I \cdot \mathit{fu}}$$

In this equation, *fu* is the fraction unbound (protein unbound), and Cl_I is the intrinsic (I) ability of the liver to metabolize the drug, which represents the Cl capabilities of an organ, independent of blood flow and protein binding.

Hepatic Cl for **low clearance drugs** is not greatly affected by changes in hepatic blood flow, but it is highly sensitive to changes that may occur with intrinsic Cl, such as variations in the activity of the hepatic microsomal

enzymes and drug–protein binding (*fu*). These drugs are considered to be **non flow limited**. The oral bioavailability of these drugs is usually not impaired by first-pass effects. Most ASDs fit the definition of low clearance drugs.

The implication of these relationships is that changes in protein binding and liver function can have a direct effect on hepatic Cl; and because Cl determines the $t_{½}$, as described above, these changes ultimately affect the ASD's $t_{½}$.

Metabolism changes that affect clearance

The enzymes involved in drug metabolism are primarily located in the liver, although there can also be extensive drug metabolism by the intestine and other tissues (e.g., kidney). In the liver, the steps involved in metabolism are referred to as "Phase I" and "Phase II" metabolism. The purpose of these metabolic phases is to convert a lipophilic drug into a more water-soluble (hydrophilic) drug (metabolite) so that it can be excreted in the urine or bile and eliminated. Converting the drug to more hydrophilic, water-soluble metabolites is essential for excretion and termination of the drug's pharmacological activity. Drug metabolites are generally more polar, hydrophilic agents with little biologic activity.

Phase I reactions are usually oxidative, but other chemical reactions can occur. Phase I reactions are predominantly mediated by enzymes belonging to the cytochrome P450 family of enzymes. There are many enzymes and these are designated by the family, subfamily, and gene. For example, CYP3A4 (a common one in people) is in the Family 3, Subfamily A, and coded by Gene 4. Importantly, these enzymes are not the same in all species (they are different between dogs and people or cats, for example).

Changes in metabolizing enzyme activity can profoundly affect drug Cl for some ASDs. Phenobarbital is known to be a potent hepatic enzyme–inducing agent. It increases its own metabolism and Cl, as well as the Cl of other coadministered drugs. Because it increases its own Cl, dose requirements change over time in order to maintain a consistent plasma/serum drug concentration in the reference range. In one study,[5] phenobarbital Cl in three groups of healthy dogs, each fed a different diet, increased by 13%, 38.5%, or 69%, after 2 months of dosing for each diet. The induced enzyme activity persisted at weeks 2 and 4, but not at weeks 6 and 8 after discontinuation.[6] The increase in Cl can also vary depending on

the dose administered (high vs low dose).[7] In a study conducted in dogs administered either a low dose (5.5 mg/kg) or a high dose (11 mg/kg) of phenobarbital, Cl was measured at days 0, 30, 60, and 90. At 90 days, this parameter had increased by 28-190% in the low dose group, with a mean increase of 99% (+/- 70%). In the high dose group, Cl had increased by 80–158%, with a mean increase of 115% (+/- 30%).

The V_D of phenobarbital does not change appreciably during multiple dosing. This was confirmed in the study by Ravis et al.,[8] in which variations in phenobarbital's $t_{½}$ were caused by differences in Cl between dogs, not in V_D.

Changes in Cl after phenobarbital administration occur as quickly as after 5–11 days of multiple doses.[5,7,8,9] After combining the results from several studies in dogs, the average increase in Cl after multiple dosing is 42%. If phenobarbital is administered in multiple doses without consideration for this change in Cl, plasma/serum concentrations will appear to be in the reference range (blue curve in Fig. 8.9). However, when a more realistic 42% higher Cl value is used, lower concentrations are predicted (red curve in Fig. 8.9), which could result in subtherapeutic concentrations in some patients.[11]

The effect of phenobarbital on the Cl of other drugs has also been demonstrated with combinations of phenobarbital and levetiracetam in dogs.[12,13] Levetiracetam does not induce its own metabolism as Cl is unchanged after multiple dosing,[14] but the addition of phenobarbital greatly shortened the $t_{½}$ of levetiracetam, with a decrease in $t_{½}$ from 3.43 hours to 1.73 hours, and an increase in its oral Cl from 124.93 to 252.99 mL/h/kg (average values).

DRUG ABSORPTION

Bioavailability refers to both the rate and the extent of drug absorption into the systemic circulation from nonintravenous drug administration (oral, IM, SC, etc.). Another term to mean the same thing is **systemic availability**.

Systemic availability is also termed **fraction absorbed** (abbreviated as F) which is used to describe the **extent** of drug absorption (e.g., the fraction

of a drug dose that reaches the systemic circulation). The fraction absorbed can range from 0% to 100%. Understanding the value of F and factors that affect F for a particular drug can be very important, particularly when it is necessary to make dosage adjustments for oral drugs, or when considering nontraditional routes such as the transmucosal or rectal routes.

Drugs may have a value of F below 100% because of extensive first-pass effects, poor dissolution of the drug in gastrointestinal fluids, binding (adsorption) of drug to feed, drug instability in stomach (inactivation by stomach acid), enzymatic inactivation of drug in the stomach or intestine, and drug interactions. For rectal and transmucosal administration, low solubility or lipophilicity are causes of poor absorption. A multidrug efflux pump (P-gp) can also "pump" a drug out of the body into the intestinal lumen and reduce bioavailability. This transport pump can be induced or inhibited by other drugs. If the drug is injected, poor availability from an IM or SC injection is often related to poor circulation at the injection site.

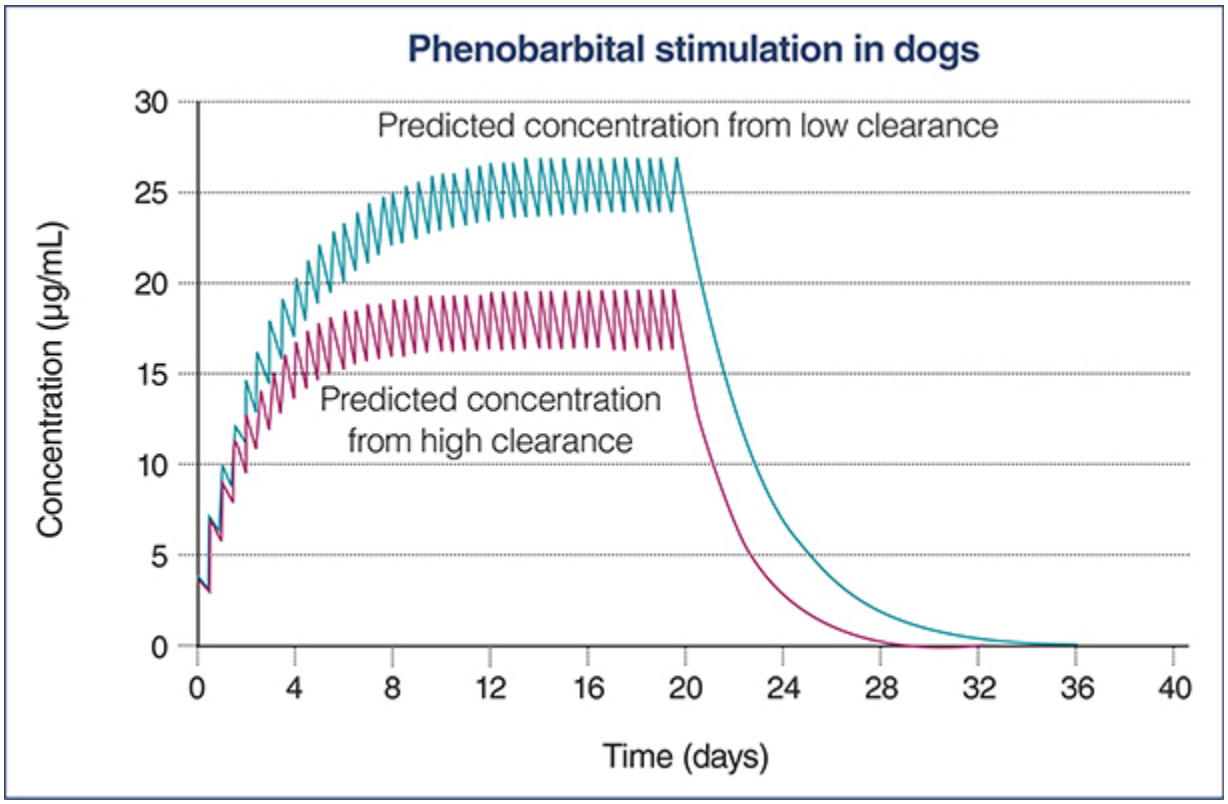


FIGURE 8.9. Simulation of phenobarbital concentration in dogs after administration at a dose of 2.5 mg/kg every 12 hours. The top curve (blue) represents the predicted concentrations if clearance did not change after the first dose. The bottom curve (red) represents the concentrations that occur after induction of enzymes and increase of clearance (clearance increases by approximately 40% in dogs after multiple dosing).

Intramuscular and subcutaneous absorption

Many drugs are administered IM and SC to animals. As one might expect, with the IM or SC route the C_{max} will be lower than with the IV route, and the time to reach C_{max} delayed. Absorption from the injection site may also vary depending on whether the drug is administered SC or IM. Absorption is more rapid with an IM injection than with a SC one because muscle is better perfused and has greater blood flow than the SC space.

Occasionally, poorly soluble drugs may form a depot and lead to poor systemic availability if they are injected IM or SC. These properties are illustrated with a comparison of midazolam and diazepam. Diazepam is not water soluble and must be injected in an organic solvent vehicle (propylene glycol). Because diazepam is insoluble, after IM injection it forms precipitates and is slowly and incompletely absorbed. This vehicle also elicits a painful reaction to the injection. Conversely, midazolam has high solubility in an aqueous vehicle and is absorbed much more rapidly and completely from an IM injection because it is taken up quickly by the blood circulation. In a study conducted in people, both drugs were injected IM and their absorption measured.[16] Absorption was two times faster with midazolam than with diazepam, and the authors concluded that midazolam has an advantage over diazepam in providing a faster onset of drug effects. After 1 hour, midazolam had been completely absorbed from the IM injection, whereas only 20–50% of diazepam had been absorbed. Because of these properties, midazolam is preferred for IM injection over diazepam for treating seizures in dogs.[1]

Transdermal absorption of drugs

It is a frequent challenge to deliver medications to animals when they are difficult to handle or resist oral or injectable drugs. Administration of oral drugs to animal patients presents several challenges, some of which are unique to each species of animal. Some drugs are not absorbed well orally because first-pass metabolism in the gastrointestinal tract and liver limits their systemic availability. There are several potential advantages to

administering a medication via the transdermal route. Transdermal (or transmucosal, as discussed below) administration overcomes the limitations previously mentioned and can be more convenient for animal owners to medicate their pets, especially cats. For a transdermal drug to be effective, it must penetrate the skin layers and achieve active blood concentrations to induce an effect at the target site. However, this will depend on the specific characteristics of each species, such as hair density, skin thickness, subcutaneous lipid layer thickness, and acceptance of a topically applied formulation. Cats may lick off the medication and dogs may chew off transdermal patches if they can reach the site of application with their mouth.

In order for a transdermal medication to be absorbed, some critical barriers must be overcome:

- The drug must be stable and sufficiently lipid soluble to penetrate the skin.[17] The thickness of the skin and the stratum corneum (the outermost layer) presents a significant barrier for most drugs.
- Transdermal drugs must be potent. The skin can absorb drugs at a rate that has been estimated to be a maximum of only 1 mg per cm^2/24 h. The surface area to which the drugs and vehicles are applied to pets is limited; therefore, the potency must be high enough to allow small total doses. For cats, one of the limitations is the small surface area to which these agents are applied (e.g., ear pinna). This limits the maximum dose that can be administered, which eliminates drugs from consideration if they require high doses.
- The drug's solubility characteristics must also be ideal. The drug must be soluble in the vehicle in which it is delivered, but also sufficiently soluble to penetrate the surface of the skin, which was designed by nature to act as a barrier. This barrier is formed by both lipid and aqueous layers. To enhance transdermal absorption, penetration enhancers (vehicles) are used as excipients in the drug formulation. Two common penetration enhancers are pluronic lecithin organogel (PLO) and a proprietary vehicle used by pharmacists, Lipoderm®.
- The drug also must be nonirritating to the skin, and not induce a topical allergic reaction.

Transdermal administration of antiseizure drugs

Many of the medications commercially formulated for transdermal delivery to animals are antiparasitic drugs for dogs and cats. These drugs are highly lipophilic, penetrate the skin, and achieve a sustained effect through sequestration in the lipid layers of the skin, hair follicles, or skin sebum. As far as ASDs are concerned, transdermal application has only been studied sufficiently in phenobarbital and levetiracetam. Transdermal administration of levetiracetam in a Lipoderm® vehicle of 350–400 mg/mL in 6 cats produced drug concentrations at the low end of the reference range, which were highly variable.[18] The dosage selected for the study (60 mg/kg every 8 hours) was three times higher than the dosage recommended for oral immediate release levetiracetam in cats.

In another study, phenobarbital in two transdermal formulations was administered at three times the oral dose to cats (9 mg/kg every 12 hours).[19] The vehicles used were PLO and Lipoderm®. Both produced concentrations in the reference range in most cats, but these were highly variable.

Transmucosal administration

A variation of transdermal administration is the transmucosal route (including sublingual administration). This route has the same challenges and limitations previously described for transdermal medications. Some drugs have been administered by the oral transmucosal route successfully (e.g., buprenorphine, fentanyl, α-2 agonists), but this route has not been explored for ASDs. The intranasal route, which is also a form of transmucosal administration, has been considered for the benzodiazepines midazolam and diazepam.

This route was first explored in dogs as a model for developing human drugs.[20] Three benzodiazepines were studied, including midazolam. The intranasal route produced faster and higher plasma drug concentrations in dogs when compared with oral administration.

After intranasal administration of diazepam to dogs, peak concentrations in blood were reached within 5 minutes after a dose of 0.5 mg/kg and bioavailability was approximately 42% in one study[21] and 80% in another study[22]. Midazolam was also well absorbed from intranasal administration at a dose of 0.5 mg/kg in dogs, with a bioavailability of 70% for a gel formulation and 52% for a solution.[23] Both drugs administered by this route have been effective for terminating status epilepticus in dogs and people[24,25,26] (see also Chapter 19).

Rectal administration

Another form of transmucosal delivery is the rectal route. Although there are several drugs (e.g., benzodiazepines and opiates) formulated as suppositories for people, none have been specifically developed for this use in animals. A diazepam rectal gel formulation containing 5 mg/mL diazepam and excipients is available for people and is indicated in the management of refractory patients with epilepsy. No formulations have been developed for animals, but there has been interest in this administration route, particularly in small animals that are sometimes difficult to medicate.

Rectal diazepam is highly and rapidly absorbed[27] and has been used successfully to treat seizures at home.[28] Further information on rectal administration of diazepam can also be found in Chapter 19. Midazolam is not as well absorbed when administered rectally, which possibly reflects differences in lipophilic properties and solubility.[1,23]

The rectal route is convenient for emergency use when there is no time to place an IV catheter, or for at-home use when a pet owner needs to treat status epilepticus or cluster seizures. In addition to diazepam, bromide (from potassium bromide) and levetiracetam are also absorbed from rectal administration in dogs. Rectal levetiracetam administration at a dose of 40 mg/kg in dogs produced concentrations that are considered in the reference range within 10 minutes,[29] or within 30 minutes.[30] When combined with standard treatment, this route provided good control of cluster seizures[31] (see also Chapter 19).

TAKE-HOME MESSAGES

- ✔ Pharmacokinetics (PK) is the study of the time course of change in the concentration of drugs in blood and plasma of animals. It includes an understanding of the absorption, distribution, biotransformation (metabolism) and excretion of drugs.
- ✔ There are four important PK components that contribute to determining the clinical dose of a medication for animals. These are systemic availability (F), clearance (Cl), volume of distribution (VD or V_D) and elimination half-life ($t_{½}$).

- ✔ Compartmental models are used to describe how a drug behaves in the body. Most practical dosing regimens used in veterinary medicine are based on simple, one-compartment PK models.
- ✔ The $t_{½}$, or time it takes for a drug concentration to decline by one half, is often used by clinicians when evaluating the PK features of a drug. It provides an indication of how often a drug should be administered to patients and how long a PK or toxic effect of a drug will persist.
- ✔ A steady-state or plateau plasma concentration is the point, after the administration of multiple doses, at which the amount of drug eliminated during a dosing interval is equal to the dose administered. If a drug is administered with multiple doses, it will take approximately 5 $t_{½}$ to attain steady state concentrations, regardless of the dose administered and the $t_{½}$ of the drug.
- ✔ A loading dose can be administered to avoid the time lag to reach steady state. A loading dose is a large initial dose designed to instantaneously produce serum or plasma drug concentrations at the desired steady-state level.
- ✔ The V_D is an indication of a drug's ability to cross biological membranes and accumulate in tissues outside the vascular compartment. Highly lipophilic drugs diffuse easily across almost all tissue membranes, and this is reflected by a high V_D. The degree of lipid solubility is one of the properties that determines how readily a drug will cross the BBB and produce antiseizure effects. Because ASDs are required to cross the BBB to produce a therapeutic effect, their volumes of distribution are large.
- ✔ A drug's $t_{½}$ is influenced by both Cl and V_D. If Cl declines (due to organ failure, for example) and the V_D is unchanged, $t_{½}$ increases. Factors that affect the V_D (body fluid shifts for example) can also affect the $t_{½}$ if clearance is unchanged.
- ✔ Most ASDs undergo metabolism, and the enzymes involved are primarily located in the liver, although substantial metabolism can occur in the intestine. The product of this metabolism is to convert a lipophilic drug into a more water-soluble hydrophilic drug (metabolite) so that it can be excreted in the urine or bile and

eliminated. Changes in metabolizing enzyme activity can profoundly affect Cl for some ASDs.

- ✔ Bioavailability refers to both the rate and the extent of drug absorption into the systemic circulation from nonintravenous drug administration (oral, IM, SC, etc.). Systemic availability (F) is used to describe the fraction of a drug dose that reaches the systemic circulation. Understanding the value of F and factors that affect F for a particular drug are important when determining dosage adjustments for oral drugs, or when considering using nontraditional routes such as the transmucosal or rectal routes.
- ✔ Nontraditional routes of ASD administration that have been evaluated in veterinary medicine include the transdermal, rectal and intranasal routes. Transdermal administration of ASDs to cats has resulted in highly variable serum concentrations, but the rectal and intranasal routes have proven to be useful in the emergency management of seizures in dogs.

REFERENCES

1. SCHWARTZ M, MUÑANA KR, NETTIFEE-OSBORNE JA et al. The pharmacokinetics of midazolam after intravenous, intramuscular, and rectal administration in healthy dogs. *J Vet Pharmacol Ther*. 2013; 36(5):471–417.
2. BRAY KY, MARIANI CL, EARLY PJ et al. Continuous rate infusion of midazolam as emergent treatment for seizures in dogs. *J Vet Intern Med*. 2021; 35(1):388–396.
3. ZHANG C, KWAN P, ZUO Z et al. The transport of antiepileptic drugs by P-glycoprotein. *Adv Drug Deliv Rev*. 2012; 64(10):930–942.
4. WEST CL, MEALEY KL. Assessment of antiepileptic drugs as substrates for canine P-glycoprotein. *Am J Vet Res*. 2007; 68(10):1106–1110.
5. MAGUIRE PJ, FETTMAN MJ, SMITH MO et al. Effects of diet on pharmacokinetics of phenobarbital in healthy dogs. *J Am Vet Med Assoc*. 2000; 217(6):847–552.
6. FUKUNAGA K, SAITO M, MATSUO E et al. Long-lasting enhancement of CYP activity after discontinuation of repeated administration of phenobarbital in dogs. *Res Vet Sci*. 2009; 87(3):455–457.
7. RAVIS WR, PEDERSOLI WM, WIKE JS. Pharmacokinetics of phenobarbital in dogs given multiple doses. *Am J Vet Res*. 1989; 50(8):1343–1347.
8. RAVIS WR, NACHREINER RF, PEDERSOLI WM et al. Pharmacokinetics of phenobarbital in dogs after multiple oral administration. *Am J Vet Res*. 1984; 45(7):1283–1286.

9. HOJO T, OHNO R, SHIMODA M et al. Enzyme and plasma protein induction by multiple oral administrations of phenobarbital at a therapeutic dosage regimen in dogs. *J Vet Pharmacol Ther*. 2002;25(2): 121–127.
10. PEDERSOLI WM, WIKE JS, RAVIS WR. Pharmacokinetics of single doses of phenobarbital given intravenously and orally to dogs. *Am J Vet Res*. 1987;48(4): 679–683.
11. PAPICH MG. Chapter 17. Anticonvulsant Drugs. In: RIVIERE JE, PAPICH MG (eds.). *Veterinary Pharmacology & Therapeutics*, 10th ed. Hoboken, New Jersey, USA: Wiley Blackwell, John Wiley & Sons; 2018. p.395-415.
12. MUÑANA KR, NETTIFEE-OSBORNE JA, PAPICH MG. Effect of chronic administration of phenobarbital, or bromide, on pharmacokinetics of levetiracetam in dogs with epilepsy. *J Vet Intern Med*. 2015; 29(2):614-9.
13. MOORE SA, MUÑANA KR, PAPICH MG, NETTIFEE-OSBORNE JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther*. 2011; 34(1):31–34.
14. MOORE SA, MUÑANA KR, PAPICH MG, NETTIFEE-OSBORNE JA. Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. *Am J Vet Res*. 2010; 71(3):337–341.
15. FUKUNAGA K, SAITO M, MUTO M, et al. Effects of urine pH modification on pharmacokinetics of phenobarbital in healthy dogs. *J Vet Pharmacol Ther*. 2008; 31(5):431–436.
16. HUNG OR, DYCK JB, VARVEL J et al. Comparative absorption kinetics of intramuscular midazolam and diazepam. *Can J Anaesth*. 1996; 43(5):450–55.
17. RIVIERE JE, PAPICH MG. Potential and problems of developing transdermal patches for veterinary applications. *Adv Drug Deliv Rev.* 2001; 50(3):175–203.
18. SMITH C, BARNES HELLER HL, REIF N et al. Serum levetiracetam concentrations after transdermal levetiracetam administration, 3 times daily, to healthy cats. *J Vet Intern Med*. 2019; 33(2):827–830.
19. DELAMAIDE GASPER JA, BARNES HELLER HL, ROBERTSON M, TREPANIER LA. Therapeutic serum phenobarbital concentrations obtained using chronic transdermal administration of phenobarbital in healthy cats. *J Feline Med Surg*. 2015; 17(4):359–363.
20. LUI CY, AMIDON GL, GOLDBERG A. Intranasal absorption of flurazepam, midazolam, and triazolam in dogs. *J Pharm Sci*. 1991; 80(12):1125–1129.
21. MUSULIN SE, MARIANI CL, PAPICH MG. Diazepam pharmacokinetics after nasal drop and atomized nasal administration in dogs. *J Vet Pharmacol Ther.* 2011; 34(1):17–24.
22. PLATT SR, RANDELL SC, SCOTT KC et al. Comparison of plasma benzodiazepine concentrations following intranasal and intravenous administration of diazepam to dogs. *Am J Vet Res.* 2000; 61(6):651–654.
23. EAGLESON JS, PLATT SR, STRONG DL et al. Bioavailability of a novel midazolam gel after intranasal administration in dogs. *Am J Vet Res*. 2012; 73(4):539–545.
24. CHARALAMBOUS M, BHATTI SF, VAN HAM L et al. Intranasal midazolam versus rectal diazepam for the management of canine status epilepticus: a multicenter randomized parallel-group clinical trial. *J Vet Intern Med*. 2017; 31(4):1149–1158.
25. CHARALAMBOUS M, VOLK HA, TIPOLD A et al. Comparison of intranasal versus intravenous midazolam for management of status epilepticus in dogs: A multi-center randomized parallel group clinical study. *J Vet Intern Med*. 2019; 33(6):2709–2717.
26. BODDU SH, KUMARI S. A short review on the intranasal delivery of diazepam for treating acute repetitive seizures. *Pharmaceutics*. 2020; 12(12):1167.

27. PAPICH MG, ALCORN J. Absorption of diazepam after its rectal administration in dogs. *Am J Vet Res*. 1995; 56:1629–1636.
28. PODELL M. The use of diazepam per rectum at home for the acute management of cluster seizures in dogs. *J Vet Intern Med*. 1995; 9(2):68–74.
29. PETERS RK, SCHUBERT T, CLEMMONS R, VICKROY T. Levetiracetam rectal administration in healthy dogs. *J Vet Intern Med*. 2014; 28(2):504–509.
30. CAGNOTTI G, ODORE R, GARDINI G et al. Pharmacokinetics of rectal levetiracetam as add-on treatment in dogs affected by cluster seizures or status epilepticus. *BMC Vet Res*. 2018; 14(1):1–6.
31. CAGNOTTI G, ODORE R, BERTONE I et al. Open-label clinical trial of rectally administered levetiracetam as supplemental treatment in dogs with cluster seizures. *J Vet Intern Med*. 2019; 33(4):1714–1718.

Principles of Antiseizure Drug Use

09

Karen R. Muñana, Luisa De Risio

Antiseizure drug (ASD) therapy is the mainstay of treatment for epilepsy. Although the underlying cause of epileptic seizures should be directly addressed whenever possible, in most cases of epilepsy the propensity for seizures is unlikely to be eradicated even if an underlying cause is identified and treated. Consequently, symptomatic therapy with ASDs is indicated, and assumes an important role in the management of the disorder.

The overall goal of ASD treatment is complete seizure remission. However, studies suggest that freedom from seizures may only be achieved in less than half of all dogs and cats with idiopathic epilepsy (IE) when treated with long-term ASDs. Because seizure freedom is often not possible, treatment is typically aimed at decreasing seizure frequency, duration and severity to an acceptable level while minimizing drug-associated adverse effects (AEs), in order to optimize both the dog's and the caregiver's quality of life. It is important to keep in mind that epilepsy is a diverse group of conditions, for which a limited number of ASDs are prescribed as treatment. Because of the variability within epilepsy, the response to treatment and outcome is difficult to predict and there is not a single "one size fits all" treatment protocol. Instead, ASD treatment must be adjusted and tailored to the individual, taking into consideration some basic principles of ASD therapy regarding:

- When to initiate therapy.
- How to choose an appropriate ASD and dose.
- How to devise a rational treatment plan.
- How to adjust ASD dosage.
- When to add on another ASD.

- How to determine treatment success.

Utilizing a systematic approach to epilepsy management is often helpful in addressing these considerations. Such an approach is outlined in Figure 9.1.

Client education regarding the goals and expectations of treatment is an extremely important component of successful ASD therapy and should be provided before any medication is prescribed. Caregivers should be aware that a realistic goal of treatment in most animals is not complete resolution of the seizures, but rather control to an acceptable level that allows for improved quality of life. Caregivers should be counseled on the scheduling and financial commitment involved in the long-term treatment of epilepsy, as once therapy is initiated, it can be assumed to be lifelong. Furthermore, a lifestyle adjustment may be required to assure that a pet receives medication at the prescribed interval each day, as even a single missed dosage of medication may precipitate a seizure. Finally, caregivers should be educated on the AEs associated with the ASDs used in veterinary practice and understand that the reduction in seizures must be balanced with minimizing AEs associated with the medication. Caregivers must be committed to the treatment at the onset of therapy. If not, client compliance will likely be an issue that will hinder treatment success. Key points to discuss with caregivers are outlined in Box 9.1.

INITIATING THERAPY

There are no evidence-based guidelines on when to initiate ASD therapy in dogs and cats. Rather, the available recommendations are often extrapolated from guidelines developed for humans. Two groups of veterinary experts have published recommendations on initiation of therapy in dogs and cats.[1,2] These guidelines are summarized in Box 9.2. It is recommended that treatment for IE be initiated based on the presence of one or more of the following criteria:

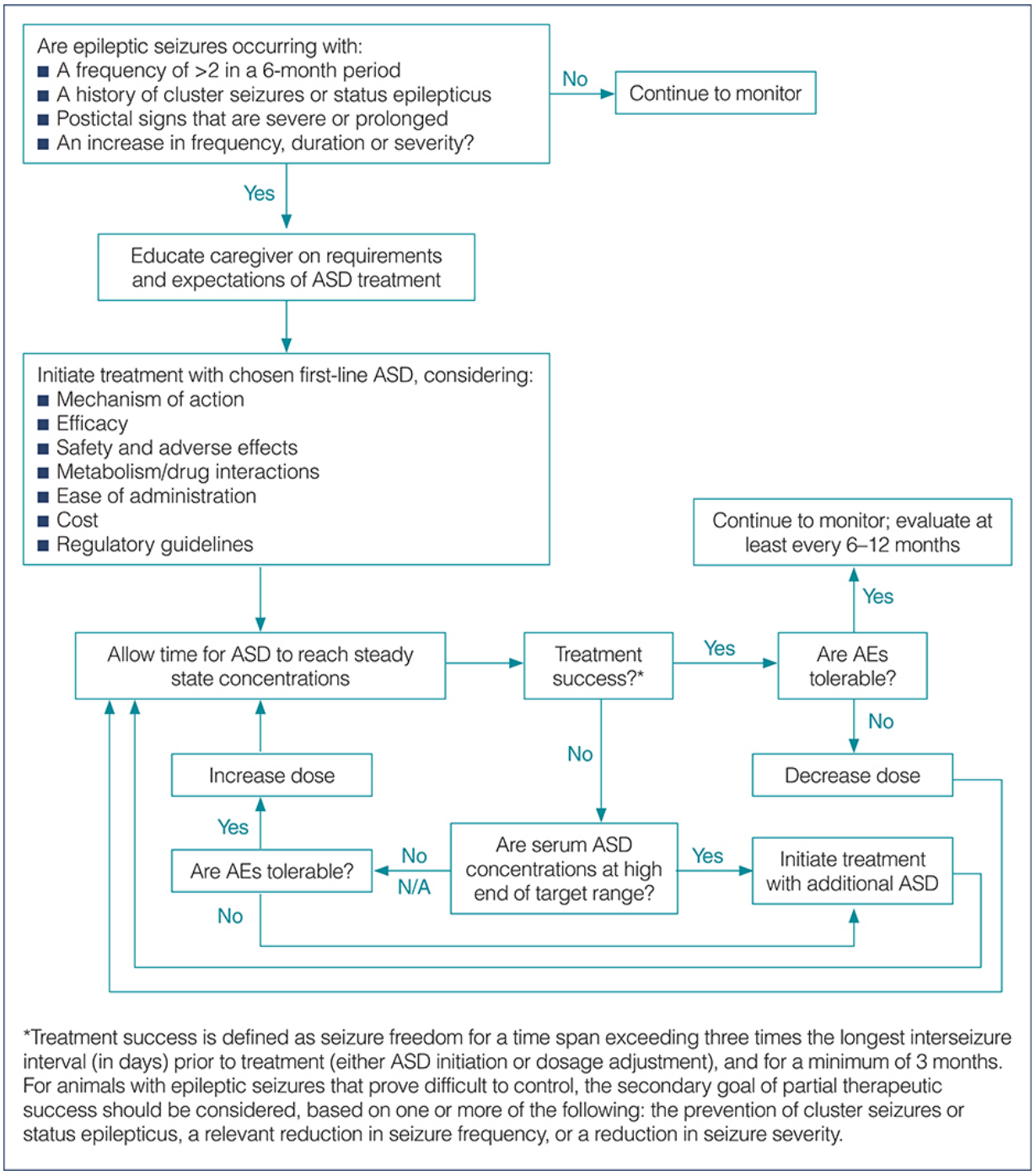


FIGURE 9.1. Algorithm for a systematic approach to epilepsy management in dogs and cats.

- Two or more epileptic seizures within a 6-month period.
- History of cluster seizures or status epilepticus.
- Postictal signs that are considered severe or prolonged (>24 hours).

- A worsening of the epileptic condition based on an increase in seizure frequency, duration, or severity noted over a timespan equal to three interictal periods.

However, the final decision on whether to initiate ASD therapy must be made on an individual basis, taking into consideration these recommendations as well as the pet's general health and the caregiver's lifestyle, financial constraints and comfort with the proposed therapeutic regimen. For example, if a caregiver has a strong desire to initiate treatment for seizures, this should be given high priority in the decision making regardless of seizure frequency. Alternatively, if a caregiver is hesitant to commit to daily administration of medication, then a shorter interictal period may be deemed acceptable without initiating treatment.

BOX 9.1. Key points of discussion with caregivers when considering initiation of antiseizure drug treatment for epileptic seizures.

- The goal of treatment is seizure control, not cure.
- Therapy is lifelong in most cases.
- Epilepsy management involves a substantial financial commitment, including the cost of drugs, drug monitoring and follow-up care.
- It is very important to administer medication at the prescribed interval each day; this may require a lifestyle adjustment.
- All medications used to treat seizures have adverse effects (AEs); the goal is to minimize AEs while maximizing seizure control.
- Antiseizure drugs can interact with other drugs and nonprescription supplements, and any introduction or change in medication or diet should be first discussed with a veterinarian.
- Each animal with epilepsy responds differently to treatment, necessitating an individualized approach.

There is data to suggest that dogs with IE respond better to treatment initiated earlier in the course of disease compared to dogs in which treatment is delayed. Heynold et al.[3] evaluated a population of 46 Labrador Retrievers with IE over time and demonstrated that dogs with a lower total number of seizures prior to treatment had a significantly better therapeutic response. However, response to treatment was not correlated with the time elapsed between seizure onset and initiation of treatment, suggesting that it may be the frequency of seizures rather than the time course that influences the therapeutic response. A more recent study in 334 dogs with IE determined that the presence of cluster seizures prior to initiating therapy negatively influenced the likelihood of achieving seizure remission,

supporting the premise that it is seizure density (the temporal pattern of seizure activity) rather than seizure frequency or total number of seizures prior to treatment that influences response.[4] Historically, the negative effect of delayed treatment has been attributed to kindling, or the notion that "seizures beget seizures". However, more recent evidence suggests that an individual's long-term response may be more of a reflection of the inherent severity of the disease rather than an effect of the timing of treatment initiation. It has been proposed that certain forms of epilepsy are programmed to become refractory, regardless of the timing of therapy.[5] In support of this premise, a prospective, observational longitudinal study of 106 dogs with new onset seizures, of which 61 were diagnosed with IE, failed to demonstrate an accelerated course of disease progression in untreated dogs compared to those in which ASD therapy was initiated, measured from the time from the first to the fifth epileptic seizure.[6] However, it should be noted that dogs with cluster seizures were significantly more likely to be in the treated group, and this is likely a reflection of the clinical impression among clinicians that cluster seizures warrant aggressive ASD therapy. Certain breeds of dogs, including the Border Collie, Australian Shepherd, German Shepherd, Italian Spinone and Boxer, have been shown to have a high incidence of cluster seizures and a more severe clinical course of epilepsy,[7–10] while Collies,[11] Labrador Retrievers[12] and Belgian Shepherds[13] have been reported to have a less severe form of the disorder. Consequently, the common epilepsy phenotype in a given breed should also be given consideration when deciding whether to initiate therapy.

BOX 9.2. Summary of recommendations of when to initiate antiseizure drug therapy in a dog with epilepsy.

International Veterinary Epilepsy Task Force (IVETF) for idiopathic epilepsy (Bhatti et al.[2])	American College of Veterinary Internal Medicine (ACVIM) Consensus Statement (Podell[1])
History of cluster seizures or status epilepticus >2 epileptic seizures within a 6-month period Postictal signs that are considered especially severe or last >24 hours Epileptic seizure frequency and/or duration is increasing and/or seizure severity is deteriorating over three interictal periods	History of cluster seizures or status epilepticus >2 epileptic seizures within a 6-month period Postictal signs that are prolonged, severe or unusual Identifiable structural lesion present or prior history of brain disease or injury

CHOOSING AN APPROPRIATE ANTISEIZURE DRUG

For many years, phenobarbital (PB) (and the related drug, primidone) was the primary maintenance ASD prescribed in veterinary patients, with benzodiazepines used less frequently. Potassium bromide (KBr) was introduced into veterinary practice in the 1980s and provided another treatment option, primarily as a second-line ASD. The introduction of newer generation ASDs for use in humans with epilepsy began around 1990, with over 20 ASDs being marketed since then. Those most commonly used in dogs and cats include levetiracetam (LEV) and zonisamide (ZNS), although there are reports of use of felbamate, gabapentin, topiramate, pregabalin, rufinamide, lacosamide and brivaracetam in veterinary practice. In addition, imepitoin (IMP) is a veterinary pharmaceutical that was licensed in the EU in 2013 for the treatment of IE in dogs and is included among the ASDs that are used in veterinary practice. The current availability of multiple ASDs allows the clinician to decide which drug is most appropriate to use in any individual case. Drug-related factors that should be considered when choosing an ASD include:

- Mechanism of action
- Efficacy
- Safety and AEs
- Route of metabolism and potential drug interactions
- Ease of administration
- Cost
- Regulatory considerations

Mechanism of action

In general, ASDs exert an antiepileptic effect by decreasing neuronal excitability in the brain. This can be accomplished by acting on the synaptic terminal to increase inhibitory neurotransmission and/or decrease excitatory neurotransmission, or by modulating ion channels on the neuronal membrane resulting in hyperpolarization. The common mechanisms of action of ASDs are summarized in Table 9.1 and discussed in greater detail in subsequent chapters on the specific ASDs.

Efficacy

One of the primary assumptions that is made when prescribing an ASD is that it is efficacious in controlling epileptic seizures. In human medicine, ASDs are approved for a specific epilepsy phenotype or disorder based on results from randomized, blinded, placebo-controlled studies evaluating the drug's safety and effectiveness in large populations of epileptic patients. In contrast, the total number of published studies on ASDs in dogs and cats, as well as the sample size and design rigor for individual studies are quite limited in veterinary medicine. It is important for a clinician to consider the quality of evidence when evaluating the efficacy and safety of an ASD. The hierarchy of evidence is often depicted in a pyramid, with case reports being at the base of the pyramid and randomized controlled seizures and systematic reviews of such studies being at the apex, and the validity increasing from bottom to top (Fig. 9.2). There is a scarcity of randomized, blinded, controlled studies evaluating ASDs in dogs and cats. Rather, most of the available data on the use of ASDs involves case series or open-label trials that are not blinded and do not include a control group. It is important to understand the details of a study design when reviewing results, in order to recognize any potential bias that can impact the validity of the findings and influence the efficacy and safety observed with the clinical use of an ASD.

TABLE 9.1. Mechanisms of action of the antiseizure drugs used in dogs and cats.

Drug	Decreased glutamate neuro-transmission	Inhibition of presynaptic calcium channels	Increased GABA# neuro-transmission	Inhibition of sodium channels	Modulation of neurotransmission via binding to synaptic vesicle 2A	Inhibition of carbonic anhydrase	Inhibition of T-type calcium channels
Phenobarbital	❍	❍	●				
Potassium bromide			❍				
Levetiracetam		❍			●		
Imepitoin			●				
Zonisamide				❍		❍	❍
Topiramate	❍			❍		❍	
Felbamate			❍	❍			
Gabapentin		❍*					
Pregabalin		❍*					
Lacosamide			●				
Brivaracetam					●		
Rufinamide		❍					
Benzodiazepines			●				

#GABA, γ-aminobutyric acid.
*Inhibits calcium release by binding to α-2-δ protein, a subunit of the presynaptic voltage-gated calcium channel.
● Primary mechanism of action
❍ Secondary, fractional, or uncertain mechanism of action

The inclusion of a control group, administered either a placebo or another ASD drug, is important in the assessment of efficacy. A placebo effect has been demonstrated in clinical trials involving dogs with IE. An analysis of three randomized, double-blind, placebo-controlled studies of antiseizure treatments involving 28 dogs with IE, including an ASD (LEV), dietary therapy (ketogenic diet) and a surgical implant (vagal nerve stimulation), demonstrated an average reduction in epileptic seizures of 26–46% during placebo administration relative to baseline.[14] This reduction in epileptic seizures with placebo administration has been attributed to regression to the mean, a statistical term used to describe fluctuations of biological variables that occur over time. Epilepsy is a waxing and waning disorder, with variations in seizure frequency occurring over the course of disease. A change in treatment for epilepsy is likely to be initiated when an increase in seizure frequency is observed, and any short-term decrease in seizure frequency is likely a reflection of the natural course of disease, but it is often erroneously attributed to the change in therapy. In addition, the randomized controlled trials that have been performed in dogs with epilepsy often involve a small sample size, such that the power of the study to detect a difference between treatment groups is low. Finally, there are other

sources of bias that can influence the results of clinical trials, including both investigator and caregiver bias, with the potential for bias being greatest in unblinded and uncontrolled studies. All these factors must be considered when assessing the validity of any report of efficacy in an individual study.

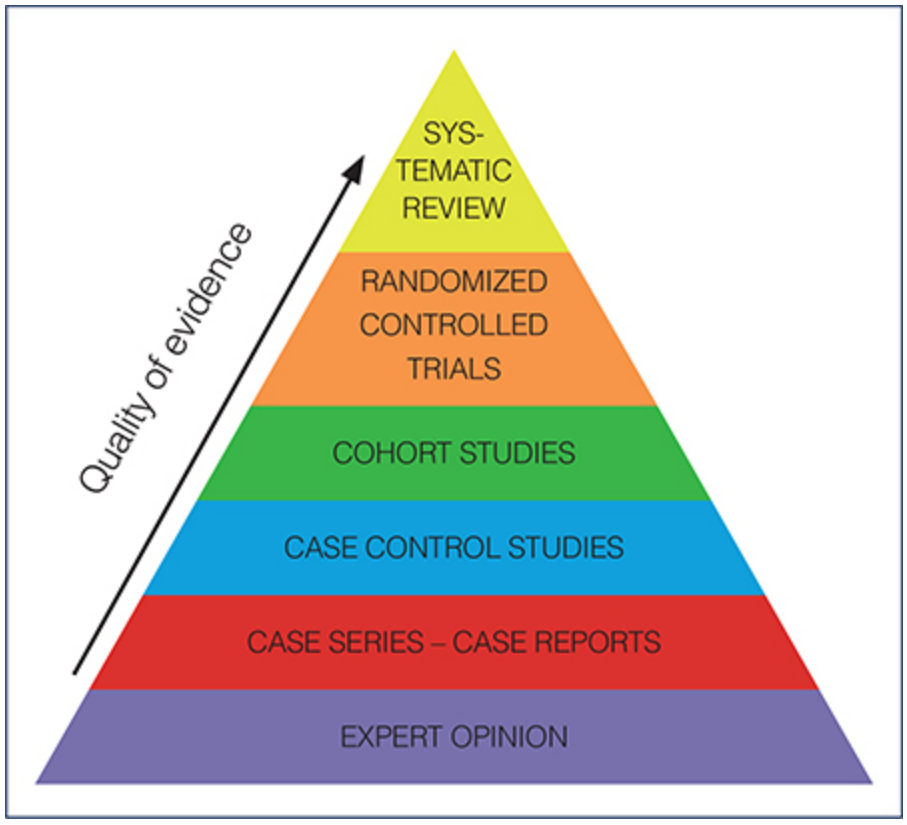


FIGURE 9.2. Pyramid that depicts both the quality and amount of evidence available. Expert opinion and case reports are at the base of the pyramid and randomized controlled studies and systematic reviews are at the apex, with the validity increasing from bottom to top.

The American College of Veterinary Internal Medicine (ACVIM) Consensus Statement on Seizure Management in Dogs aimed to critically evaluate the strength of the published trials on ASD therapy in dogs with IE, in order to make recommendations on their use.[1] For monotherapy, PB and IMP received a high recommendation, suggesting that these ASDs are likely to be effective. A similar meta-analysis performed by Charalambous et al.[15] also concluded that there was good evidence to recommend the use of PB and IMP as monotherapy in dogs. The conclusions from these two meta-analyses are summarized in Table 9.2. There are very few studies evaluating the efficacy of ASDs in cats with epilepsy. An analysis of

published studies recommended PB as the first-choice ASD in cats, followed by IMP and LEV.[16] However, data on IMP is currently limited to a small uncontrolled open-label study of 8 cats, 4 of which achieved seizure freedom following the administration of IMP for at least 8 weeks.[17] Similarly, although LEV monotherapy has been demonstrated to be efficacious for the treatment of feline audiogenic seizures,[18] the use of LEV in cats with IE has only been evaluated as adjunctive therapy in a single open-label noncomparative study of 10 cats with PB-resistant epileptic seizures. Seven of the 10 cats were considered responders with a >50% reduction in seizure frequency and a median follow-up time of 9 months.[19]

Safety

The safety of a prescribed medication is often of great concern to the caregiver. Adverse effects of medications can be categorized as type A (pharmacology-related) and type B (idiosyncratic reactions). Type A effects are predictable and dose dependent, and result from a known pharmacological property of the drug. Type A effects are common with ASD use and tend to be most severe at the onset of treatment or after a dose escalation. Effects are rarely life threatening, and are typically reversible upon dosage adjustment and infrequently require discontinuation of therapy.[20] The most common type A AEs reported in veterinary practice associated with the use of ASDs involve neurological signs, gastrointestinal signs and clinical pathological changes.[21] Sedation and ataxia are the most frequently reported neurological signs associated with ASD use, and can be seen with any ASD. Other commonly recognized AEs in dogs include polyphagia, polydipsia and polyuria; these can be seen in association with PB, KBr or IMP administration. The organ systems most commonly affected by type A reactions with ASDs include the central nervous system (presenting as neurological or behavioral signs) and the gastrointestinal system (presenting as anorexia, vomiting or diarrhea). In contrast, type B effects occur unpredictably. They are not dose dependent and cannot be explained by the drug's mechanism of action. They are often due to immune-mediated hypersensitivity reactions, or direct or indirect cytotoxicity of the drug or a metabolite.[20] These idiosyncratic reactions are often more serious, and include hepatotoxicity, blood dyscrasias, dyskinesia and superficial necrolytic dermatitis with PB; pancreatitis, panniculitis and neuromyopathy with KBr; and hepatotoxicity and renal tubular acidosis

with ZNS in dogs.[21] Idiosyncratic reactions reported in cats include pseudolymphoma, stomatitis and coagulopathy with PB; and bronchitis with KBr.[16] Oral diazepam was used as an ASD in cats for many years, until reports emerged of idiosyncratic hepatic necrosis associated with its use.[22] For this reason, diazepam is no longer recommended as a maintenance ASD in cats.

TABLE 9.2. Recommendations for antiseizure drug use in dogs based on assessment of published studies.

Antiseizure drug	Monotherapy		Adjunctive therapy	
	Strength of evidence in support of use#	Recommendation of use*	Strength of evidence#	Recommendation of use*
Phenobarbital	Good	High	Good^	Moderate
Imepitoin	Good	High	Insufficient	Low
Bromide	Fair	Moderate	Insufficient	Moderate
Levetiracetam	Insufficient	Low	Fair	Moderate
Zonisamide	Insufficient	Low	Insufficient	Moderate

#Charalambous, 2014.
*Podell, 2015.
^Evidence for phenobarbital as adjunctive therapy to imepitoin, as reported after the 2014 publication by Charalambous. The reader is referred to Chapter 13 for additional details.

Charalambous et al.[21] performed a meta-analysis of the safety of ASDs in dogs, and concluded that LEV and IMP are the safest ASDs for use in this species, followed by PB and finally KBr, with a strong level of evidence supporting the safety profile of all these drugs. In cats, IMP was considered the safest based on the available evidence, followed by LEV and PB, then ZNS, with KBr considered the least safe.[16]

Route of metabolism and drug interactions

The route of metabolism of an ASD should be taken into consideration, especially in animals with concurrent systemic disease or that are being administered other medications. Of the drugs that are commonly used in veterinary practice, PB, ZNS, and IMP undergo hepatic metabolism. Hence, these drugs should be avoided in animals with hepatic dysfunction. Levetiracetam is not metabolized by the liver, but does undergo oxidation and hydrolysis in other tissues prior to being renally excreted. Bromide is not metabolized and is excreted unchanged by the kidneys. Because LEV and KBr are primarily excreted by the kidneys, dosage adjustments may be needed in an animal with renal disease.

In addition, PB is a potent inducer of the hepatic microsomal cytochrome P450 system and can affect the clearance of other administered drugs that are dependent on hepatic metabolism. It is prudent to consult a pharmacology reference to investigate any potential drug interactions before initiating ASD therapy in an animal being administered any other medication or supplement. There can also be potential interactions between ASDs. Phenobarbital can increase the hepatic metabolism of ZNS, such that a higher dose of ZNS may be required when these ASDs are used concurrently.[23] Similarly, PB can increase the clearance of LEV by inducing its metabolic pathways outside the liver, such that dosage adjustments might be warranted when the drugs are used concurrently.[24]

Ease of administration and cost

Before deciding on an ASD, the clinician should consider the ease of administration, as this can greatly impact compliance. Ease of administration depends on the oral formulations of the drug available (capsule, tablet, or liquid) as well as the dose strengths available for each formulation. The availability of compounding pharmacies has increased the dosing options available in veterinary medicine, and this can be particularly important when prescribing ASDs to cats and small dogs. The required frequency of administration is another important consideration in the assessment of an ASD's ease of administration, which is determined by the species-specific pharmacokinetic properties of each ASD. It should be kept in mind that with the exception of IMP, all the ASDs used in dogs and cats were initially licensed for use in humans, so that much of the available data is based on administration to humans and cannot be directly extrapolated to veterinary practice.

Regulatory considerations

Finally, any regulatory considerations must be taken into account. This is currently not a consideration in the United States. However, there is a legal framework of cascade regulation for the prescription of veterinary drugs in Europe. For example, in the UK, PB and IMP have been approved as first-line ASDs and KBr is licensed as an adjunctive ASD in dogs. Similar regulations are in place in other European countries.

DEVISING A RATIONAL TREATMENT PLAN

Once an ASD is chosen, the clinician must determine the appropriate dosing and develop a plan for patient monitoring and follow-up. As a general rule, it is preferable to initiate treatment with a single ASD rather than a combination of drugs. This avoids drug–drug interactions and provides a simpler treatment regimen that may improve compliance. The following steps serve as guidelines when initiating therapy:

- Drugs are typically initiated at the low end of the recommended maintenance dose range, often rounded up to the closest tablet or capsule size if applicable.
- Loading doses can be administered in order to achieve the desired serum concentrations more rapidly. This is often indicated in animals with frequent and severe seizures for which an ASD with a longer elimination half-life has been selected. Accordingly, a loading dose is most often administered when initiating therapy with KBr, but this can be done with other ASDs as well. It should be remembered that administering a loading dose does not hasten the time to achieve steady state, which is dependent on the elimination half-life, but rather allows serum drug concentrations to enter the therapeutic range before steady state concentrations are reached (see Chapter 8).
- As mentioned previously, it is not uncommon for animals to experience transient type A AEs at the initiation of therapy; caregivers should be informed of this so they can allow their pet time (at least 2 weeks) to adjust to the medication before making any assessment of the tolerability.
- For drugs with a narrow therapeutic index, and for which a reference range has been established, such as PB and KBr, therapeutic monitoring should be performed once the ASD has reached steady-state concentrations.
- Dosage adjustments are made incrementally, based on response to therapy, which is determined by the seizure frequency once steady-state serum concentrations are achieved, the presence and severity of AEs, and serum drug concentrations (when applicable). If a dog with poorly controlled seizures has serum drug concentrations within the low therapeutic range and is experiencing no ASD-related AEs, the dosage of

the ASD should be increased. Further details on dosage adjustments for individual drugs are included in subsequent chapters.

- A follow-up examination and laboratory evaluation should be performed every 6–12 months. More frequent evaluations may be necessary, depending on the seizure frequency, severity of the AEs and the ASD being used. Recommendations for follow-up visits for individual ASDs are included in Table 9.3.
- Consider the need to prescribe short-acting ASDs for at-home emergency management of cluster seizures and status epilepticus. Owners should be provided with the relevant instructions on when and how to administer these ASDs at home. This is often recommended for animals that tend to have seizures that occur in clusters or are severe with respect to duration or semiology. See Chapter 19 for further discussion of at-home management of cluster seizures and status epilepticus.

Assessment of therapeutic outcome

When assessing therapeutic outcome in the management of epilepsy in dogs and cats, the clinician should consider the goals of therapy with respect to seizure control, tolerability of the treatment and overall quality of life for the pet and its caregiver. The primary goal of any therapeutic intervention is freedom from seizures. Since seizures can naturally wax and wane, it is important to measure a change in seizure frequency over a sufficiently long period of time to enable an accurate assessment of treatment response. In accordance with this, the IVETF has proposed that "treatment success be defined as seizure freedom for a time span exceeding three times the longest interseizure interval (in days) prior to treatment (either ASD initiation or dosage adjustment) and for a minimum of three months".[25] For an animal with new-onset seizures in which the seizure cycle has not been well documented, this minimum time span in which to evaluate treatment response is 3 months. The seizure diary should be consulted in animals with a well-documented seizure history. For example, consider a dog that has a historical seizure frequency that averages every 14 days with the longest interseizure interval being 20 days. In this dog, three times the longest interseizure interval would be 60 days, and this is shorter than the minimum designated timespan of 3 months, so the dog's therapeutic response would be measured over 3 months. As another example, consider a cat that tends

to have clusters of seizures approximately every 2 months. Review of the cat's seizure diary indicates that over the last year, the cat once went 100 days without a seizure. In this case, three times the longest interseizure interval would be 300 days, so approximately 10 months would be required to assess response to therapy.

TABLE 9.3. Recommended follow-up examinations for dogs and cats administered any of the antiseizure drugs most often used in veterinary practice. The frequency of follow-up visits applies to animals with satisfactory seizure control and minimal drug-related adverse effects. In animals with poor seizure control and/or intolerable adverse effects, more frequent monitoring is required.

Antiseizure drug	Recommended diagnostics	Frequency
Phenobarbital	Clinical examination Hematology Serum biochemistry profile Bile acid stimulation test Serum phenobarbital concentrations	Every 6–12 months
Potassium bromide	Clinical examination Hematology Serum biochemistry profile Urinalysis Serum bromide concentrations	Every 6–12 months
Imepitoin	Clinical examination Hematology Serum biochemistry profile	Every 6–12 months
Levetiracetam	Clinical examination Hematology Serum biochemistry profile Urinalysis	Every 6–12 months
Zonisamide	Clinical examination Hematology Serum biochemistry profile +/- Blood gas analysis Serum zonisamide concentrations	Every 6–12 months

However, there are dogs and cats with epilepsy that do not attain seizure freedom but nonetheless demonstrate a beneficial response to a therapeutic intervention. In acknowledgement of this, the International Veterinary Epilepsy Task Force (IVETF) has also defined a secondary treatment goal of **partial therapeutic success**,[25] to include:

- Prevention of cluster seizures or status epilepticus
- A relevant reduction of seizure frequency based on the pretreatment seizure frequency (in general, one seizure every 3 months or less)
- A reduction in seizure severity (for example, prevention of focal seizures becoming generalized)

It should be noted that the other aspect that needs to be considered in the assessment of treatment response is tolerability of the prescribed therapeutic intervention. An ideal treatment would not have any associated AEs. Although the absence of any AEs may not be achievable, it is important that any AEs that occur are considered manageable and do not put the animal's health at risk. Periodic evaluations consisting of an examination and laboratory analyses are crucial in this regard. The frequency of such evaluations will vary depending on the drug (see Table 9.3).

In summary, treatment success is measured by determining whether seizure freedom has been attained over an appropriate time span (3 months minimum) and if AEs are deemed acceptable. If either of these conditions are not met, then further adjustments to the medication regimen are required. In addition, if a worsening of seizure frequency and/or severity is noted following ASD initiation or dose adjustment and after achievement of steady state, prompt treatment modulation is warranted. Seizure control must be balanced against the presence of AEs to optimize the quality of life of the dog or cat, and of its caregiver. It is important to bear in mind that assessment of treatment response depends to a large extent on accurate owner observation. Because of this, owners should be instructed to maintain a calendar of seizure activity and to keep a record of any AEs that are observed as well as any deviations in the treatment regimen. There are several online sources and computer applications available to facilitate the record-keeping required for the successful management of a pet with epilepsy.

Therapeutic drug monitoring

Terminology

Therapeutic drug monitoring is an important component of epilepsy management and involves the measurement of ASD concentrations in the bloodstream (either serum or plasma) of patients. The clinical use of blood samples to measure ASD concentrations is based on the assumptions that 1) blood concentrations are superior to dosage in assessing an ASD's clinical effects, and 2) blood concentrations are strongly correlated with ASD concentrations achieved in the brain; consequently, this information is used to optimize patient outcome.

A variety of terms have been used in the area of therapeutic drug monitoring, which can lead to confusion. Because of this, the International League Against Epilepsy (ILAE) has recommended the use of the following terms and definitions,[26] that will be utilized in this book.

- **Reference range:** a range of drug concentrations, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur and an upper limit above which toxicity is relatively likely to occur.
- **Therapeutic range:** the range of drug concentrations which is associated with the best achievable response in a given individual. The therapeutic range differs between individuals; however, an individual's therapeutic range often lies within, or close to, the reference range provided by the laboratory.

Indications

Therapeutic drug monitoring should be routinely performed for ASDs such as PB, KBr, and ZNS, for which reference ranges has been established in veterinary medicine. Measuring ASD concentrations are used to establish a therapeutic concentration in an individual that has attained a successful clinical outcome, to provide information for the assessment of any subsequent change in treatment response; to assess for ASD toxicity; to assess for caregiver compliance in patients with poor seizure control; to guide dosage adjustments; and to monitor to potential pharmacokinetic interactions.[26] Accordingly, serum or plasma drug concentrations should be measured at the following time points:

- Once steady state has been achieved after initiation of treatment or dosage adjustment.
- When seizures persist despite an apparently adequate dosage.

- When there are concerns about drug related toxicity or pharmacokinetic interactions with other drugs.
- Every 6–12 months to screen for any changes in drug disposition over time and aim to maintain levels within the reference range (or an individual's therapeutic range, if known).

It is important to obtain an assessment of serum drug concentrations once steady-state concentrations have been achieved, and every 6–12 months thereafter—even if an animal's seizures are well controlled—as this is how an individual's therapeutic range is determined. This therapeutic range can then be used as a basis for changes in therapy if seizure frequency increases. Owners may be instructed to give additional oral ASDs when a pet has seizures, or the pet may require emergency intervention and the administration of intravenous drugs; blood collected after either of these events will not be reflective of the drug concentrations at the onset of the breakthrough seizures.

Serum drug concentrations can be used to calculate dosage adjustments, which can involve an increase in dosage in an effort to improve seizure control, or a decrease in drug dosage to lessen AEs. In general, dosage adjustments can be approximated according to the following formula, based on ASD serum concentrations measured at steady state:

$$\text{New dose (mg/kg)} = \text{current dose (mg/kg)} \times \frac{\text{desired serum concentration}}{\text{current serum concentration}}$$

Therapeutic drug monitoring is not routinely recommended for LEV, based on its wide therapeutic index (the relative safety of a drug based on the difference between the amount of drug that causes a therapeutic effect and the amount that causes toxicity). Furthermore, a reference range for LEV has not been established in dogs or cats. Nonetheless, it can be helpful

to measure trough LEV concentrations in instances where inadequate seizure control is reported, to determine whether a dosage increase might be warranted. Additional details on recommendations for dosage adjustments for individual ASDs are included in subsequent chapters.

Timing of sample collection

When performing therapeutic drug monitoring after initiation of maintenance ASD therapy or adjustment of drug dosage, samples should not be taken until the drug has reached steady-state concentrations. Knowledge of the pharmacokinetics of the ASD are important in determining this timing. In general, it takes approximately five elimination half-lives for a drug to attain steady-state concentrations (see Chapter 8 for further discussion). The timing of sample collection during the day should also be considered. In general, trough samples (collected immediately before the next dose) are most useful in the assessment of seizure control, while peak samples (collected at the time maximum concentrations are expected based on the pharmacokinetic properties of the drug) are most helpful when assessing toxicity. In certain situations, obtaining both trough and peak samples is useful to optimize the dosing schedule. For example, a report of 10 dogs with IE utilized both trough and peak PB serum concentrations to demonstrate that PB's elimination half-life decreases with chronic administration, and in such cases, altering the dosing interval from every 12 hours to every 8 hours resulted in freedom from seizures in 8 of 10 dogs.[27]

For drugs with long half-lives, such as KBr, the fluctuation in serum drug concentrations during a dosing interval is negligible, and samples can be collected at any time during the day. In contrast, for drugs with short half-lives, such as LEV, fluctuations in serum concentrations are expected throughout a dosing interval, so it is important to standardize the timing of sample collection with respect to dosing. Furthermore, it is good practice to be consistent in the timing of sample collection from one evaluation to the next for all ASDs, to best allow for direct comparison of results. In this regard, it is often most practical to schedule an appointment for sample collection before the morning dose of ASD, to allow for this consistency and obtain a trough sample. However, a trough sample should not be collected if scheduling will require more than a 1- to 2-hour delay in the administration of ASDs, in which case the timing of the sample relative to

dosing should be recorded. A summary of recommendations on timing of sample collection for individual ASDs is included in Table 9.4.

Adjunctive ASD therapy

A second ASD drug should be added when treatment success has not been achieved with the first ASD, that is, 1) when seizures continue despite the use of the maximum recommended dosage or serum concentrations being at the high end of the reference range, or 2) when unacceptable AEs develop. The choice of an adjunctive ASD involves the same considerations as when initiating monotherapy; however, potential drug interactions must now be considered. Efforts should be made to initiate adjunctive therapy with an ASD that has a different route of metabolism if the first ASD is hepatically metabolized. In addition, an ASD with a different mechanism of action is preferred, in an attempt to maximize antiepileptic properties and optimize seizure control. Finally, any potential pharmacokinetic interaction between the two drugs should be considered, as dosage adjustments might be indicated. Known interactions between the ASDs in dogs are summarized in Table 9.5.

In most instances, the second ASD is added on to the first and the animal is maintained on polytherapy, rather than treatment being switched from one ASD to the next. An abrupt switch from one ASD to another is often only attempted if the animal is displaying serious, often idiosyncratic, drug-related AEs. In such a case, the animal is started on the new ASD, with loading doses administered as appropriate to obtain serum concentrations within the desired reference range. Once targeted serum concentrations are achieved, the first ASD can be discontinued. A protocol for emergency at-home management should be prescribed to address any potential seizures that occur after discontinuation of the first ASD (see Chapter 19).

TABLE 9.4. Relevant pharmacokinetic data and recommendations on therapeutic drug monitoring in dogs and cats.

Drug	Elimination half-life	Time to reach steady state*	Recommended time interval for measuring serum concentrations after treatment initiation or dosage adjustment	Timing of sampling during the dosing interval	Timing of sampling for peak concentration (postdose administration)
Phenobarbital	Dog: 50 hours Cat: 40 hours	Dog: 14–21 days Cat: 14–16 days	2–3 weeks	Trough#, or trough and peak	4 hours
Potassium bromide	Dog: 15–46 days	Dog: 3–4 months	8–12 weeks	Anytime (minimum 2 hours after dosing)	N/A
Levetiracetam	Dog: 4 hours Cat: 3 hours	1 day	1 week	Trough	2 hours
Zonisamide	Dogs: 15 hours Cats: 30 hours	Dogs: 3–5 days Cats: 1 week	1–2 weeks	Trough, or trough and peak	3 hours

*Steady-state concentrations are achieved after approximately five half-lives.
#Trough samples are collected immediately before the next oral dosing.

TABLE 9.5. Reported antiseizure drug–drug interactions in dogs and cats.

Drug	Effects on other antiseizure drugs	Mechanism	Clinical implications
Phenobarbital	↓ LEV ↓ ZNS ↓ BZP ↓ TPM	Cytochrome P450 induction (ZNS, BZP, TPM) Induction of non-hepatic oxidative enzymes (LEV)	An increase in dose of the following ASDs may be required when coadministered with PB: LEV, ZNS, TPM Higher doses of DZP may be required for the emergency management of seizures in an animal administered PB
Clorazepate	↑ PB	Presumed to inhibit drug metabolizing enzymes	Measure PB serum concentrations before and after initiation of clorazepate; may require reduction in PB dose
Felbamate	↑ PB	Inhibits hepatic microsomal cytochrome P450 enzymes	Measure PB serum concentrations before and periodically after initiation of FBM; may require reduction in PB dose

LEV, levetiracetam; ZNS, zonisamide; BZP, benzodiazepines; TPM, topiramate; RUF, rufinamide; ASD, antiseizure drug; PB, phenobarbital; DZP, diazepam; FBM, felbamate.
Note: There are no reports of antiseizure drug–drug interactions with potassium bromide, levetiracetam, imepitoin, zonisamide, gabapentin, topiramate and pregabalin.

In lieu of loading, some practitioners will utilize bridge therapy, in which a short-acting ASD is administered for a limited period of time to provide additional seizure control until the second ASD reaches targeted serum concentrations. Levetiracetam is often used for this purpose and is administered in a similar manner for the treatment of cluster seizures (see chapters 12 and 19). Short-acting benzodiazepines, such as clorazepate and clonazepam have also been used in this manner (see Chapter 15).

Assessment of response to treatment with an adjunctive ASD should be performed in the same way as when initiating therapy or modulating

monotherapy. Again, the primary goal is seizure freedom, measured over a timespan equal to three times the longest interseizure interval before the initiation of adjunctive ASD, or a minimum of 3 months, in the presence of tolerable AEs. Adverse effects often become a greater concern with adjunctive therapy, as AEs such as sedation can be additive for ASDs. If an animal displays excessive sedation from the combination of drugs but seizure control has improved, the dosage of the first ASD can be slowly decreased in an effort to lessen sedation.

DRUG RESISTANCE

The term drug-resistant epilepsy has been defined in human medicine as "a failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[28] The IVETF has proposed that a similar definition be used in veterinary patients. Specifically, an animal should be labeled as drug resistant if seizure freedom is not achieved with two therapeutic trials. Considerations within this definition are that the ASD trial is tolerated and appropriately designed, with adequate dosing and treatment duration, in order to exclude the potential for pseudoresistance (defined as a lack of response due to inadequate dosing or treatment regimen in individual patients).[25] The IVETF definition of therapeutic success, with seizure freedom as the primary goal, is more restrictive than the definitions used in many previous veterinary studies. In these studies, an animal was considered to have drug-resistant epilepsy (also called refractory epilepsy) if a decrease in seizure frequency of ≥50% was not achieved despite treatment with a combination of at least two ASDs for a minimum of 6 months.[29–34] The IVETF has acknowledged that a more restrictive definition of drug resistance may have potential deleterious implications in that an early classification of drug-resistant epilepsy may negatively influence a clinician's efforts to continue therapeutic trials. Accordingly, the task force recommends that the term "drug resistant" always be used in relation to a specific ASD, for example PB-resistant or LEV-resistant. Furthermore, the task force has also defined partial therapeutic success (as outlined above, under section *Assessment of*

therapeutic outcome) as a secondary outcome measure in dogs and cats, recognizing that such an improvement in epileptic seizure control can be of clinical relevance to the animal and its caregiver.

More than two-thirds of dogs with IE are considered resistant to PB and/or KBr based on the IVETF definition of failure to achieve seizure freedom.[3,4,7,8,35,36] Even with use of the less restrictive definition of drug resistance previously used in veterinary medicine (<50% reduction in seizure frequency), the incidence remains at 20–30%.[37–39] Similarly, over 50% of cats with epilepsy are considered PB-resistant and fail to achieve seizure freedom with treatment, while approximately 30% can be classified as poorly controlled (defined as >10 seizures a year in this study).[40]

The incidence of refractory epilepsy in the human population is similar to that reported in dogs. Thirty to 40% of people with epilepsy continue to seizure with maximal medical therapy, and less than half of people with epilepsy are able to maintain a seizure-free status without unacceptable AEs from the medication.[41] Interestingly, despite the recent introduction of numerous new drugs with differing mechanisms of action, the overall incidence of ASD-resistance in humans has remained fairly constant. An epidemiological study of humans with epilepsy found that among patients who did not respond to a first ASD, only 3% became seizure free when treatment was attempted with a combination of two or more drugs.[41] Similarly, a recent veterinary study demonstrated that among dogs with epilepsy that had failed treatment with two ASDs, only one-fifth responded (≥50% reduction in seizure frequency) to the addition of a third-line drug.[42]

The pathophysiology of ASD-resistance remains poorly understood, but it is likely multifactorial, with genetic, disease-related, drug-related and environmental factors assuming a role. Proposed theories include:

1. The transporter or pharmacokinetic hypothesis, which suggests that overexpression of multidrug transporters, the proteins that restrict the entry of lipophilic molecules into the brain, can result in inadequate concentrations of ASDs at target sites in the brain.
2. The target hypothesis, which proposes that acquired alterations to the structure or function of target ion channels and neurotransmitter receptors leads to a lack of pharmacodynamic activity of ASDs in the brain.

3. The network hypothesis, which is based on the premise that structural brain alterations or network changes (such as hippocampal sclerosis) are involved in drug resistance.
4. The gene variant hypothesis, which suggests that inherent resistance is governed by genetic variants of proteins involved in the action of ASDs.
5. The intrinsic disease severity hypothesis, which is based on the belief that there is a continuum in severity of epilepsy reflected in the frequency of seizures in the early phase of disease that determines relative response to ASDs.[43]

Alternative, nonpharmacological therapies, including surgical resection of a seizure focus, neurostimulation and dietary modification, are often recommended for humans with drug-resistant epilepsy. Both dietary therapy and neurostimulation have been studied in dogs with IE; these topics are presented in more detail in chapters 17 and 18, respectively. Although evidence to support these treatment modalities is currently limited in veterinary medicine, they remain an area of active research, and additional data will likely become available over time to help guide recommendations on their use.

EPILEPSY REMISSION

Remission of epilepsy, defined as an absence of seizures for an extended period of time (minimum of 1 year), has been reported to occur in approximately 15% of dogs with IE.[8,35,36] Seizure remission can be further categorized as remission with treatment (seizure freedom in animals that are being administered ASDs) and spontaneous remission (seizure freedom without ASD treatment). In human medicine, an outcome of 5 years seizure free is most commonly used as the definition of epilepsy remission.[44] There is no consensus on the duration of seizure freedom necessary to be considered remission of epilepsy in veterinary medicine, with time frames of 1 to 3 years used in reported studies.[13,36]

A spontaneous remission rate of 5% in dogs with IE has been reported in three separate studies.[6,8,36] A prospective longitudinal study of Danish dogs with epilepsy that were followed up until their death reported 3 of 55 dogs

to have freedom from seizures without treatment.[36] Fredsø reported on a retrospective evaluation of survival in a university hospital population of 78 dogs with IE, in which 4 of 78 dogs achieved a 3-year remission of epilepsy without treatment.[35] A retrospective evaluation of 49 Border Collies with IE reported 2 dogs with spontaneous remission, with seizure freedom of ≥1 year.[8]

Rates of seizure remission with treatment in dogs with IE have been reported to range from 7–30%. Long term follow-up (average of 4.8 years, range 11–101 months) of 37 Labrador retrievers with IE revealed that 11 of the dogs (30%) became seizure free on PB monotherapy.[3] The longitudinal study of Danish dogs mentioned previously demonstrated a rate of seizure remission with treatment of 7% (4/55 dogs) with dogs administered either PB alone or PB and KBr in combination.[36] A retrospective study with prospective follow-up of 102 dogs with epilepsy presenting to a university hospital identified 6 of 78 dogs (9%) with IE that achieved seizure remission of ≥3 years with treatment consisting of PB alone, or PB and KBr in combination.[35] A separate retrospective study of 344 dogs with epilepsy reported a remission rate (of no minimum duration) with PB treatment of 14% and a median follow-up time of 656 days.[4] A study on disease progression and outcome in Australian Shepherds with IE reported remission for ≥1 year in 3/50 dogs (6%) with treatment involving PB alone, or PB in addition to another ASD (KBr, LEV or gabapentin).[7] A similar study in Border Collies reported remission of seizures for ≥1 year in 7/40 dogs (18%) with treatment with PB alone, or PB and KBr.[8] In cats with IE, remission rates with PB treatment have been reported to range from 42–45% after at least 2 years of treatment. Seizures recurred in 6 of 8 cats in which PB was reduced after at least 1 year of seizure freedom, necessitating a subsequent dosage increase. Two cats remained seizure free after discontinuing PB for a minimum follow-up period of 2 years.[40]

The question frequently arises as to when ASD therapy can be discontinued in an animal that is seizure free. This should be carefully considered, as one cannot be certain whether the seizure free status is due to effective medical therapy or remission of the seizure disorder. If a dog or cat has been seizure free for a year or more, and especially if serum drug concentrations are below or in the low reference range, one can consider weaning the animal off medication. This must be done slowly as an abrupt termination of ASD therapy can precipitate seizures. Furthermore, seizures

that recur with discontinuation of treatment can be more difficult to control. A study by Gessell et al. on ASD withdrawal reported on 11 dogs with IE or presumed IE in which ASD treatment was discontinued after the dogs became seizure free for a median of 1 year. Four dogs (36%) remained seizure free with a follow-up period ranging from 2–7 years. The remaining 7 dogs (64%) experienced a recurrence of seizures after discontinuation of ASD therapy; of these, only 3 dogs were able to regain seizure control with resumption of ASD therapy.[45]

If ASD reduction is attempted in an animal that has achieved seizure remission with treatment for at least 1–2 years, it should be performed slowly and systematically, based on the pharmacokinetics of the drug and the seizure pattern of the animal. The authors recommend reducing the dosage by approximately 25% and maintaining the dosage at this level for at least 2–4 weeks or the time required to achieve steady state concentrations, whichever is longer. If no seizures are observed with careful monitoring during this time, the dosage reduction is continued in a stepwise manner and ultimately discontinued.

Rapid withdrawal of ASD therapy is indicated for animals that experience severe, life-threatening (type B) AEs associated with the drug administration. Before the drug is discontinued, it is important to initiate the animal on an alternative ASD at a dosing likely to achieve serum concentrations within the reference range. This is often accomplished by administering a loading dose of the new ASD. Further discussion of loading protocols for individual drugs is included in subsequent chapters. Once the alternate drug has been administered, and serum concentrations measured as appropriate, the first ASD can be abruptly discontinued. It is recommended that the animal remain in the hospital during this drug withdrawal, in order to allow for rapid, appropriate treatment of any breakthrough seizures.

TAKE-HOME MESSAGES

- Antiseizure drug therapy is the mainstay of treatment for epilepsy. An individualized approach to seizure management is necessary for optimal results, while systematically considering some basic principles of ASD therapy, including:

- When to initiate therapy.
- How to choose an appropriate ASD and drug dose.
- How to devise a rational treatment plan.
- How to adjust ASD dosage.
- When to add-on another ASD.
- How to determine treatment success.

- Client education regarding the goals and expectations of treatment is an extremely important component of successful ASD therapy and should be provided before any medication is prescribed.
- Criteria used to support the recommendation to initiate therapy in dogs (and cats) with IE include:
  - Two or more epileptic seizures within a 6-month period.
  - History of cluster seizures or status epilepticus.
  - Postictal signs that are considered severe or prolonged (>24 hours).
  - A worsening of the epileptic condition based on an increase in seizure frequency, duration, or severity noted over a timespan equal to 3 interictal periods.
- When deciding on the choice of ASD, the following factors should be considered:
  - Mechanism of action
  - Efficacy
  - Safety and AEs
  - Route of metabolism and potential drug interactions
  - Ease of administration
  - Cost
  - Regulatory considerations
- The total number of published studies on the safety and efficacy of ASDs in dogs and cats is quite limited, and many of the available studies involve a small sample size and study design that does not prevent bias. It is important for a clinician to consider the quality of

evidence when evaluating the efficacy and safety of an ASD for use in veterinary patients.

- When initiating ASD therapy, the following guidelines should be considered:
  - Drugs are typically initiated at the low end of the recommended maintenance dosage range.
  - Loading doses can be administered to achieve the desired serum concentrations more rapidly.
  - It is not uncommon for animals to experience transient type A AEs at the initiation of therapy.
  - Therapeutic drug monitoring should be performed once the ASD has reached steady-state concentrations for drugs in which it is recommended.
  - Dosage adjustments are made incrementally, based on response to therapy, which is determined by the seizure frequency once steady-state serum levels are achieved, the presence and severity of AEs, and serum drug concentrations (when applicable).
  - A follow-up examination and laboratory evaluation should be performed every 6–12 months, and more frequently if seizures are not adequately controlled or intolerable AEs are present.
- Treatment success is defined as seizure freedom for a time span exceeding three times the longest interseizure interval (in days) in the year preceding the treatment and for a minimum of three months. Partial therapeutic success is defined as one or more of the following:
  - Prevention of cluster seizures or status epilepticus.
  - A relevant reduction of seizure frequency based on the pretreatment seizure frequency.
  - A reduction in seizure severity.
- Therapeutic drug monitoring should be routinely performed for ASDs such as PB, KBr, and ZNS, for which reference ranges have been established in veterinary medicine. This information is used to establish a therapeutic concentration in an individual that has attained a successful clinical outcome, to provide information for the assessment of any subsequent change in treatment response, to assess

ASD toxicity, to assess caregiver compliance in patients with poor seizure control, to guide dosage adjustments, and to monitor for potential pharmacokinetic interactions. Serum drug concentrations should be measured at the following times:

- Once steady state has been achieved after initiation of treatment or dosage adjustment.
- When seizures persist despite an apparently adequate dosage.
- When there are concerns about drug-related toxicity or pharmacokinetic interactions with other drugs.
- Every 6–12 months to screen for any changes in drug disposition over time.

- Drug resistance, defined as a failure to achieve seizure freedom with a minimum of two appropriately designed and tolerated ASD trials, is seen in more than two thirds of dogs with IE and more than half of cats with epilepsy.
- Remission of epilepsy, defined as absence of seizures for >1 year, is reported to occur in approximately 15% of dogs with IE. This includes dogs that experience seizure remission with ASD treatment, and those that experience spontaneous remission independent of ASD treatment.
- Antiseizure drug withdrawal can be attempted in animals that are free of seizures for a minimum of 1–2 years. This must be performed slowly and systematically. A more rapid ASD withdrawal is indicated in animals that are experiencing serious AEs. In these cases, the animal should be loaded with another ASD, and serum concentrations measured to ensure they are in the reference range prior to discontinuing the first ASD.

REFERENCES

1. PODELL M, VOLK HA, BERENDT M et al. 2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs. *J Vet Intern Med*. 2016; 30(2):477–490.

2. Bhatti SF, De Risio L, Muñana K, et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015; 11:176. doi: 10.1186/s12917-015-0464-z.
3. Heynold Y, Faissler D, Steffen F et al. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 labrador retrievers: a long-term study. *J Small Anim Pract*. 1997; 38(1):7–14.
4. Packer RMA, Shihab NK, Torres BB et al. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. *PLoS One*. 2014; 9(8):e106026. doi: 10.1371/journal.pone.0106026.
5. Rogawski MA. The intrinsic severity hypothesis of pharmacoresistance to antiepileptic drugs. *Epilepsia*. 2013; 54 (Suppl 2):33–40.
6. Fredsø N, Toft N, Sabers A et al. A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs. *BMC Vet Res*. 2017; 13(1):54. doi: 10.1186/s12917-017-0966-y.
7. Weissl J, Hülsmeyer V, Brauer C et al. Disease progression and treatment response of idiopathic epilepsy in Australian Shepherd dogs. *J Vet Intern Med*. 2012; 26(1):116–125.
8. Hülsmeyer V, Zimmermann R, Brauer C et al. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. *J Vet Intern Med*. 2010; 24(1):171–178.
9. Monteiro R, Adams V, Keys D et al. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. *J Small Anim Pract.* 2012; 53(9):526–530.
10. De Risio L, Newton R, Freeman J et al. Idiopathic epilepsy in the Italian Spinone in the United Kingdom: prevalence, clinical characteristics, and predictors of survival and seizure remission. *J Vet Intern Med*. 2015; 29(3):917–924.
11. Muñana KR, Nettifee-Osborne JA, Bergman RL et al. Association between ABCB1 genotype and seizure outcome in Collies with epilepsy. *J Vet Intern Med*. 2012; 26(6):1358–1364.
12. Berendt M, Gredal H, Pedersen LG, et al. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. *J Vet Intern Med*. 2002; 16(3):262–268.
13. Gulløv CH, Toft N, Berendt M. A longitudinal study of survival in Belgian Shepherds with genetic epilepsy. *J Vet Intern Med*. 2012; 26(5):1115–1120.
14. Muñana KR, Zhang D, Patterson EE. Placebo effect in canine epilepsy trials. *J Vet Intern Med*. 2010; 24(1):166–170.
15. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy--a systematic review. *BMC Vet Res*. 2014; 10(1):257. doi: 10.1186/s12917-014-0257-9.
16. Charalambous M, Pákozdy Á, Bhatti SFM, et al. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14(1):64. doi: 10.1186/s12917-018-1386-3.
17. Engel O, von Klopmann T, Maiolini A, et al. Imepitoin is well tolerated in healthy and epileptic cats. *BMC Vet Res*. 2017; 13(1):172. doi:10.1186/s12917-017-1087-3.
18. Lowrie M, Thomson S, Bessant C, et al. Levetiracetam in the management of feline audiogenic reflex seizures: a randomised, controlled, open-label study. *J Feline Med Surg*. 2017; 19(2):200–206.
19. Bailey KS, Dewey CW, Boothe DM, et al. Levetiracetam as an adjunct to phenobarbital treatment in cats with suspected idiopathic epilepsy. *J Am Vet Med Assoc*. 2008; 232(6):867–

872.

20. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia*. 2007; 48(7):1223–1244.
21. Charalambous M, Shivapour SK, Brodbelt DC et al. Antiepileptic drugs' tolerability and safety - a systematic review and meta-analysis of adverse effects in dogs. *BMC Vet Res*. 2016; 12:79. doi: 10.1186/s12917-016-0703-y.
22. Center SA, Elston TH, Rowland PH et al. Fulminant hepatic failure associated with oral administration of diazepam in 11 cats. *J Am Vet Med Assoc*. 1996; 209(3):618–625.
23. Orito K, Saito M, Fukunaga K et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. *J Vet Pharmacol Ther*. 2008; 31(3):259–264.
24. Moore SA, Muñana KR, Papich MG et al. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther*. 2011; 34(1):31–34.
25. Potschka H, Fischer A, Löscher W et al. International Veterinary Epilepsy Task Force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. *BMC Vet Res*. 2015; 11:177. doi: 10.1186/s12917-015-0465-y.
26. Patsalos PN, Berry DJ, Bourgeois BFD et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2008; 49(7): 1239–1276.
27. Stabile F, Barnett CR, De Risio L. Phenobarbital administration every eight hours: improvement of seizure management in idiopathic epileptic dogs with decreased phenobarbital elimination half-life. *Vet Rec*. 2017; 180(7):178. doi: 10.1136/vr.104051.
28. Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010; 51(6):1069–1077.
29. Gagliardo T, Gandini G, Gallucci A et al. ABCB1 c.-6-180T>G polymorphism and clinical risk factors in a multi-breed cohort of dogs with refractory idiopathic epilepsy. *Vet J*. 2019; 253:105378. doi: 10.1016/j.tvjl.2019.105378.
30. Volk HA, Matiasek LA, Luján Feliu-Pascual A et al. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. *Vet J*. 2008; 176(3):310–319.
31. Dewey CW, Cerda-Gonzalez S, Levine JM et al. Pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy. *J Am Vet Med Assoc*. 2009; 235:1442–1449.
32. von Klopmann T, Rambeck B, Tipold A. Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. *J Small Anim Pract*. 2007; 48(3):134–138.
33. Muñana KR, Thomas WB, Inzana KD et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled, crossover trial. *J Vet Intern Med*. 2012; 26(2):341–348.
34. Charalambous M, Van Ham L, Broeckx BJG et al. Repetitive transcranial magnetic stimulation in drug-resistant idiopathic epilepsy of dogs: A noninvasive neurostimulation technique. *J Vet Intern Med*. 2020; 34(6):2555–2561.
35. Fredsø N, Koch BC, Toft N et al. Risk factors for survival in a university hospital population of dogs with epilepsy. *J Vet Intern Med*. 2014; 28(6):1782–1788.
36. Berendt M, Gredal H, Ersbøll AK et al. Premature death, risk factors, and life patterns in dogs with epilepsy. *J Vet Intern Med*. 2007; 21(4):754–759.
37. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. *J Vet Intern Med*. 1993; 7(5):318–327.

38. TREPANIER LA, VAN SCHOICK A, SCHWARK WS et al. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992-1996). *J Am Vet Med Assoc*. 1998; 213(10):1449–1453.
39. LANE SB, BUNCH SE. Medical management of recurrent seizures in dogs and cats. *J Vet Intern Med.* 1990; 4(1):26–39.
40. PÁKOZDY Á, SARCHAHI AA, LESCHNIK M et al. Treatment and long-term follow-up of cats with suspected primary epilepsy. *J Feline Med Surg*. 2013; 15(4):267–273.
41. KWAN P, BRODIE MJ. Early identification of refractory epilepsy. *N Engl J Med*. 2000; 342(5):314–319.
42. PACKER RMA, SHIHAB NK, TORRES BB et al. Responses to successive anti-epileptic drugs in canine idiopathic epilepsy. *Vet Rec*. 2015; 176(8):203. doi: 10.1136/vr.102934.
43. TANG F, HARTZ AMS, BAUER B. Drug-resistant epilepsy: Multiple hypotheses, few answers. *Front Neurol.* 2017; 8:301. doi: 10.3389/fneur.2017.00301.
44. SILLANPÄÄ M, SCHMIDT D, SAARINEN MM et al. Remission in epilepsy: How long is enough? *Epilepsia*. 2017; 58(5):901–906.
45. GESELL FK, HOPPE S, LÖSCHER W et al. Antiepileptic drug withdrawal in dogs with epilepsy. *Front Vet Sci*. 2015; 2:23. doi: 10.3389.fvets.2015.00023.

Phenobarbital 10

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Phenobarbital (PB) (5-ethyl-5-phex2nylbarbituric acid) is widely used in veterinary medicine due to its efficacy on different seizure types, safety and its relatively inexpensive cost compared to other antiseizure drugs (ASDs).[1–3] A questionnaire study investigating ASD preferences amongst Australasian veterinarians showed that PB was the most commonly used ASD for managing chronic seizure disorders in both dogs (99%) and cats (94%).[4] In a cross-sectional survey on ASD use in dogs with suspected idiopathic epilepsy (IE) among board-certified emergency and neurology specialists, PB was the initial ASD of choice for 66% of neurologists and 64% of emergency and critical care specialists.[5] Phenobarbital is one of the ASDs recommended as first-line monotherapy by both the International Veterinary Epilepsy Task Force (IVETF) and the 2015 American College of Veterinary Internal Medicine *Small Animal Consensus Statement on Seizure Management in Dogs*.[6,7]

Phenobarbital is available as an oral solution, oral tablets of various strengths, and parenteral formulations.

In dogs, PB is one of the most powerful inducers of hepatic microsomal enzymes and therefore contributes to its own metabolism, as well as the metabolism of many other medications. Individualization of PB dosage over time based on an accurate seizure diary, tolerability, regular serum PB concentration measurements and general health monitoring is key to optimizing its use in canine and feline epilepsy.

MECHANISM OF ACTION

As with many ASDs, the exact mechanism of action of PB is not completely understood. It is known that PB binds the γ-aminobutyric acid (GABA) type A receptor (Fig. 10.1). As a consequence of this binding:

- Phenobarbital activates the $GABA_A$ receptor-gated chloride-channels, allowing a steady flow of negatively charged chloride ions into the neurons. This results in neuronal cellular membrane hyperpolarization and increases the action potential threshold.
- Phenobarbital increases the affinity of the inhibitory neurotransmitter GABA for its own receptor, thereby increasing responsiveness to GABA in the central nervous system (CNS). This results in an enhancement of postsynaptic neuronal inhibition. As such, the chloride ion channels remain open for longer, thus allowing an increased chloride influx in the neurons. This leads to an increased intracellular chloride concentration and increased hyperpolarization of the resting membrane potential of the postsynaptic neuron.[8]

It has been suggested that PB interacts with glutamate receptors decreasing neuronal postsynaptic excitation. Phenobarbital also seems involved in the inhibition of voltage-gated calcium channels, which results in decreased calcium influx into neurons and contributes to hyperpolarization. [9]

As a consequence of these interactions with inhibitory neurotransmitters and voltage-gated channels, PB increases the epileptic seizure threshold and decreases the spread of excitatory discharge to surrounding neurons in the CNS.[10]

PHARMACOKINETICS

Phenobarbital has a high bioavailability; it is reported to be approximately 90% in dogs[11,12] and 100% in cats[13,14] following oral administration. Administration with food has been reported to decrease absorption by approximately 10% compared to administration on an empty stomach in dogs.[15]

The data on pharmacokinetic (PK) parameters such as time to maximum serum PB concentration (C_{max}) and elimination half-life ($t_{1/2}$) vary between

studies depending on the dosage administered and the route and methodology used.[11–21] The PK values reported here are those considered more relevant by the authors. The PB dosages used in PK studies often differ from those recommended for clinical use.

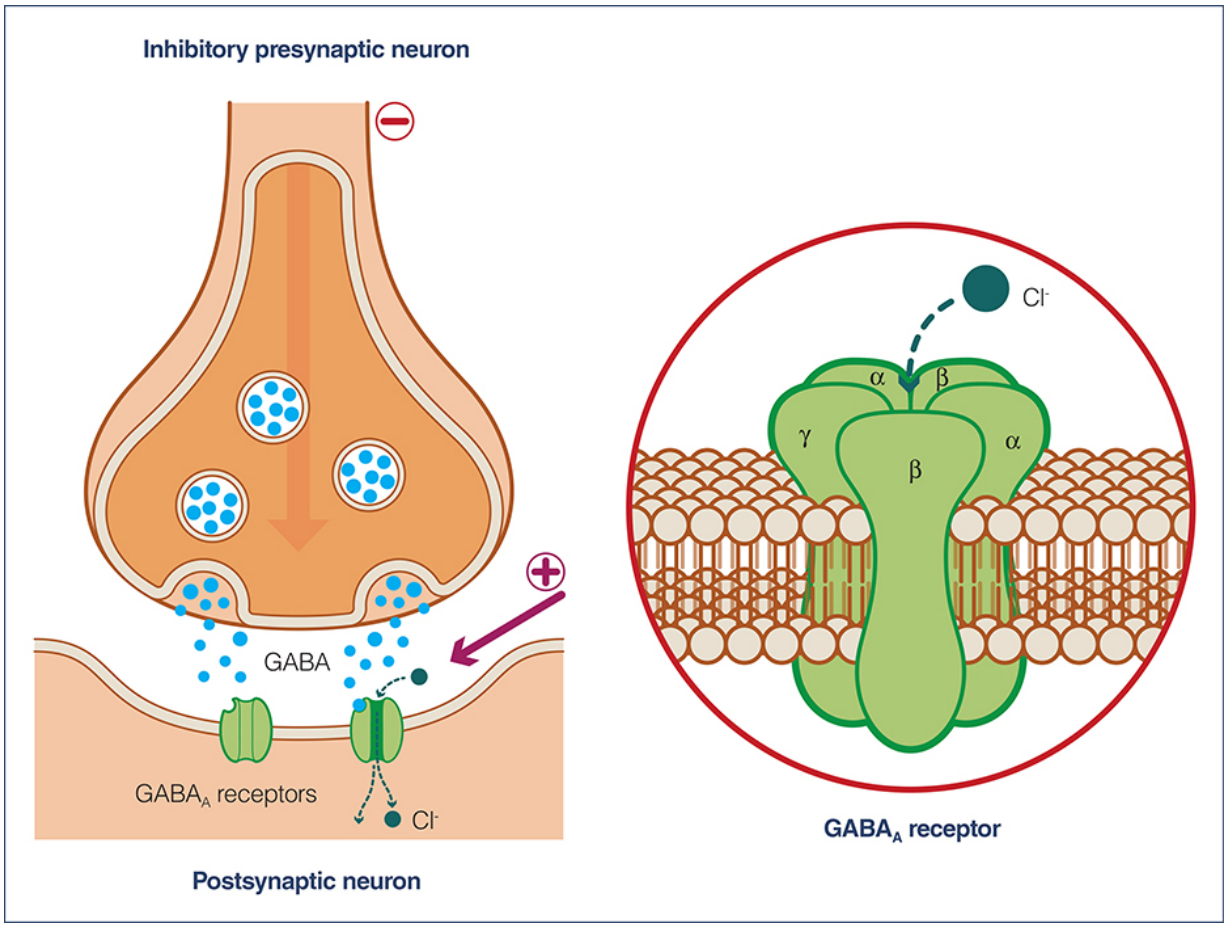


FIGURE 10.1. The primary mechanism of action of phenobarbital is to enhance the inhibitory actions of γ-aminobutyric acid (GABA) on neurons. Phenobarbital binds at the $GABA_A$ receptor to both directly activate GABA receptor-gated chloride channels and to increase the affinity of GABA for its own receptor by allosteric effect.

After oral administration:

- Phenobarbital is absorbed within 2 hours in dogs.
- Plasma protein (mostly albumin) binding is approximately 45%.[16]
- C_{max} was achieved in 4.60 ± 0.89 hours in dogs administered 5.5 mg/kg/day orally for 90 days.[18]
- C_{max} was achieved in 1.0–1.5 hours and maintained for several hours in cats administered a single 10 mg/kg oral dose.[13]

- In dogs, the mean PB $t_{1/2}$ has been reported as 47.3 ± 10.7 hours after oral administration of 5.5 mg/kg/day for 90 days and 53.0 ± 15 hours after oral administration of 2 mg/kg every 8 hours for 5 days.[18,19]
- In cats, the mean PB $t_{1/2}$ has been reported as 76 ± 6.96 hours after a single 10 mg/kg oral dose and 43.3 ± 2.92 hours after administration of 5 mg/kg/day orally for 21 days.[13,14]
- In dogs, approximately 25% of PB is excreted unchanged in urine.[11,12]
- In dogs, steady-state concentration is achieved within 14–21 days after initiation of PB oral treatment at the maintenance dosage.[18]
- In cats, steady-state concentration is achieved within 14–16 days after initiation of PB oral treatment at the maintenance dosage.[14,21]

Phenobarbital is primarily metabolized by the hepatic microsomal enzymatic system. For this reason, PB treatment is contraindicated in dogs with hepatic dysfunction. In dogs, PB is a potent inducer of the hepatic microsomal cytochrome P450 (subfamilies CYP1A, CYP2B, CYP2C, CYP3A) enzyme activity.[22] As a result, chronic PB treatment progressively accelerates the drug's metabolism by increasing its total body clearance, thus reducing its $t_{1/2,}$ and therefore potentially reducing its pharmacological effect at the same administered dosage.[22]

Phenobarbital PK values can be affected by the diet and body composition.[23] A prospective study investigated PB PK in 27 healthy Beagles treated with PB (3 mg/kg every 12 hours orally) and fed one of three diets (maintenance diet; protein-restricted diet; fat- and protein-restricted diet) for 2 months. At study end, the percentage of body fat and serum PB concentrations were significantly lower in dogs fed the fat- and protein-restricted diet than in dogs fed the other two diets. These results suggest that serum PB concentrations should be monitored closely, and dosage adjustments may be required when changes in diet and body composition (e.g., obesity or weight loss) occur.[23]

A prospective study in 5 healthy Beagles investigated the effect of urine pH on PB PK after administration of a single oral PB dose of 3 mg/kg.[24] The dogs were fed a commercially available adult-dog diet that neutralizes the urine pH by including potassium citrate and ammonium chloride for urine alkalinization and acidification, respectively. The $t_{1/2}$ of serum PB was shorter and clearance was increased in dogs with urine alkalinization compared to dogs with urine acidification.[24] This study suggests that serum

PB concentration might be altered when a pH-modifying diet is administered to dissolve or prevent uroliths.

Topical administration of transdermal PB has been investigated in healthy cats as an alternative to oral PB administration. Two different carrier molecules have been used: a pluronic lecithin organogel and a lipophilic liposomal cream (Lipoderm Activemax®).[25,26] The lipophilic liposomal cream was considered easier to administer by the cats' owners. To achieve a serum PB concentration greater than 15 µg/mL, a topical dose of 9 mg/kg every 12 hours was required. A prospective, fixed-order, crossover pilot study comparing serum PB concentrations in 9 epileptic cats treated with oral PB at 3.8 mg/kg every 12 hours for 14 weeks and then continued with transdermal PB at 9.4 mg/kg every 12 hours for 14 additional weeks suggested that target serum PB concentrations are achievable with transdermal PB administration in some cats, although they were not reliably correlated with the PB dose administered.[27] Therefore, consistent monitoring of epileptic seizure occurrence and serum PB concentrations is recommended when using transdermal PB preparations.[27]

The PK of inramuscularly (IM) administered PB have not yet been investigated in dogs and cats. However, a study in humans has demonstrated a similar absorption after IM administration compared to that observed with oral administration.[28]

Further details on the PK of PB can be found elsewhere.[29]

EFFICACY

The reported efficacy of PB monotherapy for the treatment of canine and feline epilepsy varies between studies, likely due to differences in the inclusion criteria, populations, epilepsy severity, initial monotherapy dosage, serum PB concentration monitoring and dose modulation (whether and when these were performed), follow-up duration and outcome measures.

Phenobarbital efficacy in dogs with IE

A systematic review of the efficacy of ASDs in canine IE treatment identified good evidence for recommending the use of PB monotherapy.[1]

The reported efficacy of PB monotherapy in terms of reduction in the frequency or remission of epileptic seizures varies between 60–93% in dogs with a serum PB concentration within the recommended target range.[1,30–35]

The efficacy of PB monotherapy for canine IE has been compared with that of other ASDs including potassium bromide (KBr)[32], imepitoin (IMP)[33,34] and levetiracetam (LEV)[35] (see chapters 11, 12 and 13).

In a double-blinded, randomized, parallel clinical trial comparing PB to KBr as a first-line ASD in canine IE, PB treatment resulted in seizure freedom in a significantly higher proportion of dogs (17/20 dogs, 85%) than treatment with KBr (12/23 dogs, 52%), as well as in a significantly greater reduction in seizure duration and greater tolerability than with KBr.[32] Phenobarbital monotherapy led to a significant decrease in seizure number, duration and severity, and in an increased seizure-free interval at study end (6 months) compared to baseline. This study included dogs aged 1–6 years and various breeds were represented, including those with severe IE types. Dosages of ASDs were individualized over time for each patient based on seizure occurrence and regular therapeutic monitoring.[32]

In a multicenter, randomized, blind controlled, parallel group clinical trial, seizure freedom was achieved during the 12-week study period in 58% (51/88) of dogs with IE treated with PB and in 47% (30/64) of those treated with IMP.[33] A ≥ 50% reduction in monthly seizure frequency was reported in 83% (73/88) of dogs treated with PB and in 75% (48/64) of those treated with IMP. No significant difference in the mean seizure frequency per month was identified between the PB and IMP treatment groups. This study initially included 226 dogs. A greater number of dogs (52, 45%) in the IMP group were excluded from the final analysis than in the PB group (22, 20% dogs). Reasons for exclusion from the study after initial enrolment included withdrawal of owner's consent, occurrence of status epilepticus, increased seizure frequency after PB or IMP initiation, and/or occurrence of several epileptic seizures despite administration of the maximum treatment dose allowed (i.e., 6 mg/kg every 12 hours for PB and 30 mg/kg every 12 hours for IMP).[33]

In an observational, prospective, cohort study investigating seizure frequency and cluster seizure development in dogs with IE on IMP or PB monotherapy, the reduction in seizure frequency from pre to post-ASD monotherapy initiation was significantly greater in the PB group than in the IMP group.[34] Dogs treated with IMP developed cluster seizures significantly

more frequently (68%) than those treated with PB (37%). Dogs treated with IMP also developed cluster seizures significantly earlier in the disease course than those treated with PB.[34]

In a single blind, randomized, parallel trial comparing the use of PB with that of LEV in 12 dogs with newly diagnosed IE, PB was found to be significantly more efficacious than LEV.[35] In the 6 dogs administered LEV, no significant difference in the monthly number of epileptic seizures was observed before and after treatment, whereas the 6 dogs on PB experienced significantly fewer epileptic seizures after treatment initiation. Eighty-three percent of dogs on PB were classified as responders (i.e., ≥50% reduction in epileptic seizure number/month), whereas none of the LEV-treated dogs fulfilled this criterion. Adverse effects (AEs) were reported in both groups but were more frequent in the PB group.[35]

In some dogs on prolonged PB treatment, the PB $t_{1/2}$ has been shown to become shorter than what is considered adequate for 12-hour dosing, which can compromise PB efficacy.[32,36] A retrospective case series reported that, in dogs with IE with a decreased PB $t_{1/2}$ (<20 hours) following prolonged PB treatment, administration of PB orally every 8 hours is safe and can improve epilepsy management.[36] All 10 dogs with IE included in this study experienced treatment failure (based on IVETF criteria, see Chapter 9) despite having a serum PB concentration within the target range at steady state. The mean time interval from PB treatment initiation to the time when PB $t_{1/2}$ was detected to become < 20 hours was 27 ± 17.2 months (range 5–53 months, median 26 months). At the time of the detected decrease in PB $t_{1/2}$, the mean dosage was 5.7 ± 1.8 mg/kg every 12 hours (range 3.5–8 mg/kg every 12 hours, median 5.95 mg/kg). Following administration of PB every 8 hours, the $t_{1/2}$ increased to >20 hours (mean 53.3 ± 33.1 hours) and 9 dogs (90%) experienced an improvement in epileptic seizure control, with seizure freedom (for a period of at least 3 times the longest interictal interval prior to the treatment modification) in 8/9 dogs.[36]

Dogs are considered resistant to PB treatment when excessive epileptic seizure activity persists despite serum PB concentrations in the high reference range (30–34 μg/mL) for an adequate amount of time, or when unacceptable AEs (such as sedation, ataxia, polyphagia with weight gain, and polydipsia/polyuria) persist after achievement of steady state (see Chapter 9 for further details on the definition of therapeutic success and

drug resistance). In these dogs, if the $t_{1/2}$ of PB is > 20–24 hours (and therefore administration every 8 hours is unlikely to improve seizure control), a second ASD should be initiated in combination with PB. Criteria for adjunctive ASD selection are described in Chapter 9. The PB dose can be decreased (particularly in dogs with unacceptable AEs) as soon as serum reference concentrations of the second ASD and/or adequate seizure control have been achieved. Potassium bromide (see Chapter 11) has commonly been used as an add-on ASD in PB-resistant dogs with IE. However, this combination is not always well tolerated. Approximately 50% to 70% of PB-resistant dogs administered KBr as an adjunctive therapy experience a reduction of at least 50% in seizure frequency and a decrease in seizure severity and intensity.[37,38] Discontinuation of PB or a reduction in its dosage has been reported in 53% of dogs after the addition of KBr, with maintained or improved seizure control.[38] Levetiracetam has been reported to be efficacious as an adjunctive treatment in PB-resistant dogs with IE (the details of the relevant published studies are described in Chapter 12). Other ASDs (see chapters 13 to 15) may be used as adjunctive treatments to PB or to PB and KBr. Pharmacokinetic interactions between PB and other ASDs need to be considered when choosing the drug and its dosage.

Phenobarbital efficacy in cats

Less data is available on the efficacy of PB treatment in epileptic cats than in dogs and the available studies are predominantly retrospective with relatively small sample sizes. A systematic review of the efficacy and safety of ASDs in feline epilepsy concluded that PB might currently be considered the first-line ASD for cats with epilepsy.[3]

A retrospective study including 36 cats with suspected IE reported that 43% of cats were seizure free, 21% of cats were well controlled (experiencing 1–5 seizures/year), 7% were moderately controlled (experiencing 6–10 seizures/year) and 29% were poorly controlled (experiencing more than 10 seizures/year) in the fifth and last year of the study.[39] The mean proportions of seizure-free, well-controlled, moderately controlled and poorly controlled cats in a particular year of treatment (during the 5-year study period) were 43% (range, 0–67%), 31% (range, 9–100%), 10% (range, 3–14%) and 39% (range, 29–64%), respectively. Cats were administered PB every 12 hours, at an initial mean dosage of 3.2 mg/kg/day (range, 1.8–10 mg/kg/day). The dose remained unchanged

during the study period in 6 cats (16.7%), increased in 10 cats (27.8%) and decreased in 8 cats (22.2%). Twelve cats (33%) had their dose changed multiple times. The mean PB dose at the final evaluation was 6.76 mg/kg/day) (range 1–20 mg/kg/day). In 4 cats (8.3%), other ASDs such as diazepam, gabapentin or LEV were added to PB. There was no significant difference in the mean serum PB concentrations between seizure-free cats (27.9 μg/mL, range 12–52 μg/mL) and non-seizure-free cats (31.2 μg/mL; range, 11–73 μg/mL). A shorter time interval between epileptic seizure onset and PB treatment initiation was associated with a lower number of seizures in the second year of treatment and a more rapid achievement of seizure freedom for 1 year or longer. When a seizure-free status was achieved for more than 1 year, the cats remained seizure free for as long as the PB treatment was continued. When PB dosage was reduced or discontinued after 1 seizure-free year, epileptic seizures recurred in 6 out of 8 cats. Quality of life (QoL) was assessed subjectively by the cats' owners as being good for 26 cats, impaired for 9 cats and bad for 1 cat.[39]

A multicenter retrospective study including 30 epileptic cats (11 with structural epilepsy and 19 with suspected IE) reported that seizure control was achieved in 93% (28/30) of cats with a serum PB concentration between 15 and 45 μg/mL.[21] In the remaining 2 cats (1 with structural and 1 with suspected IE), seizure control was achieved but at serum PB concentrations below 15 μg/mL. Thirteen cats (43%) became seizure free after starting PB treatment. The median PB dosage was 4.0 mg/kg/day (range, 1.5 to 8.6 mg/kg/day) and the median follow-up duration after PB treatment initiation was 14 months (range, 0.63 to 91 months) for all cats.[21]

A prospective, randomized, open-label clinical trial compared the efficacy and tolerability of PB (3–5 mg/kg every 12 hours) with those of LEV (20–25 mg/kg every 8 hours) in cats with suspected feline audiogenic reflex seizures experiencing both generalized tonic-clonic and myoclonic seizures.[40] A reduction of ≥ 50% in the number of myoclonic seizure days was observed in 100% of cats in the LEV group and in 3% of cats in the PB group, therefore suggesting that LEV is efficacious and superior to PB in the treatment of feline audiogenic reflex seizures.[40]

In cats refractory to PB, LEV (see Chapter 12) may represent a safe and effective adjunctive treatment option.

CLINICAL USE

Phenobarbital should be used in epileptic dogs and cats with normal hepatic function. Hematology and comprehensive serum biochemistry analyses and a bile acid stimulation test should be performed before starting PB treatment. The initial recommended oral dosage for maintenance treatment is:

- 2.5–3 mg/kg every 12 hours in dogs[6]
- 1.5–2.5 mg/kg every 12 hours in cats[21]

The PB oral dosage is subsequently tailored to the individual patient's needs based on an accurate epileptic seizure diary, serum PB concentration monitoring, as well as occurrence and degree of AEs.[6,7,21] Identifying the lowest efficacious PB dosage could help optimize the patient's QoL. The outcome measures to assess an ASD's therapeutic success are presented in Chapter 9 and briefly described in Fig. 10.2. As PB is a potent inducer of hepatic microsomal cytochrome P450 enzyme activity in dogs, it is common for serum PB concentrations to decrease over time when the same dose is administered, and this can compromise epileptic seizure control. Increasing the PB oral dosage may be required to maintain the desired serum PB concentration and associated epileptic seizure control during long-term treatment. Formulas that can aid when modulating PB treatment are included in Box 10.1.

There are emergency situations, such as cluster seizures, status epilepticus or development of unacceptably high seizure frequency, when a steady-state PB concentration needs to be achieved as rapidly as possible to control epileptic seizure activity. In such situations, PB can be administered in multiple 3–5 mg/kg doses in 24–48 hours to achieve a total loading dose of 15–24 mg/kg (orally, IV or IM). After loading is completed, PB is continued on a maintenance dosage. Loading should be performed in the hospitalized patient as it is often associated with dose-related AEs. After loading is completed, PB is continued on a maintenance dosage. Measuring a postloading serum PB concentration (on a sample collected just before the next scheduled PB administration and 12–24 hours after loading is completed) allows determination of the serum PB concentration achieved. This information combined with epileptic seizure occurrence can help to decide if and how the maintenance dosage should be modulated during the

initial weeks of treatment (see Fig. 10.2). A “mini” PB loading dose can be administered to patients already receiving a PB maintenance dosage that may require a rapid increase in serum PB concentrations due to poor epileptic seizure control. The PB “mini” loading dose can be calculated if the current serum PB concentration is known (see Box 10.1).

The use of PB as an adjunctive or replacement treatment in IMP-resistant dogs with IE is described in Chapter 13. The same considerations on serum PB concentration monitoring and treatment modulation discussed here apply to PB use in IMP-resistant dogs.

Recommendations for serum PB concentration monitoring are detailed in Box 10.2. Young/immature animals, kittens in particular, may metabolize PB faster than in adults. These young patients require closer monitoring of serum PB concentrations and dose adjustment as they grow into adulthood.[41]

A prospective study of 33 dogs receiving PB 0.5–5 mg/kg (mean 2.9 ± 1.2 mg/kg) every 12 hours for at least 3 weeks (median 19 months) investigated the effect of time of blood sampling on serum PB concentrations. The mean trough (C_{min}) serum PB concentration was 20.5 ± 7.1 μg/mL and the mean 3- and 6-hour serum PB concentrations were 23 ± 8.1 μg/mL and 22 ± 7.5 μg/mL, respectively.[42] Significant differences were not detected between the mean serum PB concentrations when evaluated at trough, 3 hours, and 6 hours for all dogs. However, 9% (3/33) of dogs had a >30% change in serum PB concentrations at these 3 time points.[42] Three more recent studies have reported that significant differences between peak and trough serum PB concentrations can occur in some dogs treated with PB and this may have clinically relevant consequences, including treatment failure.[32,36,43] No studies have evaluated the effect of timing of blood sampling on serum PB concentrations in cats. However, it has been recommended to monitor serum PB concentrations on a trough blood sample.[41] Consistency of time of blood sampling could help interpret serial serum PB concentration results in conjunction with details on epileptic seizure and AE occurrence over time. This information is relevant to optimize and individualize PB treatment.

Testing both peak (4 hours after oral PB administration) and trough (12 hours after oral PB administration) serum PB concentrations is recommended in dogs (on oral PB every 12 hours) with treatment failure, to investigate whether this is due to an excessively short PB $t_{1/2}$ (see Box 10.1

for $t_{1/2}$ calculation). This can help in the management of dogs with unsatisfactory epileptic seizure control despite serum PB concentrations within the reference range and those with persistent AEs that may be associated with excessive fluctuations of serum PB concentrations in the 24-hour period.[36]

Reference serum PB concentrations in dogs are between 15 μg/mL and 35 μg/mL (65–150 mmol/L). A target serum PB concentration of 25−30 μg/mL has been recommended for optimal seizure control in dogs with IE.[6] A trough (12 hours after oral administration) serum PB concentration higher than 35 mg/L has been associated with an increased risk of hepatotoxicity in dogs.[46,47] Information on the serum PB concentration reference range in cats is limited; a target range between 15–30 μg/mL (65–129 mmol/L) has been suggested.[21,48]

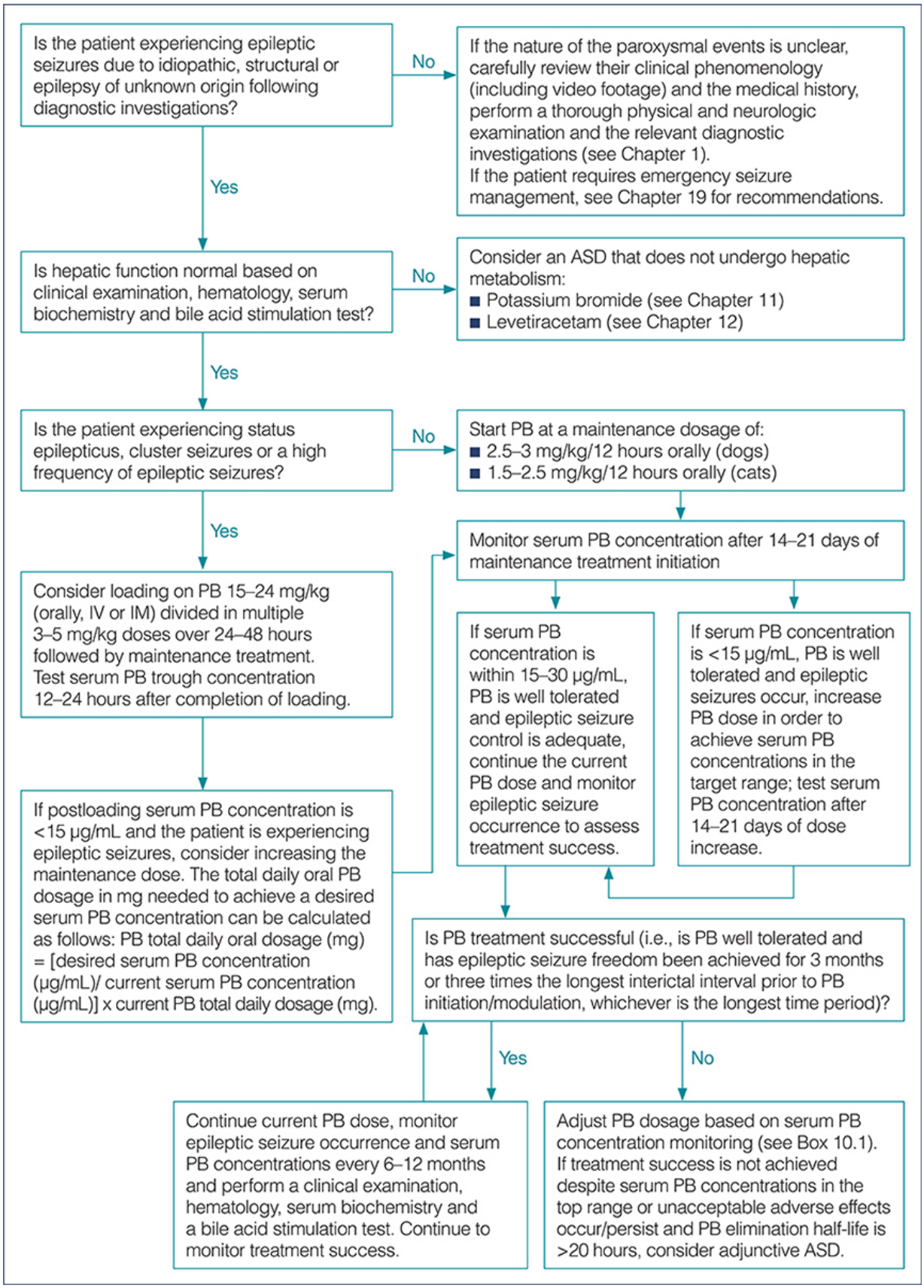

Is the patient experiencing epileptic seizures due to idiopathic, structural or epilepsy of unknown origin following diagnostic investigations?
No
If the nature of the paroxysmal events is unclear, carefully review their clinical phenomenology (including video footage) and the medical history, perform a thorough physical and neurologic examination and the relevant diagnostic investigations (see Chapter 1).
If the patient requires emergency seizure management, see Chapter 19 for recommendations.
Yes
Is hepatic function normal based on clinical examination, hematology, serum biochemistry and bile acid stimulation test?
No
Consider an ASD that does not undergo hepatic metabolism:
Potassium bromide (see Chapter 11)
Levetiracetam (see Chapter 12)
Yes
Is the patient experiencing status epilepticus, cluster seizures or a high frequency of epileptic seizures?
No
Start PB at a maintenance dosage of:
2.5–3 mg/kg/12 hours orally (dogs)
1.5–2.5 mg/kg/12 hours orally (cats)
Yes
Monitor serum PB concentration after 14–21 days of maintenance treatment initiation
Consider loading on PB 15–24 mg/kg (orally, IV or IM) divided in multiple 3–5 mg/kg doses over 24–48 hours followed by maintenance treatment. Test serum PB trough concentration 12–24 hours after completion of loading.
If serum PB concentration is within 15–30 µg/mL, PB is well tolerated and epileptic seizure control is adequate, continue the current PB dose and monitor epileptic seizure occurrence to assess treatment success.
If serum PB concentration is <15 µg/mL, PB is well tolerated and epileptic seizures occur, increase PB dose in order to achieve serum PB concentrations in the target range; test serum PB concentration after 14–21 days of dose increase.
If postloading serum PB concentration is <15 µg/mL and the patient is experiencing epileptic seizures, consider increasing the maintenance dose. The total daily oral PB dosage in mg needed to achieve a desired serum PB concentration can be calculated as follows: PB total daily oral dosage (mg) = [desired serum PB concentration (µg/mL)/ current serum PB concentration (µg/mL)] x current PB total daily dosage (mg).
Is PB treatment successful (i.e., is PB well tolerated and has epileptic seizure freedom been achieved for 3 months or three times the longest interictal interval prior to PB initiation/modulation, whichever is the longest time period)?
Yes
No
Continue current PB dose, monitor epileptic seizure occurrence and serum PB concentrations every 6–12 months and perform a clinical examination, hematology, serum biochemistry and a bile acid stimulation test. Continue to monitor treatment success.
Adjust PB dosage based on serum PB concentration monitoring (see Box 10.1). If treatment success is not achieved despite serum PB concentrations in the top range or unacceptable adverse effects occur/persist and PB elimination half-life is >20 hours, consider adjunctive ASD.

FIGURE 10.2. Decision making on phenobarbital (PB) treatment for antiseizure drug-naïve patients.

BOX 10.1. Useful formulas to be used when initiating or modulating phenobarbital (PB) oral treatment.

Conversion of serum PB concentration from mmol/L to mg/L (= µg/mL)	Serum PB concentration mg/L (= µg/mL) = Serum PB concentration (mmol/L) × 0.232
Conversion of serum PB concentration from mg/L (= µg/mL) to mmol/L	Serum PB concentration mmol/L = Serum PB concentration mg/L (= µg/mL) × 4.31
PB total daily oral dosage in mg needed to achieve a desired serum PB concentration (the calculated daily dosage can be divided in 2 administrations every 12 hours)	$\frac{\text{Desired serum PB serum concentration (µg/mL)}}{\text{Actual serum PB concentration (µg/mL)}} \times \text{actual PB total daily dosage in mg}$
Calculation of the PB elimination half-life	Elimination half-life = 0.693/Kel $\text{Kel} = \frac{\ln \frac{\text{peak serum PB concentration (µg/mL)}}{\text{trough serum PB concentration (µg/mL)}}}{(T2-T1)}$ Kel = elimination rate constant ln = natural logarithm T1 = time interval in hours from oral PB administration and the collection of the peak serum sample (4 h) T2 = time interval in hours from oral PB administration and the collection of the trough serum sample (12 h)
Calculation of the PB loading dose (in mg/kg) in PB-naïve dogs	PB total loading dose (mg/kg) = desired serum PB concentration (µg/mL) × 0.77
Calculation of the PB mini loading dose (in mg/kg) in dogs on PB treatment with recent serum PB concentration testing	PB mini-loading dose (mg/kg) = [desired serum PB concentration (µg/mL) − actual serum PB concentration(µg/mL)] × 0.77

In human medicine, loss of seizure control following switching between bioequivalent brand name and generic ASD products is a subject of concern among clinicians. In veterinary medicine the information available is limited to one study comparing the bioavailability of PB after a single-dose administration (8 mg/kg) of Luminal® vet versus Phenoleptil® with a crossover design in 8 healthy Beagle dogs.[49] Overall, the two formulations did not produce significant differences in PK parameters when mean group parameters were compared. However, 1 dog showed noticeably lower

serum PB concentrations after being administered Phenoleptil® than after receiving Luminal® vet.[49] It is currently unknown if switching PB brands can affect epileptic seizure control. Therefore, it may be prudent to test serum PB concentrations before and 14–20 days after a brand change.

In recent years in-house serum PB concentration testing has become increasingly common with the use of an in-house analyzer (Catalyst Dx®, Idexx). While this testing system has the advantage of being time- and cost-effective, a recent clinical research abstract revealed that serum PB concentrations in the same samples from dogs with IE were significantly higher when analysed with the Catalyst Dx® (Idexx) than with the laboratory system Immulite 2000® (Siemens).[50] This study showed the importance of considering which analytic instrument is used when interpreting serum PB concentrations results.[50]

BOX 10.2. Recommendations on monitoring of serum phenobarbital (PB) concentration.

Sample collection and handling:

- Collecting a trough sample (i.e., just before the next PB administration) enables assessment of the lowest serum PB concentration (C_{min}) in the 24-hour period and may facilitate comparison of serial testing results in both dogs and cats. This is particularly important in dogs receiving a PB dose greater than 5 mg/kg every 12 hours as trough serum PB concentrations have been shown to be significantly lower than non-trough concentrations.[43] When trough sample collection is not practical in animals with satisfactory epileptic seizure control, the time of the last PB administration and time of blood sampling could be recorded in the medical record to facilitate results interpretation and comparison over time.
- Testing both peak (4 hours after oral PB administration in dogs on every-12-hour dosing) and trough serum PB concentrations is recommended in dogs with treatment failure.
- Serum PB concentrations should be tested on a **fasting sample**. Serum PB concentrations can be falsely elevated in dogs with serum triglyceride concentrations >11.3 mmol/L.[44]
- **Plain serum tubes** should be used. Serum separation collection tubes containing a clot activator can falsely decrease serum PB concentration due to binding of PB.[45]

When serum PB concentrations should be tested:

- 2–3 weeks (14–20 days) after initiation of treatment at maintenance dosage or after a dosage change, as this is the expected time of steady state achievement.
- 12–24 hours after completion of PB loading or "mini" loading.
- 3 months after PB treatment initiation in patients with satisfactory epileptic seizure control, and subsequently every 6–12 months when therapeutic success is maintained; hematology and serum biochemistry (including fasting serum triglycerides concentration), bile acid stimulation test and urinalysis should also be performed every 6–12 months.
- When therapeutic success is not achieved or maintained (therapeutic success = PB is well tolerated and epileptic seizure freedom or a reduction of at least 50% in frequency has been achieved for 3 months or 3 times the longest interictal interval prior to PB initiation/dose modulation, whichever is the longest time period).
- When PB toxicity is suspected (test both peak and trough serum PB concentrations).

- When there are concerns with the pet carer's compliance with PB administration.
- Anytime a patient is administered medications or has a concurrent condition that can interfere with PB pharmacokinetics.
- Immediately before and 2–3 weeks after switching PB brands.

The changes in laboratory parameters that may occur in dogs treated chronically with PB are presented in the next section.

■ Elevation in hepatic enzyme activity

Elevation of the activity of serum alkaline phosphatase (ALP), alanine transaminase (ALT) and possibly γ-glutamyltransferase (GGT) is commonly detected in PB-treated dogs with no clinical signs of hepatic disease.[47,51,52] The challenge for the clinician is to establish if these laboratory changes are due to hepatic enzyme induction or subclinical hepatic injury. A comprehensive serum biochemistry profile including hepatic enzyme activity, total bilirubin, albumin, blood urea nitrogen, glucose, and cholesterol should be performed periodically to monitor hepatic function in dogs on chronic PB treatment (see Box 10.2). Ideally, pre- and postprandial bile acids should also be assessed. In case of abnormalities, abdominal ultrasonography and, if indicated, histology can help investigate further possible hepatic disease. A prospective study assessed the impact of long-term PB administration on serum hepatic enzyme activity and other parameters of hepatic function in 12 healthy dogs.[47] After 29 weeks of PB administration at 5 mg/kg every 12 hours, there were no clinical signs of hepatic dysfunction apart from mild liver enlargement on repeated physical examinations in 5 of the 12 dogs. Abdominal radiographs revealed hepatic enlargement in 8 dogs. Serum PB trough concentrations were within 20–40 μg/mL. Serum ALP and ALT increased significantly, GGT increased transiently, and albumin decreased transiently during the study period. There were no significant changes in aspartate transaminase, bilirubin, and fasting bile acid levels. Ultrasonographic examinations revealed no changes in liver echogenicity or architecture. No evidence of morphological liver damage was observed histopathologically. The authors of this study suggested that the increases in serum ALP, ALT, and GGT may reflect enzyme induction rather than hepatic injury during long-term PB treatment in dogs.[47] However, another study could not find evidence of PB-induced hepatic ALP and ALT enzyme activities in liver homogenates of 12 clinically healthy PB-treated epileptic

dogs when compared with controls.[51] The total daily PB dosage ranged from 2.1 to 12.9 mg/kg/day (median 5 mg/kg/day) and the total duration of PB treatment ranged from 4 months to 6.5 years (median 1.7 years). Serum PB concentrations ranged from 9.7 to 44.2 µg/mL (median 22.8 µg/mL). Of the 12 PB-treated dogs, 11 (92%) had serum ALP activities greater than two times the upper limit of the normal range and 7 of 12 (58%) had serum ALT activities greater than the upper limit of the normal range (of these, 3 had serum ALT activities greater than two times the upper limit of the normal range). Histopathological examination of liver biopsies revealed more severe and frequent abnormalities in PB-treated dogs than in controls. However, similar types of abnormalities were found in both groups. Only duration of treatment was significantly associated with overall histopathological score. No associations were identified between the scores of any histopathological parameters and the PB dose, serum PB concentrations, serum ALT or ALP activities, or liver homogenate ALT or ALP activities. The authors concluded that hepatic enzyme changes are likely not due to induction and may reflect subclinical hepatic injury.[51]

Another study evaluated serum samples from 95 dogs treated with PB for at least 2 weeks at dosages ranging from 1–5 mg/kg every 12 hours; 38/95 dogs (40%) had abnormally high activities of one or more hepatic enzymes.[52] In this study the higher the serum PB concentration, the more significant were the increases in serum ALP, ALT, GGT and glutamate dehydrogenase. In the same study, PB treatment duration was also associated with increased ALP and ALT activities.[52]

Elevation of ALP or other hepatic enzymes seems rare in cats treated with PB.[41,48] Hepatic enzyme induction does not appear to occur in the cat possibly owing to low levels of CYP2C.[21]

■ Hypercholesterolemia

Hypercholesterolemia was observed in dogs administered PB 5 mg/kg every 12 hours for 27 weeks. It resolved 3–5 weeks after PB treatment discontinuation.[53]

■ Fasting hypertriglyceridemia

Fasting hypertriglyceridemia was identified in 33% of epileptic dogs treated with PB monotherapy or PB in combination with KBr.[44]

■ **Alterations of thyroid function testing**

Long-term PB treatment can result in decreased total thyroxine (TT4) and free T4 (fT4) serum concentrations with a normal to slightly increased thyroid-stimulating hormone (TSH) serum concentration in clinically normal euthyroid dogs.[53–55] In 12 healthy dogs treated with oral PB at a dosage of 4.4–6.6 mg/kg every 12 hours for 27 weeks, serum T4 and fT4 concentrations were significantly lower and TSH concentrations were significantly higher compared to pretreatment. It has been suggested that these changes are caused by PB-enhanced metabolic clearance of T4.[53]

ADVERSE EFFECTS AND DRUG INTERACTIONS

Both type A (dose-dependent, predictable, pharmacology-related) and type B (idiosyncratic, unpredictable, unrelated to dosage) AEs have been reported with PB use. A more detailed discussion of the classification of AEs is included in Chapter 9.

When PB needs to be discontinued due to severe AEs, an alternative ASD is required to maintain/achieve epileptic seizure control in epileptic patients. The alternative ASD's PK profile has to be considered when selecting the drug and its dosage (see Chapter 9 as well as ASD-specific chapters). Loading of the new ASD may be required, particularly following rapid PB discontinuation.

A systematic review and meta-analysis of the tolerability and safety of ASDs in dogs compared ASDs in terms of frequency and prevalence of AEs. Direct comparisons suggested that LEV and IMP might have a better safety profile than PB, which has a better safety profile than KBr. However, none of these comparisons showed a statistically significant difference.[2]

Hepatotoxicity in dogs

The clinical presentation of PB-associated hepatotoxicity does not follow a classic idiosyncratic or dose-dependent pattern.[56] In a retrospective study of 18 dogs that developed hepatic disease (mostly cirrhosis) following prolonged PB treatment, the clinical signs included sedation and ataxia in

all dogs, anorexia in 5 dogs, ascites in 5 dogs, icterus in 3 dogs, and coagulopathy in 2 dogs. Hypoalbuminemia was detected in 78% of dogs, and elevations in ALP, ALT, fasting bile acids, and total bilirubin were observed in 100%, 83%, 80% and 50% of the tested dogs, respectively.[46] The average duration of PB treatment was 39 months (range, 5 to 82 months) and 72% of dogs had a serum PB trough concentration greater than 40 mg/mL.

Hepatotoxicity may be reversible if it is detected early and PB is adequately decreased or discontinued. However, if detected too late, hepatic damage can be irreversible and ultimately fatal.[46] Regular monitoring of hepatic function, including pre- and postprandial bile acids (see previous discussion on hepatic enzyme activity), as well as serum PB concentrations (see Box 10.2) is recommended to minimize the risk of PB-induced hepatotoxicity in dogs on long-term PB therapy. If the serum PB concentration is >35 mg/mL, the PB dose needs to be decreased and, depending on epileptic seizure control, it may be necessary to initiate an additional ASD (preferably one that is not hepatically metabolized).

It has been suggested that PB-induced hepatotoxicity could be related to cytochrome P450 induction by PB, with secondary bioactivation of dietary or environmental compounds.[56] In cats, PB does not cause cytochrome P450 induction and hepatotoxicity has not been reported following long-term PB treatment.

Type A adverse effects

The most commonly reported type A AEs of PB include sedation, ataxia, polydipsia/polyuria and polyphagia.[2,3,6] These AEs are dose dependent, usually occur in the initial 2–4 weeks of treatment or after a dosage increment and subside afterwards due to development of PK and pharmacodynamic tolerance in both dogs and cats.

A prospective, observational cohort study with a 3-year follow-up since initiation of PB monotherapy in 30 dogs with IE showed that 4/30 dogs (13%) experienced permanent polyphagia and polydipsia. In 16/30 dogs (53%), sedation, ataxia, polyphagia, polydipsia/polyuria were transient, resolving after achievement of steady-state concentrations. No dogs developed AEs severe enough to warrant PB discontinuation.[34]

A recent retrospective study investigated the prevalence, clinical characteristics and risk factors for the development of AEs in 77 PB-treated

epileptic cats (58 cats with IE and 19 cats with structural epilepsy).[57] The median initial dosage of PB was 2 mg/kg every 12 hours (range 0.6–4.4 mg/kg every 12 hours). The median duration of PB treatment was 22 months (range 1.5–108 months). Thirty-six cats (47%) received an adjunctive ASD (LEV in 34 cats, IMP in 1 cat and zonisamide [ZNS] in 1 cat). The median follow-up time was 24 months (range 1.5–108 months). Thirty-six (47%) cats developed one or more of the following AEs: sedation (89%), ataxia (53%), polyphagia (22%), polydipsia (6%), polyuria (6%), and anorexia (6%). These AEs were transient in 20 cats, 13 of which developed AEs in the first 4 weeks of treatment and 7 developed transient AEs during ongoing PB treatment. Eight cats showed persistent AEs. The median PB dosage was 3 mg/kg every 12 hours (range 1.25–5.0 mg/kg) at the time of AE onset in the cats that developed AEs and 2.0 mg/kg every 12 hours (range 0.6–3.5 mg/kg) during the first month of treatment in the cats that did not develop AEs. The median serum PB concentration was 36 µg/mL (range 10.3–70 µg/mL) in that cats that experienced AEs and 19.3 µg/mL (range 6–40 µg/mL) in cats that did not experience AEs. The difference in PB dosage and serum concentration between the two groups was statistically significant. A higher PB starting dosage and use of a second ASD were significant predictors of the occurrence of AEs.[57]

Transient and self-limiting hyperexcitability, hyperactivity and restlessness are of rare occurrence in dogs. Hyperactivity may resolve following increments in serum PB concentration.[31]

Type B adverse effects

Various type B AEs have been reported in dogs and cats treated with PB. However, a cause–effect relationship has not always been demonstrated. These AEs generally resolve following PB discontinuation. In cats, they appear particularly rare. In a retrospective study on PB AEs in feline epilepsy, only 1 of the 77 cats included had a type B AE.[57]

Hematological abnormalities (neutropenia, anemia, thrombocytopenia)

The reported prevalence of PB-associated hematological abnormalities in dogs ranges from 4.2%[58] to 22%.[59] In a large multicenter retrospective study,[58] 16/1766 (4.2%) dogs were identified to have PB-associated hematological abnormalities. Of these, 2 dogs had neutropenia, 3 had

anemia and thrombocytopenia, 2 had anemia and neutropenia, and the remaining 9 had pancytopenia. Phenobarbital was administered at a median dose of 3 mg/kg every 12 hours for a median period of 100 days and the median serum PB concentration was 19 µg/mL. All dogs were referred for nonspecific clinical signs including lethargy (16), anorexia/inappetence (6), pale mucous membranes (1), tachycardia (1), pyrexia (3), and petechiae/ecchymosis (1). Signs of regenerative anemia were present in 8 dogs. A bone marrow evaluation (cytology and core biopsy) was performed in 5 dogs with pancytopenia. The bone marrow aspirates were hypercellular, with active production of the erythroid, myeloid and thrombocytoid lineages and lower numbers of mature forms than expected. Phenobarbital was discontinued after diagnosis and ASDs were used. The median time to resolution of PB-associated hematological abnormalities was 17 days (range 2–110 days).[58] A case of severe PB-induced neutropenia and granulocytic hypoplasia was recently reported in a cat after 2 months of treatment with oral PB at 2.6 mg/kg every 12 hours. The cat's serum PB concentration was 45 µg/mL. Bone marrow cytology and a core biopsy showed severe granulocytic hypoplasia suggestive of neutrophil aplasia or immune-mediated destruction of neutrophil precursors. This resolved following PB discontinuation.[57] Severe pancytopenia, hyporexia and fever that required hospitalization, PB discontinuation and broad-spectrum antibiotic coverage have been reported in a cat with IE that had received PB at 3 mg/kg every 12 hours for 6 months.[60]

Cutaneous reactions

Cutaneous reactions can sometimes occur in dogs treated with PB. A study on cutaneous AEs in epileptic dogs treated with ASDs reported dermatological signs in 18% (17/93) of dogs treated with PB monotherapy during the 6-year retrospective period and in 11% (15/137) of dogs during the subsequent 2-year prospective period.[61] However, based on the Naranjo index (a scale to estimate the probability of adverse drug reactions based on various criteria), only 2 of the retrospective cases were classified as probably suffering from ASD hypersensitivity. Of the 15 dogs in the prospective part of the study, 12 dogs received PB monotherapy and 3 dogs were treated with PB in combination with other ASDs (PB/LEV, PB/KBr, PB/LEV/KBr). Based on the Naranjo index, the cutaneous signs in these 15 dogs were classified as probably due to ASD hypersensitivity in 6 (40%)

dogs (all treated with PB monotherapy), possibly due to ASD therapy in 8 (53.3%) dogs and doubtful in 1 (6.7%) dog. One of these 15 dogs developed dermatological signs shortly after initiation of LEV and the other 14 dogs within days to several months after initiation of PB. Nine of the 15 dogs underwent a complete dermatological examination performed by a dermatology specialist, the other 6 dogs were examined by other veterinarians and underwent limited dermatological assessment. The cutaneous reactions were considered severe in 4 dogs (extensive erosions or epidermal necrosis leading to skin detachment), moderate in 8 dogs (papules, pustules, erythema, and crusty lesions) and mild in 3 dogs (pruritus and/or alopecia). The periocular region, the mucocutaneous boundaries, the inguinal region, and the limbs appeared particularly affected. Antiseizure drug therapy was discontinued in 7 dogs (6 on PB and 1 on LEV). However, in 1 dog PB had to be reinstituted due to severe epileptic seizures despite KBr loading. Cutaneous signs resolved completely in 5 dogs within approximately 2 weeks and improved significantly in 1 dog.[61] Another retrospective study reported more severe dermatological signs (i.e., histologically confirmed superficial necrolytic dermatitis).[62] These cutaneous lesions developed only after prolonged PB treatment (median 6 years, range 1.7–11 years) and were associated with hepatopathy. Therefore, they may have not been the result of an idiosyncratic drug toxicity. In the 11 epileptic dogs included in this study, the mean maximum PB daily dosage was 12.4 ± 5.7 mg/kg (range, 3.8–19.8 mg/kg) and the mean trough serum PB concentration was 43.5 ± 15.1 µg/mL (range, 22.8–66 µg/mL). In 6 of the 11 dogs, PB had been discontinued a median of 4 weeks (range 2–72 weeks) before the onset of the cutaneous lesions because of persistent increases in ALT activity. The dermatological signs included alopecia, erythema, crusty lesions, skin exudation and ulceration, and most frequently affected the ventral aspect of the abdomen, the mucocutaneous junctions and the distal portions of the extremities. The footpads showed crusty, hyperkeratotic lesions with fissures.[62]

Pancreatitis

Pancreatitis has been reported as a possible AE in dogs treated with PB, with a prevalence of 0.3% in dogs on PB monotherapy and at least 10% in dogs treated with both PB and KBr.[63] A cause–effect relationship has not

been proven and it has been suggested that polyphagia, a type A AE of PB and/or KBr, could lead to dietary indiscretion and subsequently pancreatitis. Hypertriglyceridemia has been considered a possible pathophysiological mechanism for PB-induced pancreatitis. Fasting hypertriglyceridemia has been associated with high postprandial serum triglyceride concentrations, which is considered a risk factor for pancreatitis. Fasting hypertriglyceridemia was identified in 33% (19/57) of epileptic dogs treated with PB alone or in combination with KBr for 3 months or longer.[44] In this study, 16% of dogs had a previous history of pancreatitis, 27% of dogs in which canine pancreatic lipase immunoreactivity was measured had high values and 63% of dogs were overweight. It was unclear if fasting hypertriglyceridemia was related to an overweight body condition, an idiosyncratic reaction to PB or multifactorial. Feeding a low-fat diet, maintaining a healthy body condition score and monitoring fasting serum triglyceride concentrations has been recommended to reduce the risk of pancreatitis in epileptic dogs treated with PB+/-KBr.[44]

Dyskinesia

Dyskinesia characterized by persistent muscle twitching and anxiousness has been reported in an epileptic dog treated with PB for 8 weeks.[64] The PB dosage at the time of dyskinesia onset was 3.8 mg/kg every 12 hours orally. On clinical examination, the dog had fine intermittent contractions of the facial muscles and severe intermittent contractions of the cervical and shoulder muscles. An electroencephalogram recorded while the dog displayed muscle twitching did not reveal epileptic activity. The dyskinesia and anxiousness significantly improved when the PB oral dose was reduced to 0.76 mg/kg every 12 hours. After an episode of status epilepticus, PB was increased to 1.5 mg/kg orally every 12 hours and the muscle twitching increased again. Subsequently, following an increase in the dose of felbamate, PB was reduced and discontinued. No muscle twitching has been observed during the year since PB was discontinued.[64]

Hypalbuminemia

Hypalbuminemia in the absence of hepatic dysfunction or protein-losing nephropathy has been reported in a dog administered a standard maintenance dose of PB. The patient developed edema and required plasma

transfusion. The albumin returned to a normal concentration after PB discontinuation.[65]

Addisonian crisis

An Addisonian crisis has been reported in 1 epileptic dog following 3 weeks of PB treatment (2.3 mg/kg every 12 hours). The authors suggested that PB may have a role in the development of Addisonian crisis in dogs with pre-existent borderline hypoadrenocorticism by accelerating the metabolism of endogenous corticosteroids.[66]

Generalized lymphadenomegaly or "pseudolymphoma"

Generalized lymphadenomegaly or "pseudolymphoma" (with or without concurrent lethargy, hyperthermia, anorexia, cutaneous and oral mucocutaneous erythema, erosions, ulcerations and crusting) has been reported infrequently in a few cats.[67,68] In a case report, lymphadenomegaly developed 3–4 weeks after initiation of PB treatment at a standard dosage. The lymph node enlargement resolved 10 to 14 days after PB discontinuation and no other cause of lymphadenomegaly was identified.[68]

Pruritus

One study reported generalized pruritus and distal limb edema in a cat 6 weeks after initiation of PB, and transient and dexamethasone-responsive facial pruritus in another cat 1 week after initiation of PB.[41] Both cats were administered PB at 2.1 mg/kg every 12 hours. A direct cause–effect relationship between PB and the suspected type B AEs was not proven. Phenobarbital was not discontinued in the cat with transient and dexamethasone-responsive facial pruritus. The clinical signs resolved in the cat with generalized pruritus within 2 weeks of PB discontinuation.[41]

Hyperthermia

Hyperthermia has been reported in a cat 1 week after initiation of oral PB at 1.6 mg/kg every 12 hours. No other causes of hyperthermia were detected following extensive investigations. Hyperthermia resolved 24 hours following discontinuation of PB.[69]

Drug interactions

Coadministration of PB with other drugs (including other ASDs) can result in PK interactions with clinical relevance (e.g., compromised efficacy or toxicity). Box 10.3 provides details on the drugs that can be affected by PB or that can affect PB PK. Further details on the pharmacological interactions with other ASDs can be found in the relevant ASD specific chapters.

BOX 10.3. Drugs with known pharmacological interaction with phenobarbital (PB) and possible clinical implications.

Benzodiazepines	Oral administration of PB for 1 month or longer resulted in increased clearance and decreased plasma concentrations of benzodiazepines, most likely secondary to cytochrome (CYP) P450 enzyme induction in dogs.[70,71] Following administration of 2 mg/kg of diazepam rectally, significant decreases in the maximum total benzodiazepine (diazepam, nordiazepam and oxazepam) plasma concentration, area under the curve and mean residence time were observed after PB treatment (2.5 mg/kg every 12 hours for 30 days) when compared with the same values prior to PB treatment. The area under the curve was also significantly decreased after PB treatment in dogs administered 2 mg/kg of diazepam IV.[71] Higher doses of diazepam rectally or IV may be required in the emergency management of epileptic seizures in dogs treated with PB for 1 month or longer. (See Chapter 19.)
Levetiracetam (LEV)	Administration of PB at 2.0–3.3 mg/kg every 12 hours orally for 21 days in 6 healthy Beagles significantly altered the PK of LEV.[72] Concurrent administration of PB resulted in a decreased C_{max}, a decreased $t_{1/2}$ and an increased oral clearance of LEV. It was suggested that the increased disposition of LEV is caused by PB induction of oxidative enzymes.[72] (See Chapter 12.)
Zonisamide (ZNS)	Treatment with PB at 5 mg/kg every 12 hours for 30–35 days decreased the C_{max}, $t_{1/2}$ and bioavailability of ZNS and increased its clearance. Hence, an initial higher ZNS dosage (e.g., 10 mg/kg every 12 h) is required when administered concurrently with PB.[73] (See Chapter 14.)
Topiramate	Phenobarbital is a known inducer of CYP3A4, the major enzyme responsible for topiramate metabolism. In dogs treated with PB, IV and oral administration of topiramate resulted in a 5.6-fold greater clearance and an approximate 4-fold shorter $t_{1/2}$ of topiramate compared to dogs not administered PB.[74] (See Chapter 15.)
Felbamate, cimetidine, omeprazole, lansoprazole,	These drugs are inhibitors of the hepatic microsomal CYP450 enzyme activity and therefore have the potential to cause PB toxicity, by inhibiting its metabolism and increasing serum

chloramphenicol, trimethoprim, fluoroquinolones, tetracycline, ketoconazole, fluconazole, itraconazole, fluoxetine	concentrations.[10] If prolonged treatment with any of these medications is required in dogs on PB, serum PB concentrations should be tested before and periodically after initiation of these medications. Further details on PB interaction with felbamate can be found in Chapter 15.
Milk thistle (silybin and silymarin)	Silybin is the major active compound of silymarin, the extract of *Silybum marianum*, or milk thistle. These compounds are often found in hepatic support preparations and have been reported to inhibit cytochrome P450 enzymes such as CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 in vitro.[75,76] This CYP inhibition could decrease PB metabolism with subsequent increase in serum PB concentration. However, it is unknown if this effect has clinically relevant consequences in dogs administered PB.
Cyclosporine	Serum cyclosporine concentrations can be decreased in dogs and cats treated with PB.[77,78] In a study in 3 cats, concurrent oral treatment with PB (for 4 weeks) and cyclosporine resulted in a significant decrease in both cyclosporine oral bioavailability and maximum serum concentration. It was suggested that this could be due to the induction of CYP3A and intestinal P-glycoprotein by PB.[78] A higher dosage of cyclosporine and serum cyclosporine concentration monitoring may be required in both dogs and cats concurrently receiving PB.
Griseofulvin	Administration of PB can impair absorption of griseofulvin and decrease its plasma concentration and efficacy.[79]

IV, intravenously; PK, pharmacokinetics; $C_{max,}$ maximum concentration; $t_{1/2}$, elimination half-life.

TAKE-HOME MESSAGES

- ✔ Phenobarbital is efficacious in treating different seizure types in dogs and cats and generally well tolerated.
- ✔ Phenobarbital should be administered to patients with normal hepatic function (based on clinical and laboratory investigation results).
- ✔ The initial PB maintenance dosage is 2.5–3 mg/kg orally every 12 hours in dogs and 1.5–2.5 mg/kg orally every 12 hours in cats.
- ✔ A higher initial total loading dose of 15–24 mg/kg (orally, IV or IM) divided in multiple 3–5 mg/kg doses over 24–48 hours, followed by the maintenance dosage, can be used in patients with severe epileptic

seizure activity to achieve target serum PB concentrations more rapidly (i.e., 15–30 mg/L).

- ✔ The pet owner needs to be educated about the occurrence of generally transient AEs (such as sedation, ataxia, polydipsia/polyuria and polyphagia) during the initial 2–4 weeks of treatment. These AEs are more marked following PB loading.
- ✔ Regular oral administration, maintaining an accurate seizure diary and regular veterinary checkups with periodic serum PB concentration monitoring are key in optimizing and individualizing PB treatment. Identifying the lowest efficacious PB dosage could help optimize the patient's QoL.
- ✔ Reference serum PB concentrations in dogs are between 15–35 µg/mL (65–150 mmol/L). A target serum PB concentration of 25−30 µg/mL has been recommended for optimal epileptic seizure control in dogs with IE. A target range between 15–30 µg/mL (65–129 mmol/L) has been suggested in cats.
- ✔ Serum PB concentrations should be tested (preferably on a fasting sample): 2–3 weeks after treatment initiation or dose modulation; 3 months after PB treatment initiation in patients with adequate epileptic seizure control, and subsequently every 6–12 months when therapeutic success is maintained; and anytime seizure occurrence or severity increases or the animal experiences unexpected or persistent AEs. Plain serum tubes should be used.
- ✔ Testing both peak and trough serum PB concentrations is indicated when therapeutic failure or toxicity is suspected.
- ✔ Hepatotoxicity is less likely to occur when the serum PB concentration is maintained below 35 µg/mL.
- ✔ Hematological and serum biochemistry parameters should be monitored every 6–12 months in clinically normal dogs and cats treated with PB and well-controlled epilepsy.
- ✔ The most common serum biochemical change with chronic PB treatment is an increase in serum alkaline phosphatase (ALP) and to a lesser extent alanine aminotransferase (ALT). Hepatic function should be assessed by analyzing all relevant clinical and serum biochemistry parameters on a fasting sample (including glucose, albumin, total

bilirubin, blood urea nitrogen) and the results of a bile acid stimulation test.

- ✔ Adding a second-line ASD should be considered when patients are experiencing unacceptable AEs following steady state achievement and/or inadequate epileptic seizure control despite serum PB concentrations in the high reference range (28–34 mg/L) at both peak and trough testing (with sampling performed in the 24-hour period).

REFERENCES

1. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy- a systematic review. *BMC Vet Res*. 2014; 10:257. doi: 10.1186/s12917-014-0257-9.
2. Charalambous M, Shivapour SK, Brodbelt DC et al. Antiepileptic drugs' tolerability and safety-a systematic review and meta-analysis of adverse effects in dogs. *BMC Vet Res*. 2016; 12:79. doi: 10.1186/s12917-016-0703-y.
3. Charalambous M, Pakozdy, A. Bhatti SFM et al. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14:64. https://doi.org/10.1186/s12917-018-1386-3
4. Kluger EK, Malik R, Govendir M. Veterinarians' preferences for anticoagulation drugs for treating seizure disorders in dogs and cats. *Aust Vet J*. 2009; 87(11):445–449. doi: 10.1111/j.1751-0813.2009.00509.x.
5. Meland T, Carrera-Justiz S, Buckley GJ. Antiepileptic drug use patterns in suspect epileptic dogs among neurology and emergency specialists. *J Am Anim Hosp Assoc.* 2019; 55(3): 38–143. doi: 10.5326/JAAHA-MS-6795.
6. Bhatti SF, De Risio L, Muñana K et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015; 11:176. doi: 10.1186/s12917-015-0464-z.
7. Podell M, Volk HA, Berendt M, et al. 2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs. *J Vet Intern Med*. 2016; 30(2):477–490. doi: 10.1111/jvim.13841.
8. Ticku MK, Kulkarni SK. (1992) Antiepileptic actions of barbiturates. In: Faingold CL, Fromm GH (eds) *Drugs for the Control of Epilepsy: Actions on Neuronal Networks Involved in Seizure Disorders*. Boca Raton, Florida.
9. Nardou R, Yamamoto S, Bhar A, et al. Phenobarbital but not diazepam reduces AMPA/kainate receptor mediated currents and exerts opposite actions on initial seizures in the neonatal rat hippocampus. *Front Cell Neurosci*. 2011; 5:16. doi: 10.3389/fncel.2011.00016.
10. Boothe DM. Anticonvulsant and other neurologic therapies in small animals. In: Boothe DM (ed.). *Small Animal Clinical Pharmacology and Therapeutics. 2nd ed*. St Louis, Missouri: Elsevier; 2012. pp. 950–955.
11. Al-Tahan F, Frey HH. Absorption kinetics and bioavailability of phenobarbital after oral administration to dogs. *J Vet Pharmacol Ther*. 1985; 8:205–207. doi:

10.1111/j.13652885.1985.tb00946.x

12. Pedersoli WM, Wike JS, Ravis WR. Pharmacokinetics of single doses of phenobarbital given intravenously and orally to dogs. *Am J Vet Res*. 1987; 48:679–683.
13. Cochrane SM, Black WD, Parent JM, et al. Pharmacokinetics of phenobarbital in the cat following intravenous and oral administration. *Can J Vet Res*. 1990; 54(1):132–138.
14. Cochrane SM, Parent JM, Black WD, et al. Pharmacokinetics of phenobarbital in the cat following multiple oral administration. *Can J Vet Res*. 1990; 54(3):309-312.
15. Thurman GD, McFadyen ML, Miller R. The pharmacokinetics of phenobarbitone in fasting and non-fasting dogs. *J S Afr Vet Assoc*. 1990; 61(3):86–89.
16. Frey HH, Göbel W, Löscher W. Pharmacokinetics of primidone and its active metabolites in the dog. *Arch Int Pharmacodyn Ther*. 1979; 242:14–30.
17. Clemmons RM, Schubert TA, Peters RK, et al. Free-to-bound serum phenobarbital levels in dogs. *J Veterinar Sci Technolo*. 2013; 4(5):143.
18. Ravis WR, Pedersoli WM, Wike JS. Pharmacokinetics of phenobarbital in dogs given multiple doses. *Am J Vet Res*. 1989; 50(8):1343–1347.
19. Ravis WR, Nachreiner RF, Pedersoli WM, et al. Pharmacokinetics of phenobarbital in dogs after multiple oral administration. *Am J Vet Res*. 1984; 45:1283–1286.
20. Levitski RE, Trepanier LA. Effect of timing of blood collection on serum phenobarbital concentrations in dogs with epilepsy. *J Am Vet Med Assoc*. 2000; 15(217):200–204.
21. Finnerty KE, Barnes Heller HL, Mercier MN, et al. Evaluation of therapeutic phenobarbital concentrations and application of a classification system for seizures in cats: 30 cases (2004-2013). *J Am Vet Med Assoc*. 2014; 244(2):195–199.
22. Hojo T, Ohno R, Shimoda M, et al. Enzyme and plasma protein induction by multiple oral administrations of phenobarbital at a therapeutic dosage regimen in dogs. *J Vet Pharmacol Ther*. 2002; 25:121–127. doi: 10.1046/j.1365-2885.2002.00385.x.
23. Maguire PJ, Fettman MJ, Smith MO, et al. Effects of diet on pharmacokinetics of phenobarbital in healthy dogs. *J Am Vet Med Assoc*. 2000; 217(6):847-852. doi: 10.2460/javma.2000.217.847.
24. Fukunaga K, Saito M, Muto M, et al. Effects of urine pH modification on pharmacokinetics of phenobarbital in healthy dogs. *J Vet Pharmacol Ther*. 2008; 31(5):431–436. doi: 10.1111/j.1365-2885.2008.00977.x.
25. Delamaide Gasper JA, Barnes Heller HL, Robertson M et al. Therapeutic serum phenobarbital concentrations obtained using chronic transdermal administration of phenobarbital in healthy cats. *J Feline Med Surg*. 2015; 17(4):359–63. doi: 10.1177/1098612X14545141.
26. Krull D, Thomovsky SA, Chen-Allen A et al. Evaluation of transdermal administration of phenobarbital in healthy cats. ACVIM Forum 2014. *J Vet Intern Med*. 2014; 28:1016.
27. Barnes Heller HL, Trepanier LA, Robertson M et al. Prospective crossover clinical trial comparing transdermal with oral phenobarbital administration in epileptic cats. *J Feline Med Surg*. 2019; 21(12):1181–1187. doi: 10.1177/1098612X18823577.
28. Wilensky AJ, Friel PN, Levy RH et al. Kinetics of phenobarbital in normal subjects and epileptic patients. *Eur J Clin Pharmacol*. 1982; 23(1):87–92. doi: 10.1007/BF01061382.
29. De Risio L. Phenobarbital. Chapter 13. In: De Risio L, Platt S. *Canine and Feline epilepsy: diagnosis and management*. Wallingford, UK: CABI; 2014. pp. 74–396.

30. Farnbach GC. Serum concentrations and efficacy of phenytoin, phenobarbital and primidone in canine epilepsy. *J Am Vet Med Assoc*. 1984; 184:1117–1120.
31. Schwartz-Porsche D, Löscher W, Frey HH. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. *J Vet Pharmacol Ther*. 1985; 8(2):113–119. doi: 10.1111/j.1365-2885.1985.tb00934.x.
32. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. *J Am Vet Med Assoc*. 2012;240:1073–83. doi: 10.2460/javma.240.9.1073
33. Tipold A, Keefe TJ, Löscher W et al. Clinical efficacy and safety of imepitoin in comparison with phenobarbital for the control of idiopathic epilepsy in dogs. *J Vet Pharmacol Ther*. 2015; 38(2):160–168. doi: 10.1111/jvp.12151.
34. Stabile F, van Dijk J, Barnett CR et al. Epileptic seizure frequency and semiology in dogs with idiopathic epilepsy after initiation of imepitoin or phenobarbital monotherapy. *Vet J*. 2019; 249:53–57. doi: 10.1016/j.tvjl.2019.05.007.
35. Fredsø N, Sabers A, Toft N et al. A single-blinded phenobarbital-controlled trial of levetiracetam as monotherapy in dogs with newly diagnosed epilepsy. *Vet J*. 2016; 208:44–49. http://doi.org/10.1016/j.tvjl.2015.10.018
36. Stabile F, Barnett CR, De Risio L. Phenobarbital administration every eight hours: improvement of seizure management in idiopathic epileptic dogs with decreased phenobarbital elimination half-life. *Vet Rec*. 2017; 180(7):178. doi: 10.1136/vr.104051.
37. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. *J Vet Intern Med*. 1993; 7(5):318–327. doi: 10.1111/j.1939-1676.1993.tb01025.x.
38. Trepanier LA, Van Schoick A, Schwark WS et al. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992-1996). *J Am Vet Med Assoc*. 1998; 213(10):1449–1453.
39. Pakozdy A, Sarchahi AA, Leschnik M et al. Treatment and long-term follow-up of cats with suspected primary epilepsy. *J Feline Med Surg*. 2013; 15(4):267–273. doi: 10.1177/1098612X12464627.
40. Lowrie M, Bessant C, Harvey RJ et al. Audiogenic reflex seizures in cats. *J Feline Med Surg*. 2016; 18(4):328–336. doi:10.1177/1098612X15582080.
41. Quesnel AD, Parent JM, McDonell W. Clinical management and outcome of cats with seizure disorders: 30 cases (1991-1993). *J Am Vet Med Assoc*. 1997; 210(1):72–77.
42. Levitski RE, Trepanier LA. Effect of timing of blood collection on serum phenobarbital concentrations in dogs with epilepsy. *J Am Vet Med Assoc*. 2000; 15(217):200–4.
43. Monteiro R, Anderson TJ, Innocent G, et al. Variations in serum concentration of PB in dogs receiving regular twice daily doses in relation to the times of administration. *Vet Rec*. 2009; 165:556–558.
44. Kluger EK, Malik R, Ilkin WJ, et al. Serum triglyceride concentration in dogs with epilepsy treated with phenobarbital or with phenobarbital and bromide. *J Am Vet Med Assoc*. 2008; 233(8):1270–1277. doi: 10.2460/javma.233.8.1270.
45. Boothe DM, Simpson G, Foster T. Effects of serum separation tubes on serum benzodiazepine and phenobarbital concentrations in clinically normal and epileptic dogs. *Am J Vet Res*. 1996; 657:1299–1303.
46. Dayrell-Hart B, Steinberg SA, VanWinkle TJ, et al. Hepatotoxicity of phenobarbital in dogs: 18 cases (1985-1989). *J Am Vet Med Assoc*. 1991; 199(8):1060–1666.

47. MÜLLER PB, TABOADA J, HOSGOOD G et al. Effects of long-term phenobarbital treatment on the liver in dogs. *J Vet Intern Med*. 2000; 14:165–171. doi: 10.1111/j.1939-1676.2000.tb02231.x
48. BARNES HELLER H. Feline Epilepsy. *Vet Clin North Am Small Anim Pract*. 2018; 48(1):31–43. doi: 10.1016/j.cvsm.2017.08.011.
49. BANKSTAHL M, BANKSTAHL JP, LÖSCHER W. Is switching from brand name to generic formulations of phenobarbital associated with loss of antiepileptic efficacy?: A pharmacokinetic study with two oral formulations (Luminal® vet, Phenoleptil®) in dogs. *BMC Vet Res*. 2013; 9:202. doi: 10.1186/1746-6148-9-202.
50. VAN MEERVENNE S. and SÄVE S. Comparison of Immulite 2000* versus Catalyst DX* instruments for the analysis of serum concentration of phenobarbital in dogs. *Proceedings of the 31st Symposium ESVN-ECVN. Copenhagen, Denmark 20th to 22nd September 2018. J Vet Intern Med*. 2020. pp. 490–491.
51. GASKILL CL, MILLER LM, MATTOON JS et al. Liver histopathology and liver and serum alanine aminotransferase and alkaline phosphatase activities in epileptic dogs receiving phenobarbital. *Vet Pathol*. 2005; 42:147–160.
52. AITKEN MM, HALL E, SCOTT L et al. Liver-related biochemical changes in the serum of dogs being treated with phenobarbitone. *Vet Rec*. 2003; 153(1):13–16. doi: 10.1136/vr.153.1.13.
53. GIEGER TL, HOSGOOD G, TABOADA J et al. Thyroid function and serum hepatic enzyme activity in dogs after phenobarbital administration. *J Vet Intern Med*. 2000; 14:277–281.
54. GASKILL CL, BURTON SA, GELENS HC et al. Effects of phenobarbital treatment on serum thyroxine and thyroid-stimulating hormone concentrations in epileptic dogs. *J Am Vet Med Assoc*. 1999; 215(4):489–496.
55. GASKILL CL, BURTON SA, GELENS HC et al. Changes in serum thyroxine and thyroid-stimulating hormone concentrations in epileptic dogs receiving phenobarbital for one year. *J Vet Pharmacol Ther*. 2000; 23(4):243–249. doi: 10.1046/j.1365-2885.2000.00278.x.
56. TREPANIER LA. Idiosyncratic drug toxicity affecting the liver, skin, and bone marrow in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2013; 43(5):1055–1066. doi: 10.1016/j.cvsm.2013.04.003.
57. MARSH O, CORSINI G, VAN DIJK J et al. Prevalence and clinical characteristics of phenobarbitone-associated adverse effects in epileptic cats. *J Feline Med Surg*. 2021; 23(2):59–66. doi: 10.1177/1098612X20924925.
58. BERSAN E, VOLK HA, ROS C et al. Phenobarbitone-induced haematological abnormalities in idiopathic epileptic dogs: prevalence, risk factors, clinical presentation and outcome. *Vet Rec*. 2014; 175(10):247. doi: 10.1136/vr.102158.
59. HABOCK G, PAKOZDY A. Hämatologische Abweichungen während der Phenobarbital-Therapie beim Hund. *Wien Tierarztl Monatsschr*. 2012; 99:18–25.
60. LYRAKI M, WILSON H. Suspected phenobarbital-induced pancytopenia in a cat. *J Feline Med Surg- Open Reports*. 2020; 6(1):2055116920916945. doi:10.1177/2055116920916945
61. KOCH T, MUELLER RS, DOBENECKER B et al. Cutaneous Adverse Drug Reactions in Dogs Treated with Antiepileptic Drugs. *Front Vet Sci*. 2016; 3:27. doi: 10.3389/fvets.2016.00027.
62. MARCH PA, HILLIER A, WEISBRODE SE et al. Superficial necrolytic dermatitis in 11 dogs with a history of phenobarbital administration (1995-2002). *J Vet Intern Med*. 2004; 18(1): 5–74. doi: 10.1892/0891-6640(2004)18<65:sndidw>2.0.co;2.
63. GASKILL CL, CRIBB AE. Pancreatitis associated with potassium bromide/Phenobarbital combination therapy in epileptic dogs. *Can Vet J*. 2000; 41:555–558.

64. KUBE SA, VERNAU KM, LECOUTEUR RA. Dyskinesia associated with oral phenobarbital administration in a dog. *J Vet Intern Med*. 2006; 20(5):1238.

65. RUSBRIDGE, C. Choosing the right drug. 1. Anticonvulsants used for first-line therapy. *In Pract*. 2013; 35:106–113.

66. SIMERDOVA V, HAJEK I, SCHANILEC P. Addisonian crisis in a dog treated with phenobarbitone. *Aust Vet J*. 2015; 93(4):105–108. doi: 10.1111/avj.12301.

67. BAHO MJ, HOSTUTLER R, FENNER W et al. Suspected phenobarbital-induced pseudolymphoma in a cat. *J Am Vet Med Assoc*. 2011; 238(3):353–355. doi: 10.2460/javma.238.3.353.

68. LIESER J, SCHWEDES CS. Pseudolymphoma in a cat on phenobarbital treatment. *J Small Anim Pract*. 2018; 59:444–447.

69. DJANI DM, DRAPER WE. Suspected phenobarbital-induced fever in a cat. *J Feline Med Surg-Open Rep*. 2019; 5(1):2055116919830214. doi: 10.1177/2055116919830214.

70. FORRESTER SD, WILCKE JR, JACOBSON JD et al. Effects of a 44-day administration of phenobarbital on disposition of clorazepate in dogs. *Am J Vet Res*. 1993; 54(7):1136–1138.

71. WAGNER SO, SAMS RA, PODELL M. Chronic phenobarbital therapy reduces plasma benzodiazepine concentrations after intravenous and rectal administration of diazepam in the dog. *J Vet Pharmacol Ther*. 1998; 21(5):335–341. doi: 10.1046/j.1365-2885.1998.00149.x.

72. MOORE SA, MUÑANA KR, PAPICH MG et al. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther*. 2011; 34(1):31–34. doi: 10.1111/j.1365-2885.2010.01188.x.

73. ORITO K, SAITO M, FUKUNAGA K et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. *J Vet Pharmacol Ther*. 2008; 31(3):259–264. doi: 10.1111/j.1365-2885.2008.00955.x.

74. VUU I, COLES LD, MAGLALANG P et al. Intravenous Topiramate: Pharmacokinetics in Dogs with Naturally Occurring Epilepsy. *Front Vet Sci*. 2016; 3:107. https://doi.org/10.3389/fvets.2016.00107

75. SRIDAR C, GOOSEN TC, KENT UM, et al. Silybin inactivates cytochromes P450 3A4 and 2C9 and inhibits major hepatic glucuronosyltransferases. *Drug Metab Dispos*. 2004; 32(6):587–594. doi: 10.1124/dmd.32.6.587.

76. HERMANN R, VON RICHTER O. Clinical evidence of herbal drugs as perpetrators of pharmacokinetic drug interactions. *Planta Med*. 2012; 78(13):1458–1477. doi: 10.1055/s 0032-1315117.

77. ARCHER TM, BOOTHE DM, LANGSTON VC, et al. Oral cyclosporine treatment in dogs: a review of the literature. *J Vet Intern Med*. 2014; 28(1):1–20. doi:10.1111/jvim.12265

78. HOSHINO Y, INDEN T, OTAKA R et al. Interaction of cyclosporine with phenobarbital in cats: a preliminary study. *J Vet Med Sci*. 2019; 81(11):1621–1623. doi:10.1292/jvms.19-0339.

79. JAMALI F, AXELSON JE. Griseofulvin-phenobarbital interaction: a formulation-dependent phenomenon. *J Pharm Sci*. 1978; 67(4):466–470. doi: 10.1002/jps.2600670406.

Potassium Bromide 11

Michael Podell

Bromide was the first documented antiseizure drug (ASD) used for epilepsy in people in 1857[1] and was an integral part of establishing a consistent first-line therapy for epilepsy in people through the early 20th century until the advent of phenobarbital (PB) in 1912, which provided a therapeutic approach with less adverse effects (AEs). The use of potassium bromide (KBr) in veterinary medicine to treat canine epilepsy was introduced by Schwartz-Porsche in the 1990s[2] as a rescue therapy for dogs with PB-resistant epilepsy and/or those that were suffering from hepatotoxicity due to prolonged use or high dosing of PB or other drugs metabolized by the liver (e.g., phenytoin and primidone).[3,4] The use of KBr can be attributed to have not only improved, but often, saved the life of countless dogs during a time period when limited options were available for second- and third-line ASD therapy in drug-resistant canine epilepsy. Today, KBr still maintains a useful place in the drug arsenal for the treatment of canine epilepsy due to its effectiveness, lack of hepatic metabolism, minimal to no drug–drug interaction, wide availability, and relatively low cost. As KBr is not recommended for cats due to the risk of potential life-threatening allergic asthmatic reactions, this chapter is focused on treatment in dogs only.

MECHANISM OF ACTION

Antiseizure drugs can be classified into three broad mechanistic categories:

- Enhancement of inhibitory processes via facilitated action of γ amino-butyric acid (GABA)
- Reduction of excitatory transmission

- Modulation of membrane cation (Na^+ or Ca^{2+}) conductance

Unfortunately, several limitations existed in the selection of ASDs for use in veterinary medicine when KBr therapy was being used more prevalently.[4] In the past, many of the ASDs useful in people could not be prescribed to small animals either due to inappropriate pharmacokinetics (too rapid of an elimination), ineffectiveness, or the potential for hepatotoxicity. The result was that the most widely used ASDs in veterinary medicine were from the same mechanistic category, that of enhancing brain inhibition. The advent of newer ASDs with alternative mechanisms of action is now available to allow a broader selection of treatment options (see Chapter 9 for further details).

Bromide is the component of KBr with antiseizure properties, but the exact mechanism of action of bromide is unclear. Initial demonstration of bromide's anticonvulsant effect in dogs has been credited to Albertoni,[5] who reported that bromide antagonized the effects of direct electrical stimulation of the motor cortex in dogs. Bromide also blocks pentylenetetrazol-induced seizures in mice and cats, a common preclinical drug screening tool previously used.[6] This mechanism of action is thought to be related to the preferential passive movement of bromide over chloride across neuronal membranes activated by GABA. This preferential movement occurs because bromide has a smaller hydrated diameter than chloride. In theory, bromide potentiates the effect of the inhibitory postsynaptic GABA neurotransmitter by competing with chloride to result in hyperpolarization of the postsynaptic membrane (Fig. 11.1). Drugs that also enhance chloride conductance via GABAergic activity, such as PB, may act synergistically with bromide to raise the seizure threshold.[7]

PHARMACOKINETICS

Bromide is typically administered as the inorganic salt KBr. In dogs, oral KBr is well absorbed from the gastrointestinal tract, with peak absorption in 90 minutes.[8] Bromide is completely distributed within 2 hours[9] and is entirely passive outside the central nervous system.[10] Although bromide replaces chloride in the serum, the sum of the two halides is constant in

dogs. During chronic oral KBr therapy in dogs, the distribution ratio between red blood cells and serum is slightly greater for bromide than for chloride.[11]

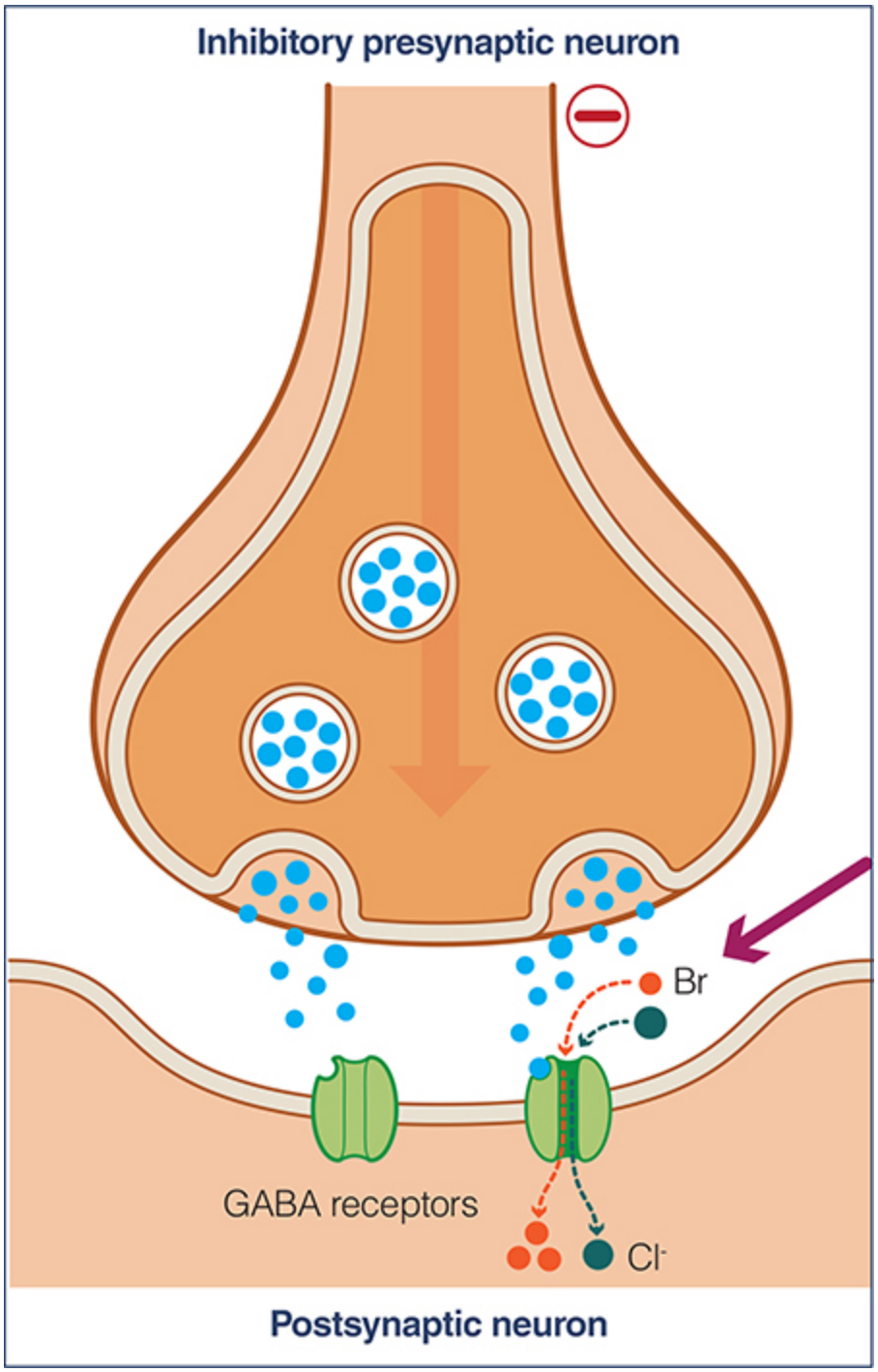


FIGURE 11.1. Postulated mechanism of action of potassium bromide. The bromide ion (Br) selectively floods the GABA chloride (Cl) channel due to its smaller size and similar charge that results in membrane hyperpolarization to raise epileptic seizure threshold.

Concentrations of bromide in the cerebrospinal fluid (CSF) and brain are higher in dogs than in humans after oral and intravenous (IV) therapy. Maximum bromide concentration in CSF occurs about 2 hours after oral administration.[9] Cerebrospinal fluid bromide concentration is relatively constant once maximal concentration is achieved due to the drug's slow rate of elimination. Bromide removal from the CSF is dose dependent and occurs via a saturable active transport mechanism across the choroid plexus.[12] In rabbits, oral bromide loading increased the bromide concentration ratio between the brain and CSF, possibly by saturating the active transport mechanism.[12]

A KBr dose of 40 mg/kg/day is slowly metabolized in the dog, with a median elimination half-life ($t_{1/2}$) of 15.2 days, an apparent total body clearance of 16.4 mL/kg/day, a volume of distribution of 0.40 L/kg and median steady-state concentrations of 2450 mg/L.[13] Steady-state concentrations with chronic oral dosing would theoretically be achieved in 5 $t_{1/2,}$or 76 days. Other studies have reported a $t_{1/2}$ ranging from 25 to 46 days,[14,15] with steady-state concentrations achieved in 125–230 days. Practically all bromide is excreted renally, and bromide is secreted into saliva to be reabsorbed in the intestines. Individual fluctuation of steady-state bromide concentration can vary between dogs, most likely due to individual differences in dietary chloride concentration, and clearance and bioavailability. Diets high in salt (i.e., sodium chloride) content can lower serum bromide concentration due to excessive renal excretion.[4] No known drug–drug interactions have been reported, as bromide has no hepatic metabolism or protein binding. As bromide is excreted in the urine, clearance may be reduced in dogs with impaired renal function, resulting in higher steady-state concentrations.[16]

EFFICACY

Evaluation of KBr monotherapy efficacy was found in only a single, double-blind, randomized study, where 74% (17/23) of dogs with idiopathic epilepsy (IE) had a >50% reduction in seizure frequency after approximately 6 months of treatment, 52% (12/23) of which became seizure free.[17] Dogs in this study were administered an initial KBr loading dose

(450 mg/kg divided into 14 equal doses administered every 12 hours over 7 days), and maintained on KBr 15 mg/kg every 12 hours. The mean serum bromide concentration at study end was 1900 mg/L (range, 900–3300 mg/L). Additional studies have focused on the efficacy of KBr as an add-on drug to PB and/or primidone. Concomitant KBr and PB administration decreased epileptic seizure number and severity in the majority of dogs in several retrospective studies, with epileptic seizure-free status ranging from 21% to 72% of all treated dogs.[2,3,18] In the original description of KBr use in dogs with epilepsy, Schwartz-Porsche reported on the administration of KBr as an add-on therapy in 22 dogs that had unsuccessfully been treated with PB and/or primidone. Dogs were administered KBr at a dose of 17–58 mg/kg/day for a mean of 21 months. Of the 19 dogs for which seizure data was available, 21% (4/19) became seizure free, and another 37% demonstrated a reduction in seizure frequency of >50%.[2] In a retrospective study evaluating the benefit of KBr as an add-on therapy to PB in 23 dogs with IE over a mean time of 15 months, 83% (19/23) had a significant reduction in seizure frequency as compared to their pre-KBr treatment period with 26% (6/23) becoming seizure-free at 1 year posttreatment.[3] In another retrospective study of 122 epileptic dogs administered KBr in combination with PB or primidone, 72% (88/122) of dogs had a >50% reduction in seizure frequency following initiation of treatment for at least 3 months.[18] Discontinuation of barbiturate treatment was possible in 19% (23/122) of those dogs originally treated with PB or primidone. Of those dogs continued on KBr and PB therapy, 45% maintained seizure control with serum PB concentrations <20 µg/mL.

A 2015 consensus statement by the American College of Veterinary Internal Medicine (ACVIM) on seizure management of dogs provided ASD treatment recommendations based on analysis of available evidence.[19] Bromide received a moderate recommendation as either monotherapy or add-on therapy, suggesting that it is most likely to be effective based on available evidence.

CLINICAL USE

Bromide is administered orally, either as a solution dissolved in double-distilled water or in tablet or capsule form. Potassium bromide was recently given provisional FDA approval as chewable tablets in the US and is also available as commercially compounded formulations. In many European countries, it is licensed as an add-on treatment in dogs with IE that are resistant to first-line ASDs.

Potassium bromide can be administered at an initial dose of 40 mg/kg/day when used as sole therapy or combined with a minimally sedating ASD (e.g., levetiracetam). A dose of 30 mg/kg/day is recommended when used as an add-on drug to PB to minimize potentiation of sedation. Once daily dosing at night is recommended to reduce postdosing sedation during the day. Dividing into two equal doses given with food in the morning and at bedtime may help if gastrointestinal signs are seen associated with its administration. Differential dosing 2 hours apart from PB can be used if excess sedation is seen with combined dosing. In this author's experience, monotherapy is recommended in dogs with underlying hepatic disease, less frequent epileptic seizure activity (<3 per year) and in some dogs with IE that can be weaned off PB. The use of KBr monotherapy is not recommended for high initial epileptic seizure frequency (>1 per month), if structural epilepsy is present, or if unwarranted AEs persist (e.g., weakness, extreme polydipsia), due to its inferior efficacy compared to PB.[17] Since bromide is excreted renally, clearance may be reduced in dogs with impaired renal function, necessitating a dosage reduction.

Bromide serum concentration measurements are recommended at the first steady-state concentration point between 8 to 12 weeks after KBr initiation or dose modulation, if two or more breakthrough epileptic seizures occur within a 6-month period, or if signs of toxicity are suspected. Due to the long $t_{1/2}$, collection can be done at any time point 2 hours after dosing and prior to the next dose to avoid any peak effect variability.[4,15] The reported therapeutic range is individualized according to the high variability of patient response and tolerance to the drug. Studies have shown that bromide concentrations between 810 to 2500 mg/L with PB combination therapy are effective,[7,18] whereas monotherapy efficacy was seen with higher values of up to 3000 mg/L.[17,18]

The recommendation of this author is to have serum bromide concentrations at or above 2500 mg/L for optimal seizure control for

monotherapy in canine IE. For combined therapy with PB, the recommended goal is to achieve steady-state trough serum concentrations of 20–25 µg/mL for PB and 2000 mg/L for bromide. Again, the range is highly individualized according to the epileptic seizure pattern of each dog. Further reductions in PB can be attempted if a seizure-free period is maintained for 6 months. By allowing a reduction in the use of drugs metabolized by the liver, KBr therapy may also reduce the incidence of hepatotoxicity.

Dose adjustments of KBr therapy can be calculated once steady-state concentration is achieved, typically after 2 months of therapy as follows:

(Target Css – Actual Css*) ×
(Clearance/Bioavailability**)
=
mg/kg/day added to existing dose

* Css = steady-state concentration
** Clearance/Bioavailability = 0.02

Hospitalized dogs on bromide therapy that require IV therapy should be administered 0.45% sterile saline solution, as 0.9% saline solutions (or higher) will enhance bromide renal excretion and therefore reduce serum concentrations, which could potentiate recurrent epileptic seizure activity.

Bromide loading has been used to increase serum and CSF concentration more rapidly. The challenge presented is that bromide has a very long $t_{1/2}$, is rapidly excreted in the urine, can be caustic to the gastrointestinal tract with high oral doses, and has a low therapeutic index, meaning that the gap between creating a therapeutic drug level can be very close to, and/or overlap, levels that result in AEs.

Oral bromide loading has the benefit of ease of administration, yet it carries a higher risk of potential AEs. Gastrointestinal upset with vomiting and diarrhea can occur due to mucosal irritation from high bromide concentrations, and could progress to pancreatitis. Dogs also appear to be more susceptible to lethargy and ataxia that could progress to stupor with higher doses. Oral KBr loading at 600 mg/kg divided in multiple doses over

24–48 hours resulted in 84% of dogs achieving a serum concentration between 1000 and 3000 mg/L at 24 hours postloading.[20] A slower oral loading dose schedule of 100 mg/kg/day given with food over 6 days may be used to reduce the risk of excessive sedation and gastrointestinal AEs.

Intravenous continuous rate infusion is this author's preferred method for bromide loading, as it is better tolerated without potential for gastrointestinal effects compared to oral loading. Sterile 3% sodium bromide in sterile water infusion at 800 mg/kg administered over 24 hours using a microfilter achieves a rapid rise in serum bromide concentrations to 2000 mg/L and can be easily performed.

TABLE 11.1. Potassium bromide dosing and monitoring recommendations.

	Epileptic seizure type	Epileptic seizure etiology	Initial dose	Drug monitoring
Monotherapy	All	Idiopathic	40 mg/kg/day (as a single administration or divided every 12 hours)	Between 8 and 12 weeks after treatment initiation, every 12 months, 1 month after dose change, or if two or more epileptic seizures within 6 months Range: 1000–3000 mg/L Target: 2500 mg/L
Combined therapy	All	Idiopathic Secondary to hepatic disease	30 mg/kg/day (as a single administration or divided every 12 hours)	Between 8 and 12 weeks after treatment initiation, every 12 months, 1 month after dose change, or if two or more epileptic seizures within 6 months Range: 800–2500 mg/L with phenobarbital Target: 2000 mg/L with phenobarbital concentration of 20–25 µg/mL
Oral loading	Cluster seizures or frequent seizures		Oral bromide loading at 600 mg/kg (divided in multiple doses of 100 mg/kg) over 24–48 hours (rapid) or 6 days (slow)	At end of loading dose and 1 and 3 months later
Intravenous loading Sterile 3% sodium bromide	Cluster seizures		800 mg/kg over 24 hours by constant rate infusion in sterile water	At end of loading dose and 1 and 3 months later

Potassium bromide dosing and monitoring recommendations in dogs are included in Table 11.1.

Sodium bromide can be used instead of KBr in dogs with hypoadrenocorticism or other conditions where administering the potassium salt may be contraindicated. Because of the relative difference in the percentage of bromide in sodium bromide (78%) compared to KBr (67%), the dose of sodium bromide is 15% less than that for KBr. For example, a KBr dose of 30 mg/kg is equivalent to 25 mg/kg of sodium bromide.

ADVERSE EFFECTS AND DRUG INTERACTIONS

Adverse effects can be categorized as type A (predictable and directly related to pharmacological effects in a dose-dependent fashion) and type B (idiosyncratic and maybe life-threatening). The reader is referred to Chapter 9 for a more detailed discussion of AE classification.

Potassium bromide is generally well tolerated in the dog. The most common type A AEs seen with KBr alone or in combination with PB therapy are polydipsia and/or polyuria, polyphagia, lethargy, and ataxia.[21] While lowering the dose may reduce the lethargy and ataxia effects, polydipsia and polyphagia is often less dose dependent. See Figure 11.2 for a summary of bromide AEs.

Bromide toxicosis, or bromism, has been reported in dogs on KBr therapy. Intoxication to the point of stupor is rare, but pelvic limb ataxia, weakness and altered behavior are more likely with serum concentrations > 3000 mg/L[22] (Fig. 11.2) Caution should be used when treating dogs with underlying renal insufficiency, due to reduced urinary elimination.[16] Therapy for KBr intoxication consists of IV administration of normal saline (0.9%) to enhance renal excretion.[22] Careful monitoring is advised as dogs may become more susceptible to epileptic seizure activity with lowering of the drug's serum concentration.

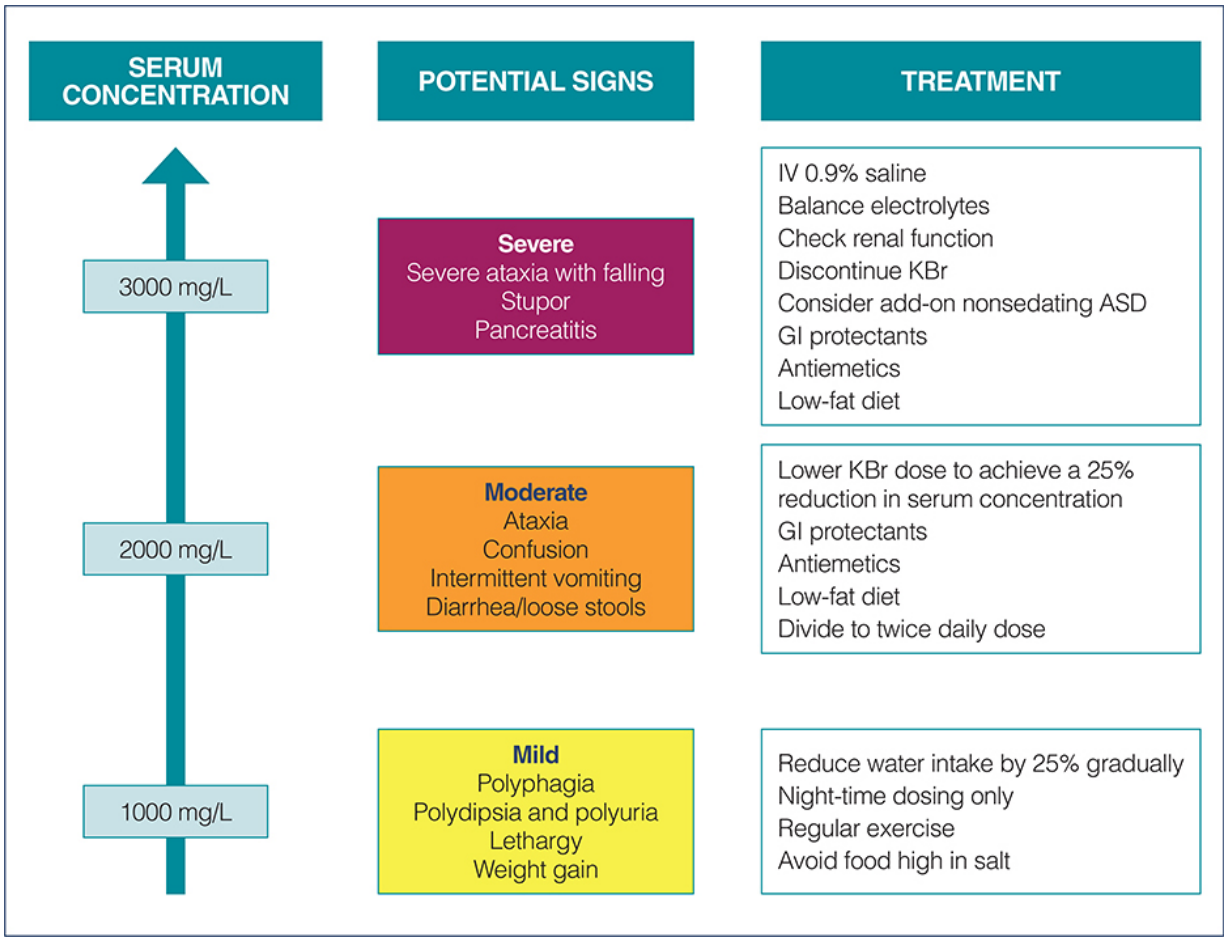


FIGURE 11.2. Clinical signs and treatment of bromide adverse effects.
KBr, potassium bromide; IV, intravenous; ASD, antiseizure drug; GI, gastrointestinal.

Of the type B AEs, gastrointestinal signs are most common. Potassium bromide is a known mucosal irritant. Tablet or capsular formulation may cause increased gastric irritation due to the direct contact of a concentrated amount of the drug with the gastric lining, resulting in inappetence, vomiting and/or diarrhea. Gastrointestinal intolerance and pancreatitis, especially in the face of hyperlipidemia, have also been reported.[23] A retrospective study of dogs receiving KBr monotherapy or KBr concurrently with PB reported 10% (7/68) of dogs with evidence of suspected pancreatitis, based on laboratory evaluation and clinical signs in 6 dogs and necropsy diagnosis in 1 dog. In comparison, a retrospective evaluation of dogs administered PB monotherapy identified pancreatitis in 0.3% (2/698) of dogs, suggesting that KBr administration in combination with PB is associated with an increased risk of pancreatitis.[23]

A systematic review of the tolerability of ASDs in dogs with IE suggests that, although AEs are typically mild with all ASDs and subside with dosage reductions or drug withdrawal, KBr has a worse safety profile when compared to PB, imepitoin, or levetiracetam.[24]

Laboratory values may be altered with chronic bromide treatment. Factious increases in chloride serum concentrations can occur as bromide and chloride have similar valences and sizes, which alters accurate chloride detection on chemistry panels. While no thyroid disorders have been reported with bromide therapy, thyroid function should be monitored periodically, as the thyroid gland is a known target organ for accumulation.[21]

No known drug–drug interactions have been reported with KBr administration, as bromide has no hepatic metabolism or protein binding. As bromide is excreted by the kidneys and competes with chloride for tubular reabsorption, alterations in dietary salt (NaCl) ingestion can result in fluctuations in serum bromide concentrations. Consequently, it is important that dogs being treated with KBr be kept on a consistent diet. A 0.4% sodium chloride dietary content on a dry matter basis offers the best balance to maintain therapeutic bromide serum concentrations at the recommended doses.[7] Any dietary adjustments should be made slowly, with serum bromide concentrations measured. Considerations surrounding the interaction between bromide and chloride with the use of KBr as an ASD are summarized in Box 11.1.

Bromide therapy is not recommended in cats due to risk of potential life-threatening type B allergic asthmatic reactions in this author's experience. In one retrospective study, KBr administration was associated with AEs in 8 of 17 cats. Coughing developed in 35% (6/17) of cats and did not appear to be associated with serum drug concentration or duration of treatment, leading to euthanasia in 1 cat and discontinuation of KBr administration in 2 cats.[25]

BOX 11.1. Points to consider with the use of potassium bromide (KBr) regarding the interaction of bromide and chloride.

- Bromide is renally excreted and competes with chloride for tubular reabsorption, so that alterations in dietary salt (NaCl) ingestion can result in fluctuations in serum bromide concentrations.
- Dogs being treated with KBr should be kept on a consistent diet; this includes the feeding of treats and supplements.

- A diet containing 0.4% NaCl on a dry matter basis should achieve therapeutic bromide serum concentrations with administration of KBr at recommended doses.
- Any dietary adjustments should be made slowly, with serum bromide concentrations measured 8–12 weeks after the introduction of a new diet, or sooner if seizure control worsens or AEs develop.
- Hospitalized dogs on bromide therapy that require IV therapy should be administered 0.45% sterile saline solution, as 0.9% saline solutions (or higher) will enhance bromide renal excretion and therefore reduce serum concentrations, which could potentiate recurrent epileptic seizure activity.
- Similarly, dogs being administered KBr should avoid swimming in the ocean, as ingestion of the salt water can lead to a decrease in serum bromide concentrations and the potential for breakthrough seizures.

TAKE-HOME MESSAGES

- ✔ Potassium bromide was the first ASD shown to consistently provide a therapeutic benefit for epileptic people.
- ✔ Its introduction into veterinary medicine to treat drug-resistant epilepsy in dogs improved the quality of life for many dogs while serving as a bridge until newer ASDs became available in the early 21st century.
- ✔ Bromide therapy has the advantages of being easy to administer on a daily dosing schedule and rapidly distributed into the brain. It works synergistically with PB, has shown good clinical efficacy as an add-on drug with PB, and is relatively inexpensive.
- ✔ Dosing:
  - ✔ A starting dose of 40 mg/kg/day is recommended for monotherapy or when combined with a minimally sedating ASD (e.g., levetiracetam).
  - ✔ A starting dose of 30 mg/kg/day is recommended when used as an add-on drug to PB to minimize potentiation of sedation.
  - ✔ Once daily dosing at night is recommended to reduce postdosing sedation during the day.
  - ✔ Dosing with food can help prevent gastrointestinal AEs.
  - ✔ Dividing into two equal doses given with food in the morning and at bedtime may also help reduce gastrointestinal signs if present.
  - ✔ Loading dose protocols:

- For dogs with a high seizure frequency or recent cluster seizures:
  - Oral KBr 600 mg/kg over 48 hours administered in equal doses every 6 hours. Higher risk of AEs of lethargy, ataxia, and gastrointestinal upset.
  - Continuous rate IV infusion of sterile 3% sodium bromide in sterile water at 800 mg/kg administered over 24 hours using a microfilter. Reduces risk of AEs of lethargy, ataxia, and gastrointestinal upset.
- For dogs without urgent need for a rapid rise in bromide serum concentration: slower oral loading dose schedule of 100 mg/kg/day given with food over 6 days. Reduces the risk of excessive sedation and gastrointestinal AEs.

✔ Monitoring:
- Bromide serum concentration measurements are recommended at the first steady-state concentration point between 8 to 12 weeks, if two or more breakthrough epileptic seizures occur within a 6-month period, or if signs of toxicity are suspected.
- For monotherapy, steady-state serum bromide concentrations at or above 2500 mg/L are recommended for optimal seizure control.
- For combined therapy with PB, the recommended goal is to achieve steady-state trough serum concentrations of 20–25 µg/ml for PB and 2000 mg/L for bromide.
- False increases in chloride serum concentrations can occur as bromide and chloride have similar valences and sizes, which alters accurate chloride detection on chemistry panels.

✔ Adverse effects:
- In general, bromide is well-tolerated, with chronic AEs such as polydipsia, polyuria and possible pelvic limb weakness, which are reversible with lower doses.
- The greatest risks revolve around gastrointestinal irritation and potential for pancreatitis.

REFERENCES

1. Locock C. Discussion of paper by Sieveking: Analysis of 52 cases of epilepsy observed by the author. *Med Times Gazette*. 1857; 1:524–526.
2. Schwartz-Porsche D, Jurgens U. [Effectiveness of bromide in therapy resistant epilepsy of dogs]. *Tierarztl Prax*. 1991; 19(4):395–401.
3. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. *J Vet Intern Med*. 1993; 7(5):318–327.
4. Trepanier LA. Use of bromide as an anticonvulsant for dogs with epilepsy. *J Am Vet Med Assoc*. 1995; 207(2):163–166.
5. Albertoni P. Untersuchungen über die Wirkung einiger Arzneimittel auf die Erregbarkeit des Grosshirns nebst Beiträgen zur Therapie der Epilepsia. *Arch Exp Pathol Pharmakol.* 1882; 15:248–288.
6. Grewal MS, Swinyard EA, Jensen HV et al. Correlation between anticonvulsant activity and plasma concentration of bromide. *J Pharmacol Exp Ther*. 1954; 112(1):109–115.
7. Podell M, Fenner WR. Use of bromide as an antiepileptic drug in dogs. *Compend Contin Educ Vet*. 1994; 16(6):767–773.
8. Van Dyke HB, Hastings AB. Studies of bromide distribution in the blood. II. The distribution of bromides and chlorides in the blood of dogs following the oral administration of sodium bromide. *J Biol Chem*. 1931; 92(1):27–32.
9. Greenberg DM, Aird RB, Boelter MD et al. A study with radioactive isotopes of the permeability of the blood-cerebrospinal fluid barrier to ions. *Am J Physiol*. 1943; 140(1):47–64.
10. Weir EG, Hastings AB. The distribution of bromide and chloride in tissues and body fluids. *J Biol Chem*. 1939;129(2): 547–558.
11. Mason M. Halide distribution in body fluids in chronic bromide intoxication. *J Biol Chem*. 1936; 113(1):61–74.
12. Pollay M. The processes affecting the distribution of bromide in blood, brain, and cerebrospinal fluid. *Exp Neurol*. 1967; 17(1):74–85. doi: 10.1016/0014-4886(67)90123-9.
13. March PA, Podell M, Sams RA. Pharmacokinetics and toxicity of bromide following high-dose oral potassium bromide administration in healthy Beagles. *J Vet Pharmacol Ther*. 2002; 25(6):425–432.
14. Schwartz-Porche D, Jurgens N, May T et al. Pharmacokinetics of bromide and bromide therapy in canine epilepsy. P*roceedings of the 4th Annual Symposium of the European Society of Neurology.* Bern, Switzerland, pp. 32-34.
15. Trepanier LA, Babish JG. Pharmacokinetic properties of bromide in dogs after intravenous and oral administration of single doses. *Res Vet Sci*. 1995; 58(3):248-251.
16. Nichols ES, Trepanier LA, Linn K. Bromide toxicosis secondary to renal insufficiency in an epileptic dog. *J Am Vet Med Assoc*. 1996; 208(2):231–233.
17. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. *J Am Vet Med Assoc*. 2012; 240(9):1073–1083.
18. Trepanier L, Van Schoick A, Schwark WS et al. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992-1996). *J Am Vet Med Assoc*. 1998;213(10): 1449–1453.

19. PODELL M, VOLK HA, BERENDT M et al. 2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs. *J Vet Intern Med*. 2016; 30(2):477–490. doi: 10.1111/jvim.13841.
20. GINDICIOSI B, PALUS V, EMINAGA S et al. Serum bromide concentrations following loading dose in epileptic dogs. *J Small Anim Pract*. 2014; 55(2):108–111. doi: 10.1111/jsap/12173
21. BAIRD-HEINZ HE, VAN SCHOICK AL, PELSOR FR. A systematic review of the safety of potassium bromide in dogs. *J Am Vet Med Assoc*. 2012; 240(6):705–715.
22. ROSSMEISL JH, INZANA KD. Clinical signs, risk factors, and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy. *J Am Vet Med Assoc*. 2009; 234(11):1425–1431.
23. GASKILL CL, CRIBB AE. Pancreatitis associated with potassium bromide/phenobarbital combination therapy in epileptic dogs. *Can Vet J*. 2000; 41(7):555–558.
24. CHARALAMBOUS M, SHIVAPOUR SK, BRODBELT DC et al. Antiepileptic drugs' tolerability and safety--a systematic review and meta-analysis of adverse effects in dogs. *BMC Vet Res*. 2016; 12:79 doi:10.1186/s12917-016-0703-y.
25. BOOTHE DM, GEORGE KL, COUCH P. Disposition and clinical use of bromide in cats. *J Am Vet Med Assoc*. 2002;221(8): 1131–1135.

Levetiracetam 12

Karen R. Muñana

Levetiracetam (LEV) is a pyrrolidine derivative with a chemical composition unrelated to any antiseizure drug (ASD) that preceded it. It is one of the newer-generation ASDs, having received regulatory approval for use in humans in the United States and Europe in 1999 and 2000, respectively. In humans, LEV is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalization, myoclonic seizures due to juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures associated with idiopathic epilepsy (IE). It is also approved as monotherapy for focal-onset seizures. Levetiracetam is used globally and has become one of the leading ASDs in human medicine, due to its ease of administration, minimal drug interactions, and excellent efficacy and safety profile.[1] These favorable pharmacological characteristics led to its rapid introduction into the veterinary field after its approval. Levetiracetam has gained widespread use in dogs and cats, although it is not licensed for use in veterinary medicine.

MECHANISM OF ACTION

Preclinical studies revealed LEV had a distinctive profile when compared to other ASDs. Levetiracetam was shown to control chronic epileptiform activity both in vitro and in vivo, but did not exert a significant antiseizure effect in most acute seizure models. Furthermore, LEV demonstrated no intrinsic effect on normal neuronal function, leading early investigators to speculate that LEV possessed a unique mechanism of action that did not involve the typical ion channels or receptor targets that other ASDs act

upon.[2] It has since been determined that LEV exerts its antiepileptic effect by selectively binding to synaptic vesicle protein 2A (SV2A),[3] an integral membrane protein present on all synaptic vesicles. The binding of LEV to SV2A on presynaptic nerve terminals results in modulation of synaptic vesicle exocytosis and the prevention of neurotransmitter release, reducing neurotransmission (Fig. 12.1). There is evidence to suggest that the alteration in synaptic exocytosis only occurs under pathologic conditions, and not in a normal brain.[3]

Studies have demonstrated that LEV possesses other potential antiepileptic properties, including reducing current through voltage-gated calcium channels, inhibiting the release of intraneuronal calcium, suppressing potassium currents, and inhibiting glutamate receptors.[4] The role these other mechanisms play in the ability of LEV to suppress seizures is currently unknown. It has been hypothesized that they may be involved in seizure control following the acute administration of LEV, while SV2A binding is responsible for the control of seizures when LEV is administered chronically as part of a maintenance epilepsy treatment regimen.[4]

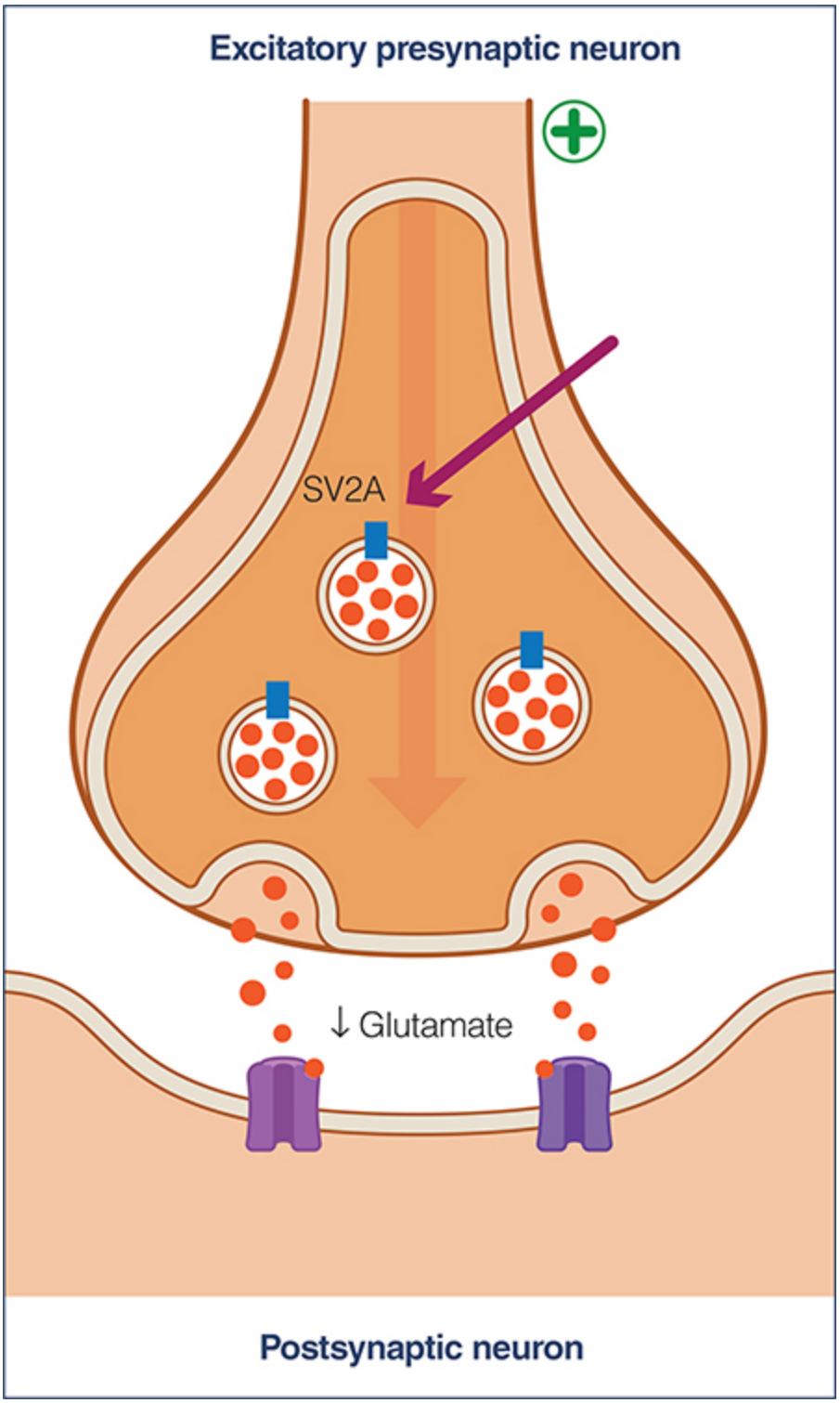


FIGURE 12.1. Mechanism of action of levetiracetam. Levetiracetam exerts its effect by selectively binding to synaptic vesicle protein 2A (SV2A), decreasing the rate of neurotransmitter release.

PHARMACOKINETICS

Initial pharmacokinetic (PK) studies performed on healthy dogs demonstrated LEV is rapidly and completely absorbed after oral administration, with a maximum serum concentration (C_{max}) of 30–60 µg/mL achieved within 30–150 minutes.[5–7] The drug binds minimally to plasma proteins,[5] and displays linear PK.[8] Levetiracetam undergoes primary renal excretion in dogs,[5] with an elimination half-life ($t_{1/2}$) of approximately 3 hours.[5–9] Furthermore, repeated oral LEV dosing over 7 days does not appreciably change the drug's PK profile.[9] A diurnal difference in plasma drug concentrations has been described, with higher morning trough concentrations compared to those achieved in the afternoon, that are presumed to reflect diurnal changes in glomerular filtration rate.[9] Concurrent administration of phenobarbital (PB) has been shown to alter the PK characteristics of LEV.[7] In this study, healthy dogs were administered a single oral LEV dose of approximately 20 mg/kg, and LEV concentrations were measured in blood samples collected at set times over a 24-hour period. Study dogs were then administered oral PB (2.0–3.3 mg/kg) every 12 hours for 21 days, after which time the experiment was repeated. Coadministration of PB resulted in a decrease in LEV C_{max} and $t_{1/2}$, and an increase in oral clearance. This has been postulated to be due to PB-associated induction of enzymes involved in the oxidation of LEV.[7] Although LEV is renally excreted, approximately half of the drug is metabolized through hydrolysis, and to a lesser extent, through oxidative processes prior to excretion.[5] These metabolic pathways are independent of the hepatic cytochrome P450 pathway, but in the dog, they are subject to induction by PB.[5] A subsequent study involving client-owned dogs with IE yielded similar findings, with dogs administered concurrent PB displaying an increased LEV clearance when compared to dogs that had been coadministered LEV and potassium bromide (KBr).[10]

An extended-release formulation of LEV (LEV-XR) became commercially available in the United States in 2009, providing the benefit of a reduced frequency of administration. A few studies have been performed evaluating the PK profile of LEV-XR in dogs. Like the immediate-release formulation, the drug has an oral bioavailability of 100%. Following the administration of 30 mg/kg LEV-XR to healthy dogs,

a C_{max} of 26–30 μg/mL was achieved within 3–8 hours, with a $t_{1/2}$ of approximately 4 hours.[11] Dogs that were administered LEV-XR with food had a significantly longer mean time to C_{max} compared to fasted dogs (6.6 vs 3.4 hours), suggesting that food slows the disposition of this drug formulation.[11] A second crossover PK study, in which healthy, fasted dogs were administered 500 mg of the immediate- and extended-release formulations of LEV (18–23 mg/kg), demonstrated LEV-XR had a significantly lower C_{max} (mean, 21.9–29.4 μg/mL vs 34.9 μg/mL) and a longer time to C_{max} (5.33–8.0 hours vs 2.29 hours), but a similar $t_{1/2}$ (approximately 4 hours) compared to the immediate-release formulation.[12] A study in dogs with IE evaluated the PK characteristics of LEV-XR when administered alone or in combination with PB or zonisamide (ZNS). The PK parameter values in dogs administered LEV-XR alone were similar to those from previous reports, with a C_{max} of 33.01 μg/mL and a $t_{1/2}$ of approximately 5 hours. Coadministration of PB resulted in significant alterations in the disposition of LEV-XR, as described for the immediate-release formulation, but concurrent administration of ZNS was not shown to alter the PK profile of LEV-XR.[13]

The PK features of LEV administered parenterally have also been evaluated in healthy dogs. Intramuscular (IM) administration of LEV (20 mg/kg) achieves a bioavailability of 100%, with a mean time to maximum concentration of 40 minutes and a C_{max} of 30.3 μg/mL.[6] The $t_{1/2}$ for intravenously (IV) administered LEV in dogs has been reported to range from 3–4 hours.[6,8,14] Finally, rectal administration of LEV in healthy dogs at a dose of 40 mg/kg achieved a C_{max} of 36 μg/mL in approximately 1.7 hours,[15] with the presence of feces in the rectum significantly decreasing the maximum serum concentrations obtained.

There is limited information on the PK characteristics of LEV in cats. A study involving healthy cats demonstrated similar parameter values to those reported for dogs, with an oral bioavailability approaching 100%, a mean time to maximum concentration of 1.7 hours, and a $t_{1/2}$ of approximately 3 hours.[16] Additional PK data were described in a study on cats with presumed IE coadministered LEV and PB.[17] After 1 week of administration of LEV at an oral dose of 20 mg/kg every 8 hours, blood samples were collected before, and at 2, 4 and 6 hours after dosing. A median C_{max} of

25.5 µg/mL was achieved at 2 hours, with a $t_{1/2}$ of 2.9 hours. Finally, the disposition of LEV-XR has been evaluated in healthy cats administered a single oral 500 mg tablet (median dose of 86.2 mg/kg). Cats achieved a mean C_{max} of 89.8 µg/mL at 4.9 hours, with a $t_{1/2}$ of 4.1 hours.[18]

The transdermal route of LEV administration has been evaluated in cats.[19] In this PK study, the drug was compounded to a concentration of 400 mg/mL and applied to the inner pinna of healthy cats to achieve a dosage of 60 mg/kg every 8 hours for 6 days. The estimated median maximum and minimum serum concentrations were 22.0 µg/mL and 11.9 µg/mL, respectively, suggesting that this route may be an alternative when administration of oral medication is difficult.

The clinically relevant PK parameters for LEV from published studies in dogs and cats are summarized in Table 12.1.

EFFICACY

There is relatively little data on the efficacy of LEV as a treatment for epilepsy in dogs and cats to provide strong evidence in support of its use in clinical practice. There are only two published studies evaluating LEV as monotherapy in dogs. Fredsø et al. performed a single-blind, randomized, parallel trial comparing the use of LEV with PB in dogs with newly diagnosed IE.[20] Twelve dogs were enrolled in the yearlong study. Therapy was initiated with either LEV, administered at a dose of 10 mg/kg orally every 8 hours (2 dogs) or 20 mg/kg orally every 8 hours (4 dogs), or PB administered at a dose of 2 mg/kg orally every 12 hours (6 dogs). Dogs with more than one epileptic seizure over a 3-month timespan received a dosage increase of 10 mg/kg/day for LEV or 1 mg/kg/day for PB. The primary outcome measure was monthly epileptic seizure frequency during treatment compared to a retrospective 6-month baseline. Five of the 6 dogs (83%) administered LEV and 1 of the 6 dogs (17%) administered PB withdrew from the study due to insufficient seizure control. No difference in epileptic seizure frequency during treatment compared to baseline was demonstrated for the dogs administered LEV, and none of the dogs were considered responders with a ≥50% reduction in epileptic seizure frequency. In comparison, a significant decrease in epileptic seizure frequency was noted

in the PB-treated dogs, with 5 of 6 dogs (83%) classified as responders. Results from this study failed to demonstrate LEV to be efficacious when used as monotherapy in dogs with IE. Levetiracetam monotherapy has also been evaluated retrospectively in 19 dogs with structural epilepsy. This study population included dogs with underlying inflammatory, vascular, neoplastic, traumatic and congenital disease.[21] The initial LEV dose was 20 mg/kg orally every 8 hours, and additional medications were administered as needed for treatment of the underlying condition. At the time of follow-up, between days 12 and 426 after treatment initiation, 9 dogs (47%) were still being administered LEV, 7 (37%) of which were reported to be free of seizures. The results of this study suggest that LEV may be a reasonable option for dogs with structural epilepsy, but the quality of evidence in this study is low due to its retrospective nature, the lack of a control group, and the fact that dogs were being administered additional medications to treat their underlying condition.

To date, three published studies have described the use of LEV as an adjunctive therapy in dogs with drug-resistant IE. A retrospective study described the use of LEV in 52 dogs, 29 of which received maintenance therapy with LEV (approximately 20 mg/kg orally every 8 hours) and 23 dogs that received pulse therapy for cluster seizures (initial oral dose of approximately 60 mg/kg after an epileptic seizure or at the onset of preictal signs, followed by 20 mg/kg orally every 8 hours until 48 hours with no seizures).[22] Approximately 2/3 of dogs treated with LEV were classified as responders, with a ≥50% reduction in epileptic seizure frequency, and 15% of dogs were reported to be free from epileptic seizures over an average follow-up period of approximately 1 year.

TABLE 12.1. Summary of clinically relevant pharmacokinetic parameters from published studies on dogs and cats.

Reference	Study animals	Route of administration	Dose and duration	Absorption (%)	C_{max} (μg/mL)	T_{max} (h)	$t_{1/2}$ (h)	Duration (h) with LEV >5 μg/mL
DOG								
Isoherranen[8]	6 healthy mixed-breed dogs	IV	20 mg/kg, once	NA	NR	NA	3.6	NR
Dewey[14]	6 healthy mixed-breed dogs	IV	60 mg/kg, once	NA	254*	NA	4.0	8**
Beasley[11]	12 healthy client-owned dogs	IV	30 mg/kg	NA	70*	NA	4.0	9.5
Patterson[6]	6 healthy hounds	IV	20 mg/kg, once	NA	37*	NA	3.0	NR
		IM	20 mg/kg, once	100	30.3	0.67	3.0	8
		PO-IR	20 mg/kg, once	100	30	1.35	3.0	11
Moore[9]	6 healthy dogs (5 Beagles, 1 hound)	PO-IR	20 mg/kg, once	NR	59.9	0.62	2.9	10
		PO-IR	20 mg/kg every 8 h for 6 days	NR	52.4	1.0	3.6	12
Moore[7]	6 healthy dogs (3 Beagles, 3 hounds)	PO-IR	20 mg/kg, once	NR	32.4	0.74	3.5	10
Boozer[12]	6 healthy, client-owned mixed breed dogs	PO-IR	20 mg/kg, once	NR	34.9	2.29	4.17	12
		PO-XR (Keppra®)	20 mg/kg, once	NR	29.4	6.0	4.47	12
		PO-XR (generic 1)	20 mg/kg, once	NR	21.9	5.33	4.44	12
		PO-XR (generic 2)	20 mg/kg, once	NR	27.8	8.0	4.42	12
Beasley[11]	12 healthy client-owned dogs	PO-XR	30 mg/kg, once (fasted)	100	26.6	3.4	4.4	19.8
		PO-XR	30 mg/kg once, (fed)	100	30.7	6.6	4.2	20.7
Muñana[13]	6 epileptic client-owned dogs	PO-XR	30 mg/kg every 12 h for ≥1 week	NR	33.01	3.28	NR	12
Peters[15]	6 healthy client-owned dogs	PR	40 mg/kg, once	NR	36.0	103	NR	6**
CAT								
Carnes[16]	10 healthy cats	IV	20 mg/kg, once	NA	37.5	NA	2.86	9 (7 of 10 cats)
		PO-IR	20 mg/kg, once	100	25.54	1.67	2.95	9 (7 of 10 cats)
Bailey[17]	12 epileptic client-owned cats	PO-IR (concurrent PB)	20 mg/kg for ≥1 week	NR	25.5	2.0	2.9	6**
Barnard[18]	7 healthy client-owned cats	PO-XR	500 mg (median 86 mg/kg), once	NR	89.8	4.9	4.1	18

C_{max}, maximum serum concentration; Tmax, time to maximum serum concentration; $t_{1/2}$, elimination half-life; IR, immediate release; XR, extended release; IV, intravenous; IM, intramuscular; PO, oral; PR, rectal; PB, phenobarbital; NR, not reported; NA, not applicable.

* For IV administration, the reported value for C_{max} is the initial concentration (C0).

** Final measurement was obtained at this time point.

Volk et al. reported on 22 dogs with drug-resistant IE that were treated with LEV as an add-on therapy to PB and KBr.[23] Eight dogs that were administered LEV at a dose ranging from 10–33 mg/kg orally every 8 hours were retrospectively evaluated. Dogs were reported to have an average reduction in monthly epileptic seizure frequency of 60%, with 5 of 8 dogs (63%) classified as responders. This led to a prospective, open-label, noncomparative study in 14 additional dogs. Dogs were initially administered LEV at a dosage of 10 mg/kg orally every 8 hours for 2 months, and in those that did not respond, the dose was increased to 20 mg/kg orally every 8 hours for an additional 2 months. After 2 months of treatment, 8 of 14 dogs (57%) were classified as responders with a 51% decrease in monthly epileptic seizure frequency. One additional dog was classified as a responder after an increase in the LEV dose. However, 6 of the 9 dogs (67%) experienced a subsequent increase in epileptic seizure frequency after 4–8 months of treatment.

Levetiracetam was evaluated as an adjunctive treatment for drug-resistant IE in a prospective, randomized, placebo-controlled study involving 34 dogs that were being administered either PB and KBr (27 dogs), PB alone (4 dogs), KBr and ZNS (1 dog), PB and gabapentin (1 dog) or PB, KBr and gabapentin (1 dog). Twenty-two dogs completed the study.[24] A significant decrease in the primary outcome variable of weekly epileptic seizure frequency was demonstrated during LEV administration at a dosage of 20 mg/kg orally every 8 hours compared to a prospective baseline (1.9 vs 1.1); however, the reduction in weekly epileptic seizure frequency associated with LEV administration was not significant when compared to placebo administration (1.1 vs 1.5). Furthermore, there was no statistically significant difference between the number of dogs classified as responders with LEV (56%) and with the placebo (30%). This study failed to demonstrate the efficacy of LEV over a placebo, but was limited by a small sample size.

Levetiracetam has been evaluated as a prophylactic treatment for postoperative seizures in dogs having undergone portosystemic shunt attenuation. A retrospective study analyzed data from 126 dogs that had undergone surgical correction of an extrahepatic congenital portosystemic shunt. One third of dogs were administered LEV at a dose of 20 mg/kg orally every 8 hours for a minimum of 24 hours prior to surgery, while the remaining dogs received no preoperative ASD.[25] None of the dogs

administered LEV experienced postoperative seizures, while 5% (4/84) of the untreated dogs did. Furthermore, the relative risk for seizures was <1 for LEV-treated dogs, suggesting that LEV decreases the risk of postoperative seizures in dogs with congenital portosystemic shunts. However, a second retrospective study evaluating 940 dogs administered either LEV at two different dosing regimens prior to surgery or no preoperative ASD failed to identify any difference in the incidence of postattenuation seizures between the groups.[26]

The American College of Veterinary Internal Medicine (ACVIM) published a consensus statement on seizure management of dogs in 2015, in which the available evidence for each ASD was analyzed to provide treatment recommendations.[27] Levetiracetam monotherapy received a low recommendation based on the limited evidence to support its efficacy. As an add-on therapy, LEV received a moderate recommendation, with an indication that it is most likely to be effective based on the available evidence. A similar systematic review performed by Charalambous et al. in 2014 concluded that there is fair evidence for recommending LEV as an adjunctive treatment for seizures in dogs.[28]

There are very few studies evaluating the efficacy of LEV therapy in cats with epilepsy. One trial assessed the efficacy of LEV monotherapy (20–25 mg/kg orally every 8 hours) compared to PB monotherapy (3–5 mg/kg orally every 12 hours) in 57 cats with feline audiogenic seizures presenting with >12 myoclonic seizures per day.[29] The study was prospective, randomized and open-label in design, with a treatment duration of 12 weeks. A significant difference in the number of cats classified as responders in the LEV (100%) and PB (3%) groups was identified. In addition, a significant difference was noted in the number of cats that achieved seizure freedom (50% with LEV compared to 0% with PB). Results from this study suggest that LEV is effective and superior to PB in the treatment of feline audiogenic reflex seizures.

Bailey et al. reported on the use of LEV as an adjunctive therapy in cats with presumed IE.[17] In this open-label, noncomparative clinical trial, 12 cats with PB-resistant epileptic seizures were administered LEV (20 mg/kg orally every 8 hours). Cats were followed up for a median of 9 months (range, 6–24 months). Seizure logs were maintained in 10 cats, and analysis of these logs identified 7 of 10 cats (70%) as responders, with a ≥50% reduction in epileptic seizures. Median monthly epileptic seizure frequency

with LEV treatment (0.42) was significantly decreased compared to before the initiation of LEV therapy (2.1).

A systematic review of drugs used to treat feline epilepsy assessed the level of evidence for LEV's safety and efficacy profile as weak.[30] However, because there is limited evidence to support the use of any ASD in cats, the analysis concluded that LEV was likely a reasonable first-line therapy in cats, behind PB.

CLINICAL USE

Dosing recommendations for LEV in dogs and cats are based on the results of PK studies that dictate the dosage and dosing frequency required to achieve serum LEV concentrations within the targeted range. However, it is important to keep in mind that a therapeutic range for LEV has not been established in dogs and cats. Rather, the targeted reference range of 5–40 µg/mL frequently used in animals has been extrapolated from the established reference range in humans, and its validity in animals is not known. Serum LEV concentrations ranging from <2 to 50.8 µg/mL were reported in 22 dogs with IE administered LEV (20 mg/kg orally every 8 hours), with no association identified between LEV serum concentration and either weekly epileptic seizure frequency or responder classification.[24]

The recommended initial oral maintenance dose for LEV in both dogs and cats is 20 mg/kg every 8 hours. Because of the short $t_{1/2}$ of 3–4 hours, dosing should not be less frequent than every 8 hours. Pharmacokinetic studies in dogs support the administration of the parenteral formulation of LEV by either the IM (20 mg/kg)[6] or rectal (40 mg/kg)[15] route if oral administration is not possible. These alternate routes have not been evaluated in cats.

Because of its primary renal excretion, guidelines have been established for LEV dosage adjustments in humans with renal impairment. Similar recommendations have not been proposed in veterinary medicine, but a dosage reduction might be indicated in dogs and cats with renal dysfunction. In addition, a dosage increase may be warranted in dogs coadministered LEV and PB, based on the previously discussed increase in LEV clearance induced by PB.[7,10]

The recommended maintenance dose for LEV-XR in dogs is 30 mg/kg orally every 12 hours. To transition a dog from immediate-release LEV to LEV-XR, the same daily dose is administered, but the LEV-XR formulation is divided into two daily doses instead of the three doses used for the immediate-release formulation. It is important to remember that LEV-XR must not be altered prior to administration, as splitting or crushing the tablet will negate the extended-release properties; consequently, this formulation may not be appropriate for small dogs. There is currently insufficient data to recommend use of LEV-XR in cats.

Levetiracetam has a wide therapeutic index, and serum concentrations are not routinely measured in clinical practice. Furthermore, there are no established recommendations for LEV dosage adjustments in dogs and cats. It has been suggested that the dose be increased by 20 mg/kg increments until efficacy is achieved or adverse effects become apparent.[31] This is comparable to the recommendation for dosage adjustments in humans. The human guidelines also include a maximum dosage, but this is not routinely considered in dogs and cats. However, there is a point at which an additional increase in dosage is not likely to confer any additional benefit, and measuring LEV serum concentrations may be of value in this determination. In addition, measurement of serum LEV concentrations may be of value under certain circumstances to individualize treatment, such as in dogs concurrently receiving PB. A treatment algorithm with recommendations on LEV dosing and measuring serum concentrations is outlined in Figure 12.2.

Pulse therapy, or the administration of intermittent dosing to enhance the therapeutic effect, has been advocated as a home treatment for cluster seizures. An initial oral LEV dose of 60 mg/kg can be administered after an epileptic seizure or at the onset of preictal signs, and oral dosing is continued at 20 mg/kg every 8 hours until the animal has been seizure-free with an absence of preictal signs for a minimum of 48 hours, at which time the treatment can be discontinued.[22]

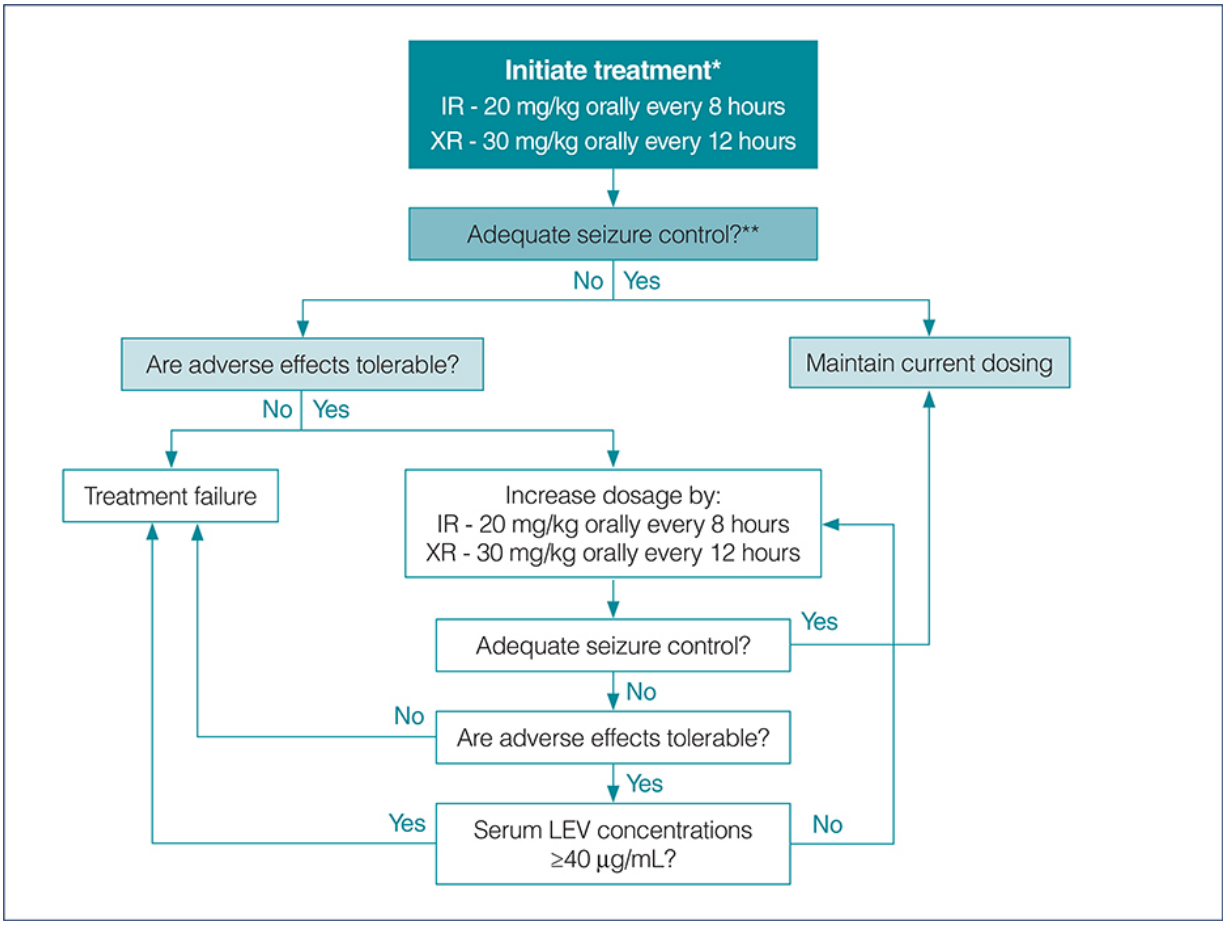


FIGURE 12.2. Algorithm outlining a treatment protocol for levetiracetam (LEV) in the management of epilepsy in dogs and cats.
* A higher initial LEV dose can be considered in dogs treated concurrently with phenobarbital (PB).
** Adequate seizure control is defined as freedom from epileptic seizures for a time span greater than three times the longest pretreatment interseizure interval or a minimum of 3 months (see Chapter 9).
IR, immediate release; XR, extended release.

ADVERSE EFFECTS AND DRUG INTERACTIONS

The likelihood of LEV producing or being subject to drug interactions is low, due to its negligible protein binding, lack of hepatic metabolism, and absent influence on enzyme induction systems. Aside from PB's effect on LEV metabolism in the dog as discussed earlier in this chapter, no other drug–drug interactions have been reported with LEV use in dogs or cats.

To date, most of the adverse effects (AEs) associated with LEV are classified as type A (predictable, dose-dependent) (see also AE classification, Chapter 9). Adverse effects of LEV that involve the central nervous system in humans can be categorized as:

- Somnolence and fatigue
- Coordination difficulties
- Behavioral abnormalities[32]

Neurological AEs reported in dogs include ataxia, sedation, restlessness, and behavioral changes, including aggression.[33] Gastrointestinal-related AEs are also described. Vomiting has been most often reported, but decreased appetite, polyphagia and diarrhea have also been described.[33] The AEs in dogs are typically considered mild.

The AEs that have been reported with the use of LEV in dogs with epilepsy are summarized in Table 12.2.

A retrospective study was undertaken to investigate the incidence of behavioral changes in dogs administered LEV.[34] The study population included dogs with IE, structural epilepsy, or reactive seizures secondary to hepatic encephalopathy, and several dogs were administered other ASDs in addition to LEV. Alterations in behavior were documented in approximately half of the 84 dogs in the study, with a worsening of pre-existing behavioral abnormalities in 14 (17%) dogs, a negative behavioral change in 14 (17%) dogs, and a positive behavioral change in 15 (18%) dogs. Negative behavioral changes included anxiety, depression, aggression, attention seeking behavior, aimless behavior, decreased learning ability and hyperexcitability, and positive changes included calmer mood, joyful mood and increased activity. Worsening of behavioral changes were reported with escalating doses of LEV, while changes tended to resolve if the drug was discontinued.

Parenteral administration of LEV is safe in dogs. No tissue damage was noted with either IM injection of LEV or with extravascular injection of LEV designed to approximate drug extravasation associated with IV injection.[6] The only report of a type B (idiosyncratic) AE associated with LEV is of a dog developing an immediate serious reaction to the rapid IV administration of undiluted LEV at a dose of 60 mg/kg, with clinical signs of tachycardia, hyperglycemia, hypotension and dull mentation.[35] Such anaphylactic-like reactions are considered rare.

Type A AEs reported in cats include sedation, lethargy, ataxia, hypersalivation, inappetence, diarrhea and polydipsia.[16–18] A clinical trial evaluating LEV in 12 cats with IE reported sedation in 1 cat (8%) and inappetence in 2 cats (17%).[17] An evaluation of 28 cats administered LEV as a treatment for audiogenic reflex seizures reported AEs in 5 cats, including lethargy in 4 cats (14%), mild inappetence in 3 cats (11%), ataxia in 2 cats (7%) and polydipsia in 1 cat (4%), with resolution of clinical signs noted after approximately 2 weeks.[29] Pharmacokinetic studies in healthy cats have described hypersalivation, sedation and diarrhea in some cats after the oral administration of LEV.[16,18]

TABLE 12.2. Frequency of adverse events reported with the use of levetiracetam (LEV) in dogs. The number of dogs affected with each adverse event is listed in parentheses.

Reference	Fredsø[20] (n=6)	Kelly[21] (n=19)	Packer[22] (n=29)	Packer*[22] (n=23)	Volk[23] (n=12)	Muñana[24] (n=28)	Overall (n=117)
Neurological adverse events							
Sedation	17% (1)	5% (1)	10% (3)	39% (9)	8% (1)		13% (15)
Ataxia	33% (3)		17% (5)	43% (10)		39% (11)	24% (28)
Restlessness	50% (3)			4% (1)		14% (4)	7% (8)
Aggression				4% (1)			1% (1)
Disobedience	33% (2)						2% (2)
Attention seeking	17% (1)						1% (1)
More interactive					67% (8)		7% (8)
Gastrointestinal adverse events							
Vomiting	17% (1)		3% (1)			11% (1)	3% (3)
Decreased appetite	17% (1)					7% (2)	3% (3)
Diarrhea			3% (1)				1% (1)
Other adverse events							
Weight gain	17% (1)						1% (1)
Polyphagia	67% (4)	42% (8**)	10% (3)	13% (3)			15% (18)
Polydipsia	50% (3)	32% (6**)	3% (1)	9% (2)			10% (12)
Polyuria	33% (2)	32% (6**)					7% (8)
Inappropriate urination		5% (1)					1% (1)

* Dogs were administered LEV as pulse therapy.
** 6 dogs in this study were administered corticosteroids concurrently with LEV.

TAKE-HOME MESSAGES

- ✔ Levetiracetam is used as both monotherapy and add-on therapy in dogs and cats with epilepsy, although its efficacy is not well established. There is fair evidence to support LEV's use as adjunctive therapy in dogs with IE, but its use as monotherapy has not been substantiated. Levetiracetam has been demonstrated to be efficacious in the treatment of reflex audiogenic seizures in cats, but further evidence to support its use in cats with epilepsy is lacking.
- ✔ The mechanism of action of LEV is unique among ASDs, in that it acts presynaptically on the SVA2 protein to modulate neurotransmitter release and thereby prevent hypersynchronous activity.
- ✔ The recommended starting dose for LEV is 20 mg/kg orally every 8 hours for the immediate-release formulation, and 30 mg/kg orally every 12 hours for LEV-XR. If epileptic seizure control is inadequate, the dose can be doubled. Higher doses may be required in dogs coadministered PB. A reference range has not been established in dogs and cats, but monitoring of serum concentrations may be useful to individualize therapy, using the human reference range of 5–40 µg/mL.
- ✔ Pulse therapy can be used for home treatment of cluster seizures, by administering 60 mg/kg of oral LEV after an epileptic seizure or at the onset of preictal signs, and continuing dosing at 20 mg/kg orally every 8 hours for a minimum of 48 hours after the last seizure or preictal episode.
- ✔ In general, the AEs of LEV are considered mild. The central nervous system and gastrointestinal tract are most commonly involved.

REFERENCES

1. STEINHOFF BJ, STAACK AM. Levetiracetam and brivaracetam: a review of evidence from clinical trials and clinical experience. *Ther Adv Neurol Disord*. 2019; 12:1756286419873518.
2. KLITGAARD H, MATAGNE A, NICOLAS JM et al. Brivaracetam: Rationale for discovery and preclinical profile of a selective SV2A ligand for epilepsy treatment. *Epilepsia*. 2016;

57(4):538–548.

3. LYNCH BA, LAMBENG N, NOCKA K et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci USA*. 2004; 101(26):9861–9866.
4. SURGES R, VOLYNSKI KE, WALKER MC. Is levetiracetam different from other antiepileptic drugs? Levetiracetam and its cellular mechanism of action in epilepsy revisited. *Ther Adv Neurol Disord*. 2008; 1(1):13–24.
5. BENEDETTI MS, COUPEZ R, WHOMSLEY R et al. Comparative pharmacokinetics and metabolism of levetiracetam, a new anti-epileptic agent, in mouse, rat, rabbit and dog. *Xenobiotica*. 2004; 34(3):281–300.
6. PATTERSON EE, GOEL V, CLOYD JC et al. Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics. *J Vet Pharmacol Ther*. 2008; 31(3):253–258.
7. MOORE SA, MUÑANA KR, PAPICH MG, NETTIFEE-OSBORNE JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther.* 2011; 34(1):31–34.
8. ISOHERRANEN N, YAGEN B, SOBACK S et al. Pharmacokinetics of levetiracetam and its enantiomer (R)-alpha-ethyl-2-oxo-pyrrolidine acetamide in dogs. *Epilepsia*. 2001; 42(7):825–830.
9. MOORE SA, MUÑANA KR, PAPICH MG, NETTIFEE-OSBORNE J. Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. *Am J Vet Res*. 2010; 71(3):337–341.
10. MUÑANA KR, NETTIFEE-OSBORNE JA, PAPICH MG. Effect of chronic administration of phenobarbital, or bromide, on pharmacokinetics of levetiracetam in dogs with epilepsy. *J Vet Intern Med*. 2015;29(2): 614–619.
11. BEASLEY MJ, BOOTHE DM. Disposition of extended release levetiracetam in normal healthy dogs after single oral dosing. *J Vet Intern Med*. 2015; 29(5):1348–1353.
12. BOOZER LB, PLATT SR, HALEY AC et al. Pharmacokinetic evaluation of immediate- and extended-release formulations of levetiracetam in dogs. *Am J Vet Res*. 2015; 76(8):719–723.
13. MUÑANA KR, OTAMENDI AJ, NETTIFEE JA et al. Population pharmacokinetics of extended-release levetiracetam in epileptic dogs when administered alone, with phenobarbital or zonisamide. *J Vet Intern Med*. 2018; 32(5):1677–1683.
14. DEWEY CW, BAILEY KS, BOOTHE DM et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emerg Crit Care (San Antonio)*. 2008; 18(2):153–157.
15. PETERS RK, SCHUBERT T, CLEMMONS R et al. Levetiracetam rectal administration in healthy dogs. *J Vet Intern Med*. 2014;28(2): 504–509.
16. CARNES MB, AXLUND TW, BOOTHE DM. Pharmacokinetics of levetiracetam after oral and intravenous administration of a single dose to clinically normal cats. *Am J Vet Res*. 2011; 72(9):1247–1252.
17. BAILEY KS, DEWEY CW, BOOTHE DM et al. Levetiracetam as an adjunct to phenobarbital treatment in cats with suspected idiopathic epilepsy. *J Am Vet Med Assoc*. 2008; 232(6):867–872.
18. BARNARD L, BARNES HELLER H, BOOTHE DM. Pharmacokinetics of single oral dose extended-release levetiracetam in healthy cats. *J Vet Intern Med*. 2018; 32(1):348–351.
19. SMITH C, BARNES HELLER HL, REIF N et al. Serum levetiracetam concentrations after transdermal levetiracetam administration, 3 times daily, to healthy cats. *J Vet Intern Med*. 2019; 33(2):827–830.

20. Fredsø N, Sabers A, Toft N et al. A single-blinded phenobarbital-controlled trial of levetiracetam as mono-therapy in dogs with newly diagnosed epilepsy. *Vet J*. 2016; 208:44–49.
21. Kelly D, Raimondi F, Shihab N. Levetiracetam monotherapy for treatment of structural epilepsy in dogs: 19 cases (2010-2015). *Vet Rec*. 2017; 181(15):401.
22. Packer RMA, Nye G, Porter SE et al. Assessment into the usage of levetiracetam in a canine epilepsy clinic. *BMC Vet Res*. 2015; 11(1):25.
23. Volk HA, Matiasek LA, Luján Feliu-Pascual A et al. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. *Vet J*. 2008; 176(3):310–319.
24. Muñana KR, Thomas WB, Inzana KD et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled, crossover trial. *J Vet Intern Med*. 2012; 26(2):341–348.
25. Fryer KJ, Levine JM, Peycke LE et al. Incidence of postoperative seizures with and without levetiracetam pretreatment in dogs undergoing portosystemic shunt attenuation. *J Vet Intern Med*. 2011; 25(6):1379–1384.
26. Mullins RA, Sanchez Villamil C, de Rooster H et al. Effect of prophylactic treatment with levetiracetam on the incidence of postattenuation seizures in dogs undergoing surgical management of single congenital extrahepatic portosystemic shunts. *Vet Surg*. 2019; 48(2):164–172.
27. Podell M, Volk HA, Berendt M et al. 2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs. *J Vet Intern Med*. 2016; 30(2):477–490.
28. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy--a systematic review. *BMC Vet Res*. 2014; 10(1):257.
29. Lowrie M, Thomson S, Bessant C et al. Levetiracetam in the management of feline audiogenic reflex seizures: a randomised, controlled, open-label study. *J Feline Med Surg*. 2017; 19(2):200–206.
30. Charalambous M, Pákozdy Á, Bhatti SF et al. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14(1):64.
31. Dewey CW. Anticonvulsant therapy in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2006; 36(5):1107–1127.
32. Klitgaard H, Verdru P. Levetiracetam: the first SV2A ligand for the treatment of epilepsy. *Expert Opin Drug Discov*. 2007; 2(11):1537–1545.
33. Charalambous M, Shivapour SK, Brodbelt DC et al. Antiepileptic drugs' tolerability and safety - a systematic review and meta-analysis of adverse effects in dogs. *BMC Vet Res*. 2016; 12(1):79.
34. Erath JR, Nessler JN, Riese F et al. Behavioral changes under levetiracetam treatment in dogs. *Front Vet Sci*. 2020; 7:169.
35. Biddick AA, Bacek LM, Taylor AR. A serious adverse event secondary to rapid intravenous levetiracetam injection in a dog. *J Vet Emerg Crit Care (San Antonio)*. 2018; 28(2):157–162.

Imepitoin 13

Andrea Tipold

Imepitoin (IMP) (former names AWD 131-138 and ELB 138; 1-(4-chlorophenyl)-4-morpholino-imidazolin-2-one) was developed for use as an antiseizure drug (ASD) in dogs.[1] Its antiseizure properties were first discovered in experimental rodent models that showed broad-spectrum anticonvulsant and anxiolytic properties with a high therapeutic index.[1,2] After it was discovered that the substance stimulated different recombinant isoforms of the rat γ-aminobutyric acid $(GABA)_A$ receptor through the benzodiazepine binding site, IMP was initially developed for human medicine.[2,3] Although the substance was shown to be highly tolerable, this project was not pursued any further because of existing pharmacokinetic (PK) differences between nonsmokers and smokers.[3] In a dog seizure model, it was proven that IMP elevated the threshold for pentylenetetrazole-induced convulsions.[1,4] After this discovery, the drug was tested in a clinical pilot study in dogs with epilepsy[1,5] and further developed in controlled multicenter studies leading to marketing approval in the European Union (EU) for treatment of canine idiopathic epilepsy (IE) in 2013.[4,6] Imepitoin is not licensed for the treatment of epilepsy in cats, but the drug is well tolerated as described in a pilot study.[7]

MECHANISM OF ACTION

Imepitoin is an imidazolone derivative.[3] In addition to some effects on voltage-dependent calcium channels, IMP acts as a low-affinity, partial agonist at the benzodiazepine binding site of the $GABA_A$ receptor (Fig. 13.1) and as such offers a new mechanistic category of ASDs.[3] It was found

that the low-affinity binding is sufficient to induce GABA potentiation.[3] Additionally, IMP's low partial agonistic intrinsic activity, which represents about 10–20% of the activity of a full agonist, may explain the drug's good tolerability.[3] Low-affinity binding is associated with a short interaction time with the receptor, which explains the drug's different mechanism of action when compared with full agonists such as benzodiazepines. It also explains why IMP causes fewer adverse effects (AEs) than benzodiazepines and is useful for long-term treatment.[3]

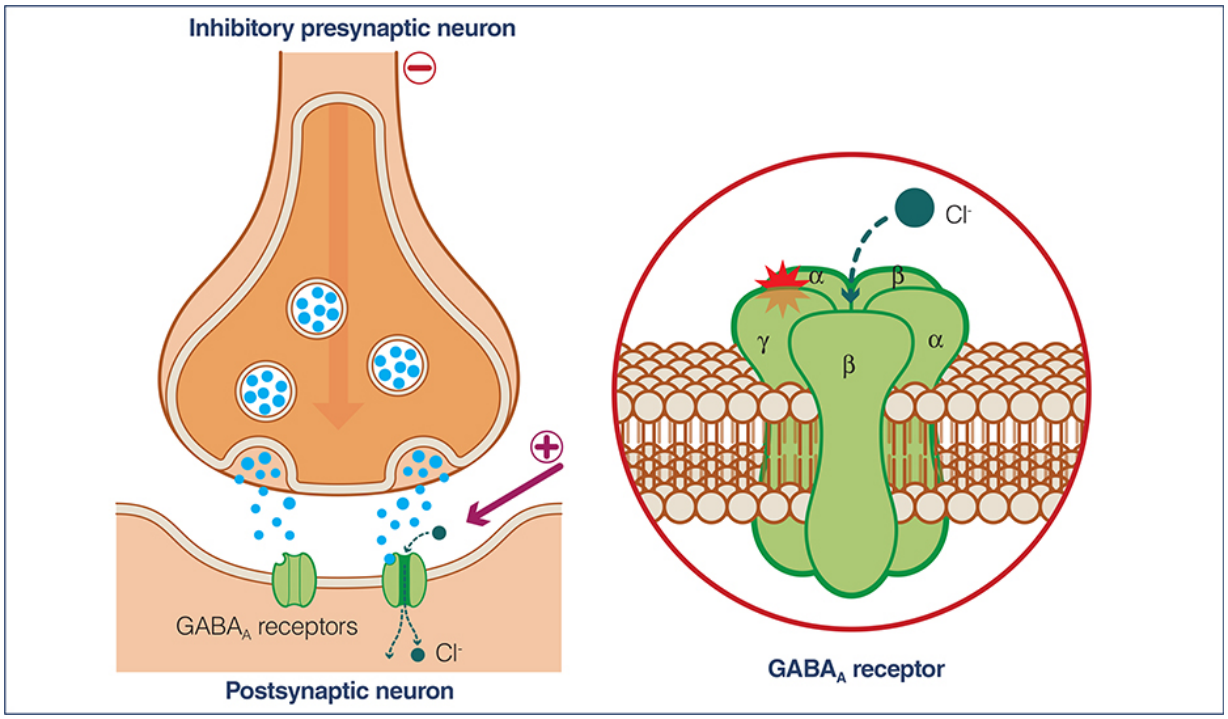


FIGURE 13.1. Mechanism of action of imepitoin. Imepitoin exerts its effect at the benzodiazepine binding site of the $GABA_A$ receptor (red star), where it acts as a low-affinity, partial agonist.

PHARMACOKINETICS

Extensive studies have been performed on the PK parameters and metabolism of IMP in dogs.[4] Based on the described data, twice daily oral dosing of IMP was recommended for this species. The PK profile was evaluated comparing single and multiple dosing at 30 mg/kg orally, and administration under fasted and fed conditions.[4] Peak plasma concentrations were reached 2–3 hours after drug administration because of a relatively

slow absorption in the gastrointestinal tract, which is correlated with the average small intestine passage time of dogs.[4] Although higher maximum plasma concentrations of IMP were reached in fasted dogs, the trough plasma concentration at 12 hours after dosing was higher in dogs fed before drug administration. This slight difference in PK parameter values between fasted and fed dogs was not considered to be clinically relevant. Nevertheless, the author recommends keeping the timing of drug administration constant in relation to feeding.[4] The half-life ($t_{1/2}$) of IMP was determined to be 1.5–2 hours, but dosing twice daily was recommended and proven efficacious in dogs with IE.[1,4] This has been attributed to IMP's high lipophilicity and affinity for membranes, and low solubility in plasma, leading to accumulation of IMP in cell membranes.[4] It is suspected that IMP's pharmacological activity is therefore not coupled with its concentration in plasma.[4] This was proven in the pilot study by Rieck et al. (2006), in which IMP's antiseizure activity was not clearly correlated with plasma concentrations.[5] Indeed, other PK studies have shown an average $t_{1/2}$ of 6.2 hours after oral dosing with 40 mg/kg.[1] Prolonged administration of higher doses of IMP leads to accumulation of the drug and an associated increase in plasma concentrations, such that effective drug concentration can be maintained with twice-daily administration.[1] The slight differences observed in PK values between male and female dogs are not considered to be clinically relevant.[4] Metabolic adaptation could not be detected with peak and trough plasma concentrations even at high dosages;[4,5] plasma levels were measured 21 days after treatment initiation and at different time points (<90 days) and (>120 days) after the first administration of IMP to obtain this conclusion.[5] Increasing the oral dosage from 10 to 20 or even 30 mg/kg might be necessary for effective treatment of dogs with IE. To be able to recommend such a regimen without measuring plasma concentrations, dose linearity is the prerequisite and this was demonstrated in PK studies.[4] Rectal administration of IMP was evaluated in a recent study, but systemic exposure and maximum plasma concentrations of IMP were significantly lower with rectal than with oral administration. Therefore, rectal administration of IMP is not recommended.[8]

Imepitoin has a low protein-binding capacity both in vivo and in vitro, making an interaction with highly protein-bound drugs unlikely.[4] Induction of the cytochrome P450 hepatic enzymes was not detected[4] and PK

interaction with phenobarbital (PB) could not be proven.[5] Imepitoin peak and trough concentrations were similar in 19 dogs treated with a combination of IMP and PB and comparable to levels in dogs with IMP monotherapy.[5]

The metabolism of IMP was evaluated, and the primary enzyme involved in its clearance is CYP1A1, which is expressed in many organs, such as the liver, lung, kidneys and small intestine.[4] Using radiolabeled IMP, it was shown that the primary route of excretion is the fecal route, most likely through biliary excretion.[4] This route encompassed 56–78% of the drug's excretion, while 27–38% was excreted in urine.[4] Most of the drug's excretion took place within the first 48 hours. The author suspects that impaired kidney or liver function will not greatly influence the PKs of IMP.[4] Since clinical trials are not available, IMP is not licensed for the treatment of epileptic dogs with severe liver or kidney disease.

EFFICACY

Imepitoin was developed to symptomatically suppress epileptic seizures in dogs with IE, and as such is the first ASD developed specifically for use in veterinary medicine. Efficacy was initially tested experimentally and in a clinical pilot study[1,5] and then verified in double-blinded, randomized multicenter studies.[9,10] A systematic review to evaluate the efficacy of ASD treatment in dogs with IE revealed good evidence for the efficacy of oral IMP as monotherapy.[11] The evidence for IMP's efficacy in the treatment of cats with epilepsy is weak, but the drug's safety profile in cats is well-established based on the results of a study that included 30 healthy cats and 8 epileptic cats.[7,12] To evaluate treatment protocols in cats with epilepsy, it is still necessary to conduct large cohort studies. In a small uncontrolled open-label study, 4 out of 8 cats achieved seizure freedom under treatment with IMP for at least 8 weeks.[7]

In the first multicenter study that included 127 dogs with untreated epilepsy, the potential superior activity of a high oral IMP dose of 30 mg/kg every 12 hours over a low oral IMP dose of 1 mg/kg every 12 hours was evaluated under double-blinded conditions.[9] Dogs with two to ten generalized tonic-clonic seizures, cluster seizures, or status epilepticus

within the 3-month baseline period were included. Three dogs were excluded due to nonadherence to the study protocol and the remaining 124 dogs were enrolled to assess efficacy of seizure reduction (64 in the high-dose group and 60 in the low-dose group). Twenty-nine dogs (45%) in the high-dose group and 30 dogs (50%) in the low-dose group completed the full observation period of 12 weeks. The most common reasons for exiting the study were predetermined exclusion criteria, such as occurrence of four generalized tonic-clonic seizures or cluster seizures in both the high- and low-dose groups. A significant difference in reduction in monthly seizure frequency was observed between the high-dose and the low-dose groups.[9] However, there was no significant difference in the number of dogs becoming seizure free or the rate of cluster seizures between groups.[9] All the animals that completed the treatment period or were withdrawn due to lack of efficacy were allowed to continue in the open-label phase of the trial, where all dogs were administered oral IMP at 30 mg/kg every 12 hours (53 from the former high-dose group, 47 from the low-dose group). Efficacy was maintained in the high-dose group over the entire observation period of 24 weeks. The increase in dosage in the low-dose group resulted in a statistically significant reduction in the frequency of generalized and focal seizures, but not of cluster seizures.[9] At the end of the study period, 32% (17/53) of dogs in the high-dose group and 46% (22/47) of dogs in the former low-dose group were free of generalized seizures. The safety profile revealed more AEs in the high-dose group; these reactions were related to the central nervous system, transient, and observed during the first weeks of treatment.[9]

In the second multicenter study that included 226 dogs newly diagnosed with IE, the efficacy of IMP was compared to that of PB in a randomized, double-blinded, controlled parallel group trial.[10] Dogs with single generalized tonic-clonic seizures and cluster seizures were enrolled, while dogs with status epilepticus were not included. Imepitoin treatment was initiated at an oral dose of 10 mg/kg every 12 hours, and an increase to a maximal dose of 30 mg/kg every 12 hours was allowed when seizures were not controlled. Treatment with oral PB was initiated at 2 mg/kg every 12 hours, with a maximum allowed dosage of 6 mg/kg every 12 hours. Based on the predetermined exclusion criteria or due to protocol deviations, 52 (45%) dogs were excluded from the IMP group and 22 (20%) dogs from the PB group. A total of 152 dogs were included in the final analysis (64 treated

with IMP and 88 with PB). During the 12-week study period, a ≥50% reduction in monthly seizure frequency was observed in 75% (48/64) of dogs treated with IMP and in 83% (73/88) of dogs treated with PB; seizure freedom was achieved in 47% (30/64) of dogs treated with IMP and in 58% (51/88) of dogs treated with PB. No significant difference in the mean monthly seizure frequency was identified between the PB and IMP treatment groups. The frequency of AEs was significantly higher in the PB group.[10]

After it was licensed in the EU, an increasing number of clinical studies on IMP have been published. Galluci et al. performed a retrospective evaluation of 56 dogs with IE administered IMP monotherapy.[13] At the 3-, 6-, and 12-month follow-ups, 36 (64%), 29 (52%), and 30 (54%) dogs showed a ≥50% reduction in monthly seizure frequency, and 23 (41%), 12 (21%), and 14 (25%) dogs were seizure free, respectively. Responders included dogs with cluster seizures. Imepitoin was discontinued due to inefficacy in 3 dogs (5%) at the 6-month follow-up and in 16 dogs (29%) at the 12-month follow-up. These dogs were classified as nonresponders. Statistical analyses suggested that ≥19 mg/kg twice a day is the most effective minimal oral IMP dosage.[13]

An observational prospective cohort study performed by Stabile et al.[14] included 61 ASD-naïve dogs with IE: 31 were placed in the IMP group (commenced at 10–20 mg/kg orally every 12 hours and increased up to 30 mg/kg every 12 hours as needed), and 30 in the PB group (commenced at 2.5–3.3 mg/kg orally every 12 hours and increased up to 5.2 mg/kg every 12 hours as needed). Dog owners could choose the treatment (IMP or PB) following discussion with the veterinary neurologist. Follow-up duration was 3 years. Pretreatment median seizure frequency was significantly higher in the PB group (2.46 per month; range, 1–7 per month) than in the IMP group (1.5 per month; range 1–4 per month). Post-treatment median seizure frequency was 0.36 per month (range, 0 per 3 years to 1 per month) in the PB group and 0.95 per month (range, 1 per 6 months to 3 per month) in the IMP group. Posttreatment seizure frequency was significantly lower in the PB group than the IMP group, and the seizure frequency decrement from pre- to posttreatment initiation was significantly greater in the PB group than the IMP group.[14] Compared with the PB group, dogs in the IMP group developed cluster seizures significantly more frequently (68% in the IMP group versus 37% in the PB group) and earlier in the course of the

disease (4.5 months in the IMP group versus 17.2 months in the PB group). Aggression and discontinuation of the initial monotherapy occurred significantly more frequently in the IMP group.[14]

In dogs that do not achieve adequate seizure control with IMP monotherapy (at the maximum recommended dosage of 30 mg/kg orally every 12 hours), adjunctive treatment with oral PB or potassium bromide (KBr) can result in treatment success, and results can be maintained following IMP discontinuation in some dogs.[15,16] In a prospective, randomized, controlled clinical trial that included 27 dogs with IE refractory to IMP, adjunctive treatment with PB (initiated at 2 mg/kg orally every 12 hours and increased based on serum concentration monitoring and seizure occurrence) or KBr (oral loading dose followed by 20 mg/kg orally every 12 hours) resulted in a ≤50% reduction in monthly seizure frequency in 11/14 (79%) and 9/13 (69%) dogs in the PB and KBr groups, respectively. Seizure freedom was achieved in 14% and 23% of the dogs in the PB and KBr groups, respectively. Overall, the number of dogs with cluster seizures decreased significantly following adjunctive treatment.[15]

In an open-label prospective clinical trial including 13 IE dogs well-controlled on IMP and PB (n = 4), IMP and KBr (n = 7), or IMP, PB and KBr (n = 2), gradual reduction (over 3 months) and discontinuation of IMP resulted in no change or a decrease in monthly seizure frequency in 12/13 (92%) dogs as well as improvement or disappearance of AEs.[16] The follow-up period after IMP withdrawal was 9–12 months.

Imepitoin was also evaluated as an add-on treatment to PB in two studies. In the first study, IMP was used as an add-on to PB or primidone in 17 dogs. Oral dosing was initiated at 5 mg/kg every 12 hours for 1 week, then increased to 10 mg/kg every 12 hours, and up to 30 mg/kg every 12 hours if seizures persisted. A reduction in monthly seizure frequency was observed in 10 out of 17 (59%) dogs, from 2.4 seizures per month before IMP to 1.1 seizures per month after adjunctive treatment with IMP. The reduction in seizure frequency was statistically significant.[5] Combination of IMP with PB was also investigated in an open-label, monocentric cohort study in dogs with drug-resistant epilepsy.[17] The study included 34 dogs with IE divided in three different groups: 16 dogs were PB-resistant and administered add-on oral IMP starting at 10 mg/kg every 12 hours (titrated up to 30 mg/kg every 12 hours), 11 dogs were PB-resistant and administered add-on oral IMP starting at 5 mg/kg every 12 hours (titrated

up to 30 mg/kg every 12 hours), and 7 dogs were IMP-resistant and administered add-on oral PB starting at 0.5 mg/kg every 12 hours (titrated up to 6 mg/kg every 12 hours). A ≥50% reduction in monthly seizure frequency was observed in 36–42% of all dogs, with no significant difference between the 3 groups. However, it could be shown that, when IMP is used as an add-on treatment, a starting oral dose of 5 mg/kg every 12 hours is better tolerated than the usual 10 mg/kg every 12 hours.[17] On the higher starting oral IMP dose, 6/16 dogs developed an increase in seizure frequency or cluster seizures.[17] In addition, when PB was used as an add-on drug, an oral dose of 1.5 mg/kg every 12 hours was sufficient in several cases to achieve a reduction in seizure frequency. The IMP or PB add-on treatment did not reduce the frequency of occurrence of cluster seizures.[17]

CLINICAL USE

The aim of antiseizure treatment is to reduce seizure frequency and severity while ensuring the AEs of medication are as mild as possible. The animal's and the owner's quality of life has to be kept in mind to enhance owner compliance (see chapters 3 and 9). Imepitoin is generally well tolerated. The advantage of IMP is a rapid onset of action, and discontinuation is relatively uncomplicated when AEs occur or seizure frequency or severity is not satisfactorily diminished.[4,17] Imepitoin can be tapered off relatively quickly; upon termination of treatment in experimental studies, no withdrawal hyperexcitability was seen, which indicates a lack of physical dependence to IMP.[3] However, the only clinical study on IMP tapering in dogs involved dose reductions over 3 months.[16] Gradual dose increases to effectiveness are based only on seizure frequency and tolerability and not on plasma concentrations.

Imepitoin is marketed under the name Pexion™, and is available as 100 mg and 400 mg tablets. The drug only exists as an oral formulation and cannot be administered parenterally.

When used as monotherapy in dogs, it is recommended that IMP be orally administered at an initial dose of 10 mg/kg every 12 hours.[10,13,18] Adverse effects are minimized with this starting dose and some dogs respond to this low dosage.[5] However, a rapid increase to 20 mg/kg every

12 hours is recommended in case of insufficient efficacy.[13] The timing of drug administration should be kept constant in relation to feeding.[4] If sufficient effectiveness is obtained (see Chapter 9 for treatment success definition), the dose should be maintained. Conversely, if seizure frequency or severity is not satisfactorily reduced, titration of the oral dose in approximate 10 mg/kg increments up to a maximum of 30 mg/kg every 12 hours is recommended.[10] If seizures remain uncontrolled, add-on therapy with a different ASD should be instituted, e.g., PB at an initial oral dose of 1.5–2.5 mg/kg every 12 hours[15–17] (Fig. 13.2). Initiating PB administration at the lower end of the dose range can help minimize adverse effects of combined therapy. Once PB steady-state target serum concentrations (see Chapter 10 for further details on PB) and satisfactory seizure control have been achieved, or when combined therapy is poorly tolerated, the IMP dose can be decreased and sometimes discontinued without a negative effect on seizure control.[16] Transitioning IMP-resistant dogs to PB monotherapy may result in improvement or disappearance of AEs associated with combined IMP and PB therapy.[16]

When IMP is used as an add-on treatment in PB-resistant dogs, the recommended initial oral dose is 5 mg/kg every 12 hours.[17] Note that this dose is lower than the IMP monotherapy initial dose. The IMP dose can be gradually increased as needed up to 30 mg/kg every 12 hours.

Regular follow-up examinations of dogs with IE are recommended. These are usually performed every 6–12 months in dogs with satisfactory seizure control and minimal AEs. Such periodic reevaluations are also necessary for dogs treated with IMP. Dogs should be assessed anytime seizure control is not adequate or AEs have a negative impact on their quality of life. Measurement of plasma IMP concentrations is not necessary, since the pharmacological activity of IMP is not coupled with its plasma concentration.[4,5] Dosage adjustments depend on tolerability and effectiveness in reducing seizure frequency and severity. Measurement of IMP concentrations might be helpful when concerns about owner compliance arise, but a commercially available assay for IMP plasma concentrations is not currently available.

Imepitoin treatment did not result in changes in blood chemistry, even with overdosing.[18] An exception was a slight increase in blood creatinine concentrations, which did not exceed the reference range and were not associated with renal failure.[18] Therefore, regular serum biochemistry

analyses should be performed based on the patient's clinical signs; they are not strictly necessary at every follow-up visit, since serum biochemistry changes associated with the administration of IMP are not expected.[4]

In cats, an oral dosage of 30 mg/kg every 12 hours was administered and generally well tolerated in a small open-label study on IMP monotherapy in this species.[7] Additional efficacy data are required to recommend the clinical use of IMP in cats.

Imepitoin is also licensed for the control of anxiety and fear associated with noise phobia in dogs,[18,19] but no improvement in anxiety-related behavior in dogs with IE was identified in an online survey with data on 85 dogs.[20] Imepitoin was also evaluated for the treatment of idiopathic head tremor in dogs in a small randomized, blinded, placebo-controlled study. The responder rate was 17% (2/12 dogs), leading to the conclusion that a significant overall positive effect was not proven and only a subgroup of dogs with idiopathic head tremor might benefit from treatment with IMP.[21]

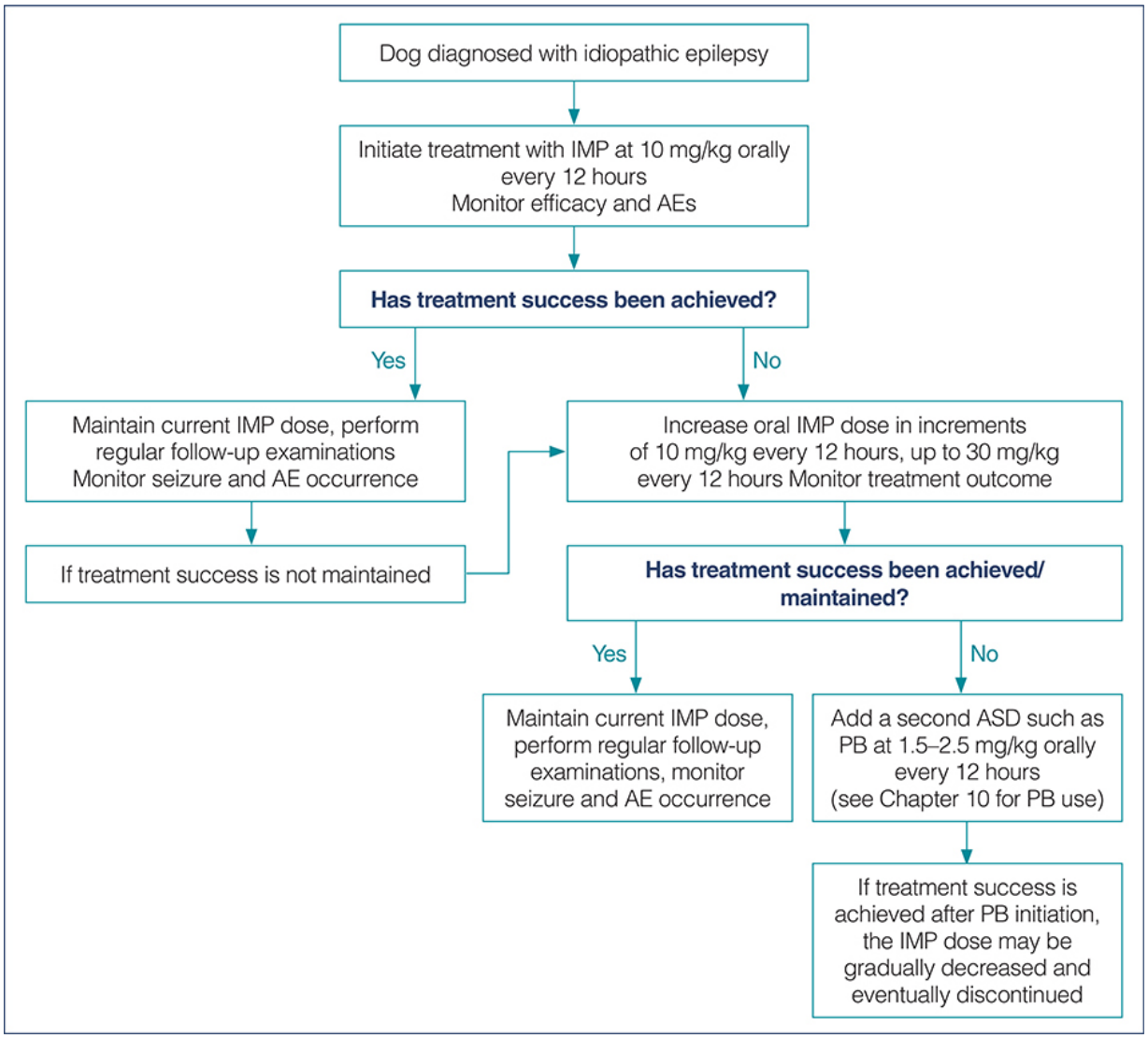


FIGURE 13.2. Recommended treatment protocol for imepitoin (IMP) as initial monotherapy in dogs with idiopathic epilepsy.
AEs, adverse effects; ASD, antiseizure drug; PB, phenobarbital. Therapeutic success is defined as: IMP is well tolerated and epileptic seizure freedom, or a reduction in seizure frequency by at least 50%, has been achieved for 3 months or three times the longest pre–IMP treatment interictal interval, whichever is longer.

ADVERSE EFFECTS AND DRUG INTERACTIONS

Adverse effects were carefully evaluated in experimental and clinical studies in dogs and cats, and IMP is generally considered to be a safe drug

in these species.[1,4,7,10] However, in some cases the AEs caused by IMP treatment have resulted in discontinuation of the drug.[14,22]

In overdosage experiments in dogs, the no-observable-effect level (NOEL) for IMP was 90 mg/kg every 12 hours.[3,10] Even at high dosages, clinical signs of toxicity were mild and included salivation, vomiting, body weight loss, transient ataxia and decreased activity.[3] Studies on IMP tolerance and physical dependence were also performed.[3] No indication of tolerance development was found, and withdrawal signs after abrupt termination of IMP treatment in overdosage did not occur.[3] In further experimental studies, toxicokinetic evaluation of plasma concentrations reflected the applied dosage.[10] Additional findings at the highest oral dosage (150 mg/kg every 12 hours) were lacrimation, eye dryness, intermittent tremor, and nystagmus.[10] Biochemistry parameters remained within the reference range, and although creatinine concentrations increased slightly, this was not associated with renal dysfunction.[10] Gross pathology or histopathology did not reveal any abnormalities in the kidneys.[10]

No severe AEs were found in tolerability studies in cats administered oral IMP at doses of 30–80 mg/kg every 12 hours.[7] Occasional AEs such as vomiting, salivation and slightly reduced food consumption were observed.[7] Hematology and serum biochemistry analyses did not reveal any pathological findings.[7] In cats with IE, AEs were mild and intermittent. Lethargy, vomiting, salivation, decreased or increased appetite and ataxia were each reported in a single cat.[7]

In clinical studies in dogs with IE, polyphagia was the most frequently reported AE.[1,20] In a multicenter study, at least one AE could be observed in 46.6% of dogs under IMP treatment. In this study, IMP treatment was compared to PB treatment. In the PB group, 57.3% of dogs had at least one AE.[10] Additional AEs reported with IMP included sedation, polydipsia and polyuria, and neurological signs such as ataxia,[10,20] hyperactivity,[5,10,20] aggression[14] and dermatological lesions consistent with a lupoid drug reaction in 1 dog.[22] Serum biochemistry parameters in clinical studies in IMP-treated epileptic dogs remained in the reference range, except for creatinine concentrations, which were elevated in 6.2% of the dogs.[10]

The frequency of AEs reported with the use of IMP in dogs is summarized in Table 13.1.

Drug interactions are not yet known. Imepitoin has a low protein-binding capacity in vivo and in vitro, making an interaction with highly

protein-bound drugs unlikely.[4] Induction of the cytochrome P450 hepatic enzymes was not detected[4] and PK interaction with PB could not be proven in one study.[5] Dogs on IMP treatment requiring emergency ASD treatment (e.g., for status epilepticus or cluster seizures) can be administered benzodiazepines without the need to discontinue IMP. Imepitoin, as a partial agonist, does not completely activate the benzodiazepine binding site and quickly dissociates from the $GABA_A$ receptor since it has a lower affinity than benzodiazepines.

TABLE 13.1. Frequency of adverse effects (AEs) reported with the use of imepitoin (IMP) in dogs. The number of dogs included in each study and affected with each AE is indicated in parentheses. An "X" has been used to indicate when an AE was mentioned in a study, but the affected number of dogs was not specified.

Reference	Rieck et al.[5] (n=29)	Rundfeldt et al.[9] (n=66)*	Tipold et al.[10] (n=116)	Gallucci et al.[13] (n=56)	Stabile et al.[14] (n=31)	Schneider et al.[21] (n=13)
Central nervous system AEs (summary)		**72% (48)**	**47% (54)**	**29% (16)**		
Sedation			X	11% (6)	48% (15)	
Ataxia	7% (2)#	X			48% (15)	8% (1)
Restlessness		X				8% (1)
Aggression				2% (1)	13% (4)	
Disorientation		X				
Hyperactivity		X	X	14% (8)		
Gastrointestinal system AEs (summary)		**48% (32)**		**2% (1)**		
Diarrhea			X			8% (1)
Other AEs						
Polyphagia	58% (17)		X	4% (2)	22% (7)	8% (1)
Polydipsia			X		22% (7)	
Polyuria			X		19% (6)	
Pruritus						8% (1)

* Study compared high-dose IMP (30 mg/kg orally every 12 hours) to low-dose IMP (1 mg/kg orally every 12 hours); reported AEs in the table were associated with the high dose.
# IMP was used as add-on to phenobarbital.

TAKE-HOME MESSAGES

- ✔ Imepitoin is the first ASD developed primarily for dogs with IE.
- ✔ Imepitoin acts as a low-affinity, partial agonist at the benzodiazepine site of the $GABA_A$ receptor.

- ✔ The pharmacological activity of IMP is not coupled with its plasma concentration.
- ✔ IMP as monotherapy for canine IE has been reported to decrease seizure frequency by at least 50% in 54–75% of patients and to eradicate seizures in 25–47% of patients, in different studies with a follow-up time of 3 to 12 months.
- ✔ There is conflicting evidence on IMP efficacy in dogs with cluster seizures and limited evidence in dogs with status epilepticus. Therefore, the use of IMP needs to be carefully considered in these dogs.
- ✔ When IMP is used as monotherapy, the starting oral dose is 10 mg/kg every 12 hours. Dosage can be incrementally increased to a maximum of 30 mg/kg every 12 hours.
- ✔ The timing of IMP administration should be kept constant in relation to feeding.
- ✔ When therapeutic success is not achieved or maintained on IMP monotherapy (therapeutic success = IMP is well tolerated and the animal is epileptic seizure free, or a reduction in seizure frequency by at least 50% has been achieved for 3 months or three times the longest pre–IMP treatment interictal interval, whichever is longer), PB can be added at 1.5–2.5 mg/kg orally every 12 hours (see Chapter 10 for further details on PB). Once PB steady-state target serum concentrations and adequate seizure control have been achieved, the initial oral IMP may be decreased and IMP eventually discontinued without a negative effect on seizure control.
- ✔ When IMP is administered as an adjunctive treatment to PB (when therapeutic success is not achieved in dogs on PB monotherapy), the IMP starting dose is 5 mg/kg every 12 hours. The IMP dose can be gradually increased as needed up to 30 mg/kg every 12 hours.
- ✔ There are no commercially available methods for the measurement of plasma IMP concentrations and such measurements have been reported to not be relevant in treatment modulation.
- ✔ Adverse effects are mild and transient in most cases. Polyphagia is the most frequently observed AE in dogs, but sedation, ataxia,

hyperactivity, dermatological lesions and aggression have also been reported.

- ✔ Drug interactions are not known, but unlikely.
- ✔ Data on IMP efficacy in cats are currently insufficient to recommend its use in this species.

REFERENCES

1. Löscher W, Potschka H, Rieck S et al. Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. *Epilepsia*. 2004; 45:1228–1239.
2. Sigel E, Baur R, Netzer R, Rundfeldt C. The antiepileptic drug AWD 131-138 stimulates different recombinant isoforms of the rat GABA A receptor through the benzodiazepine binding site. *Neurosci Lett.* 1998; 245:85–88.
3. Rundfeldt C and Löscher W. The pharmacology of imepitoin: the first partial benzodiazepine receptor agonist developed for the treatment of epilepsy. *CNS Drugs*. 2014; 28:29–43.
4. Rundfeldt C, Gasparic A, Wlaź P. Imepitoin as a novel treatment option for canine idiopathic epilepsy: pharmacokinetics, distribution, and metabolism in dogs. *J Vet Pharmacol Ther*. 2014; 37:431–434.
5. Rieck S, Rundfeldt C, Tipold A. Anticonvulsant activity and tolerance of ELB138 in dogs with epilepsy: a clinical pilot study. *Vet J*. 2006; 172:86–95.
6. Bialer M, Johannessen SI, Levy RH et al. Progress report on new antiepileptic drugs: a summary of the twelfth Eilat conference (EILAT XII). *Epilepsy Res*. 2015; 111:85–141.
7. Engel O, von Klopmann T, Maiolini A et al. Imepitoin is well tolerated in healthy and epileptic cats. *BMC Vet Res*. 2017; 13:172.
8. Martlé V, Devreese M, Rauch S et al. Comparative pharmacokinetics of imepitoin after oral and rectal administration in healthy dogs. *Vet J*. 2020; 259–260: 105459.
9. Rundfeldt C, Tipold A, Löscher W. Efficacy, safety, and tolerability of imepitoin in dogs with newly diagnosed epilepsy in a randomized controlled clinical study with long-term follow up. *BMC Vet Res*. 2015; 11:228.
10. Tipold A, Keefe TJ, Löscher W et al. Clinical efficacy and safety of imepitoin in comparison with phenobarbital for the control of idiopathic epilepsy in dogs. *J Vet Pharmacol Ther*. 2015; 38: 160–168.
11. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy – a systematic review. *BMC Vet Res*. 2014; 10:257.
12. Charalambous M, Pakozdy A, Bhatti SFM, Volk HA. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14:64.
13. Gallucci A, Gagliardo T, Menchetti M et al. Long-term efficacy of imepitoin in the treatment of naive dogs affected by idiopathic epilepsy. *Vet Rec*. 2017; 181:144.

14. Stabile F, van Dijk J, Barnett CR, De Risio L. Epileptic seizure frequency and semiology in dogs with idiopathic epilepsy after initiation of imepitoin or phenobarbital monotherapy. *Vet J*. 2019; 249:53–57.
15. Royaux E, Van Ham L, Broeckx BJ et al. Phenobarbital or potassium bromide as add-on antiepileptic drug for the management of canine idiopathic epilepsy refractory to imepitoin. *Vet J*. 2017; 220:51–54.
16. Stee K, Martlé V, Broeckx BJG et al. Imepitoin withdrawal in dogs with idiopathic epilepsy well-controlled with imepitoin and phenobarbital and/or potassium bromide does not increase seizure frequency. *Vet J*. 2017; 230:1–5.
17. Nessler J, Rundfeldt C, Löscher W et al. Clinical evaluation of a combination therapy of imepitoin with phenobarbital in dogs with refractory idiopathic epilepsy. *BMC Vet Res*. 2017; 13:33.
18. European Medicines Agency. *Pexion: EPAR – European public assessment report*. First published 26.3.2013, amended 2018. Available from: https://www.ema.europa.eu/en/medicines/veterinary/EPAR/pexion. 822522. [Accessed 23 June 2021]
19. Engel O, Müller HW, Klee R et al. Effectiveness of imepitoin for the control of anxiety and fear associated with noise phobia in dogs. *J Vet Intern Med*. 2019; 33:2675–2684.
20. Packer RMA, De Risio L, Volk HA. Investigating the potential of the anti-epileptic drug imepitoin as a treatment for co-morbid anxiety in dogs with idiopathic epilepsy. *BMC Vet Res*. 2017; 13:90.
21. Schneider N, Potschka H, Reese S et al. Imepitoin for treatment of idiopathic head tremor syndrome in dogs: a randomized, blinded, placebo-controlled study. *J Vet Intern Med*. 2020; 34:2571–2581.
22. Royaux E, Bhatti S, De Cock H et al. Cutaneous adverse drug reaction in a dog associated with imepitoin. *Vet Dermatol*. 2016; 272:118-21e32.

Zonisamide 14

Daisuke Hasegawa, Miyoko Saito

Zonisamide (ZNS) is one of the newer generation antiseizure drugs (ASDs), which was licensed for use in humans in the US in 2000 and in Europe in 2005 (Zonegran®). However, ZNS was first synthesized in 1972 and has been available in Japan as an ASD since 1989. Consequently, ZNS is a popular ASD for dogs among Japanese veterinarians despite the limited scientific evidence for veterinary use.[1,2] Zonisamide is a synthetic sulfonamide compound with benzisoxazole as its basic skeleton (1,2-benzisoxazole-3-methanesulfonamide) (Fig. 14.1). In human medicine, ZNS has a comparatively broad epileptic seizure spectrum and is indicated as monotherapy for the treatment of focal seizures with or without evolution to generalized seizures in adults, and as monotherapy or adjunctive therapy for all types of generalized seizures in adults and children.[3] In veterinary medicine, ZNS is considered a second- or third-line ASD for dogs in the US or Europe,[1,2] but has become a first-line ASD for dogs in Japan. The characteristics of ZNS that support its use include:

- A shorter time to achieve steady state concentration (5–7 days) compared to phenobarbital (PB) or potassium bromide (KBr).
- A different antiepileptic mechanism from those of PB and KBr, in that ZNS suppresses excitation while PB and KBr enhance inhibition.
- Lack of enzyme induction (although it can be affected by enzyme inducers).
- The requirement of only twice-daily administration, while many of the other newer generation ASDs require a higher frequency of administration.

Although ZNS exerts an antiseizure effect in cats, it should be used with caution in this species.[4] The reasons for this are described in detail in this

chapter.

Recently, the use of ZNS has been expanded to include treatment for Parkinson's disease, essential tremor, some psychoses and obesity in human medicine. Therefore, new indications may be expected in veterinary medicine in the future.

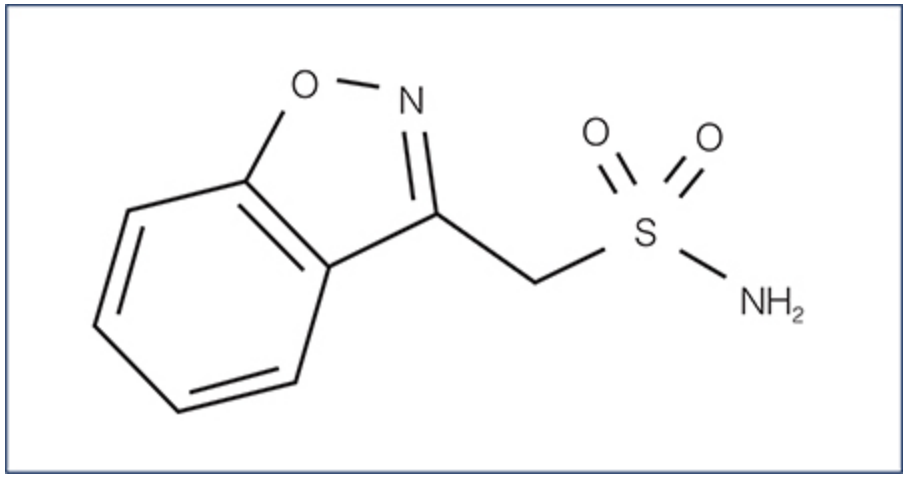


FIGURE 14.1. Structural formula of zonisamide. The molecular formula and molecular weight of zonisamide are $C_8H_8N_2O_3S$ and 212.23, respectively.

MECHANISM OF ACTION

The mechanism of action of ZNS is not completely understood. However, its antiseizure effect is mainly thought to be due to inhibition of both T-type calcium channels and voltage-gated sodium channels (Fig. 14.2).[5] Inhibition of these ion channels leads to suppression of neuronal hypersynchronization, so that ZNS is considered in the group of ASDs that act to inhibit excitation. Zonisamide therefore differs from many of the other first-line ASDs such as PB, KBr and imepitoin (IMP), the mechanisms of action of which function to enhance inhibition. However, ZNS does possess some inhibitory-enhancing effects. Zonisamide has been shown to allosterically bind to γ-aminobutryic acid $(GABA)_A$ receptors to increase their function, and also upregulates glutamate transporters and downregulates GABA transporters, resulting in decreased glutamate and increased GABA at the synaptic cleft.[6] Furthermore, ZNS exerts a neuroprotective effect by acting as a free-radical scavenger.[5] In addition to

the antiseizure effects mentioned above, ZNS acts to inhibit the enzyme monoamine oxidase (MAO) B, resulting in the increased synthesis and release of dopamine, and enhances the function of the δ1 glutamate receptor. These mechanisms are thought to contribute to the anti-Parkinsonian and neuroprotective effects of ZNS.[7] The anti-tremor effect of ZNS is believed to be due to T-type calcium channel inhibition.[8] Finally, ZNS functions as a weak inhibitor of carbonic anhydrase activity, with a potency that is 100–1000 times less than that of acetazolamide.[5] In summary, ZNS has multiple mechanisms of action; its antiseizure effect is primarily due to inhibition of excitatory mechanisms, but it also enhances inhibition, which explains its antiseizure, anti-Parkinsonian, anti-tremor and neuroprotective effects.

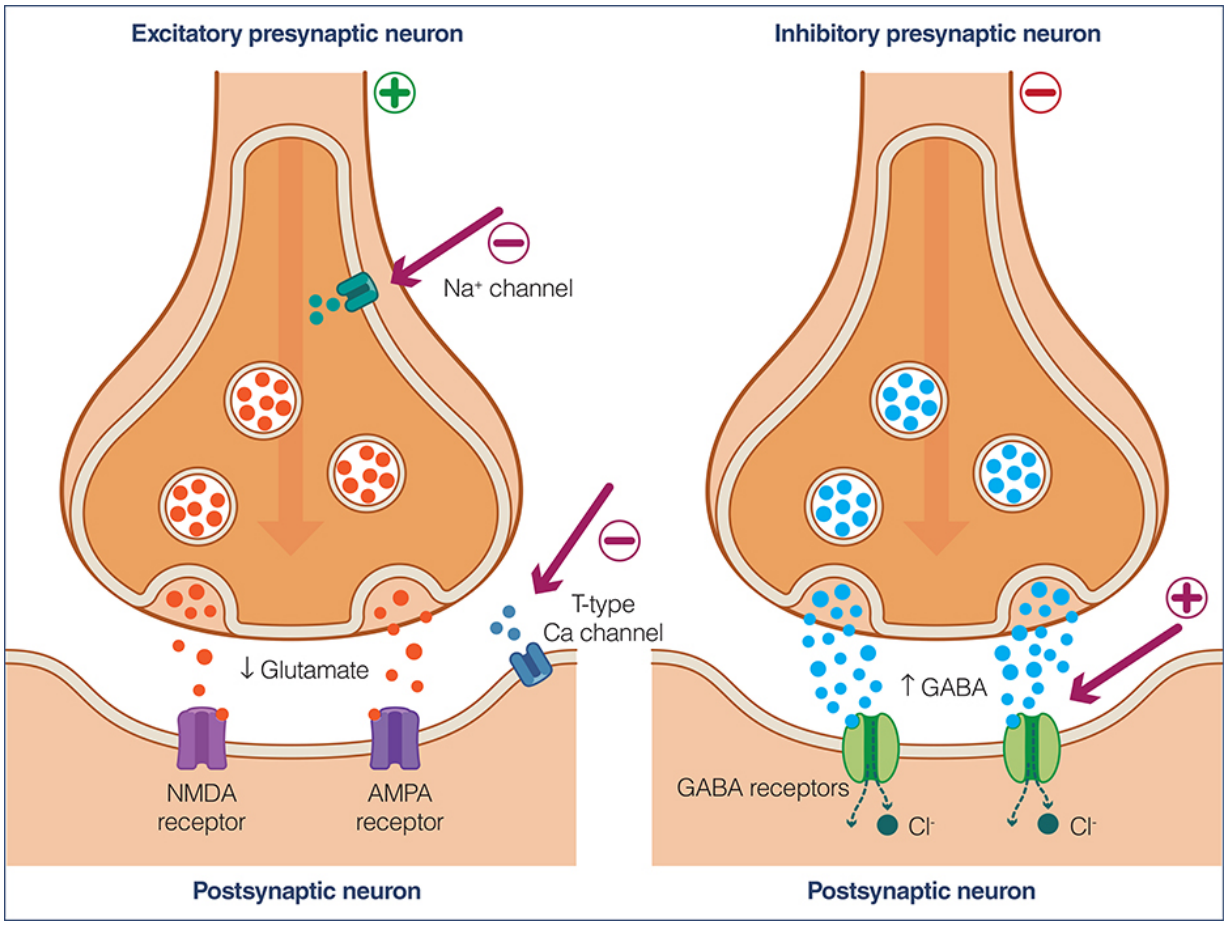


FIGURE 14.2. Proposed mechanism of action of zonisamide. The primary antiepileptic effect of zonisamide is thought to be due to inhibition of both T-type calcium channels and voltage-gated sodium channels in excitatory neurons, leading to suppression of neuronal hypersynchronization. Zonisamide has also been shown to bind to GABA receptors to increase their function, thereby enhancing inhibition.

PHARMACOKINETICS

Distribution and protein binding

Following oral administration, ZNS is rapidly absorbed into the bloodstream via the gastrointestinal tract. The drug's oral bioavailability and protein binding in dogs is approximately 70% and 40%, respectively.[9] Information on distribution and protein binding is not available for cats, but the parameters are thought to be similar to those in dogs. Zonisamide possesses a high affinity for, and accumulates in, red blood cells (RBCs).[9,10] Because of this, serum, plasma and RBC or whole-blood ZNS concentrations differ from one another; however, concentrations and pharmacokinetic (PK) parameters are similar between serum and plasma, and between RBCs and whole blood. The peak concentration of ZNS in serum and plasma is significantly lower than that in RBCs and whole blood and its elimination half-life ($t_{1/2}$) is shorter in serum and plasma samples than in RBCs and whole blood.[9] In rats, the distribution of radio-labeled ZNS was similar to plasma concentrations in most tissues, but slightly higher concentrations were achieved in the liver and kidney.[11] Zonisamide has good penetration across lipid membranes and the blood–brain barrier and, in a study in rats, ZNS was shown to remain in the central nervous system longer than in plasma.[11]

Metabolism and elimination

In dogs, ZNS is primarily excreted in urine (83%) within 72 hours of administration, with the remaining portion (17%) excreted in feces.[11] Approximately 70% of renally excreted ZNS is metabolized (in other words, about 10% of ZNS is excreted unchanged in urine). In humans, ZNS is acetylated to N-acetyl ZNS and reduced to 2-sulfamoylacetyl phenol, being primarily metabolized by the cytochrome P450 (CYP) isozyme 3A4 in the liver.[5] Although the metabolism of ZNS in dogs has not been elucidated, it is believed to be similar to that in humans given that concurrent PB administration facilitates ZNS elimination.[12] The clinical significance of this is discussed later in the section on drug interactions. Zonisamide does not induce liver enzymes in either humans[5] or dogs[13]. In addition, species differences in metabolism, such as the deficiency of N-acetylation or glucuronidation in dogs and cats, are thought to contribute to

the difference in PK parameters (described below) between humans, dogs and cats.[4,12]

Clinical pharmacokinetics

Although ZNS has a high affinity for RBCs, its concentration is typically measured in serum (or plasma) in veterinary practice, because its uptake and elimination in RBCs occurs in a nonlinear manner. The PK parameter values obtained from studies evaluating a single orally administered ZNS dose of 10 mg/kg in dogs[9] and cats[4] are shown in Table 14.1. Based on these data and the results of PK studies on the chronic administration of ZNS,[4,9–15] it is generally thought that the time to peak concentration (T_{max}), $t_{1/2}$ and time to steady state of ZNS at clinically relevant doses in dogs is approximately 3–6 hours, 15 hours and 5 days and that values in cats are 4 hours, 30 hours and 7 days, respectively. Fortunately, there is a linear relationship between the ZNS dose administered and both the steady-state concentration and the area under the curve (AUC),[13] so this information can be used to predict the serum or plasma concentration that will be achieved with a given dose (or vice versa) (Fig. 14.3). Administration of ZNS with food delays PK parameters to some extent, but the delay does not appear to have any clinical significance in dogs.[14] The effect of feeding on the PK features of ZNS in cats is unknown.

TABLE 14.1. Plasma pharmacokinetic parameters (mean ± standard deviation) of zonisamide in dogs and cats.

	Dogs (10 mg/kg, PO, once, n=8)[9]	Cats (10 mg/kg, PO, once, n=5)[4]
C_{max} (μg/mL)	14.4 ± 2.3	12.7 ± 1.8
T_{max} (h)	2.75 ± 1.25	4.0 ± 2.45
$t_{1/2}$ (h)	17.2 ± 3.6	31.5 ± 9.1
AUC (h·μg/mL)	347 ± 80	680 ± 76

C_{max}, peak concentration; T_{max}, time to peak concentration; $t_{1/2}$, elimination half-life; AUC, area under the curve

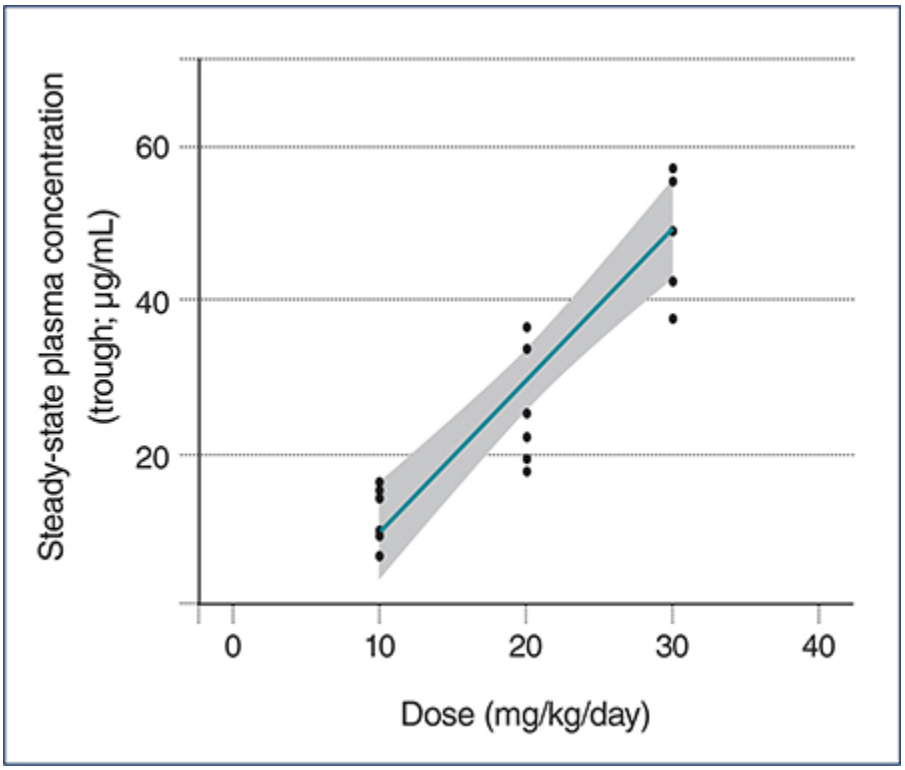


FIGURE 14.3. Dose–concentration curve demonstrating the linear relationship between mean trough plasma zonisamide concentration at steady state and oral zonisamide dose administered in normal dogs (n=6).

EFFICACY

Randomized clinical trials and open-label extension studies have demonstrated the efficacy of ZNS as monotherapy and add-on therapy for various types of focal and generalized epileptic seizures in humans.[16–19] Zonisamide also has a favorable safety and tolerability profile.[16–19] Several of these human studies are published in Japanese, but an English review is available.[20] Based on data from these studies, the Japanese Society of Neurology guidelines for epilepsy recommend ZNS as a first-line drug to treat adults with focal seizures and as a second-line drug to treat adults with generalized tonic-clonic seizures.[21]

Zonisamide is used as a first-line ASD in veterinary medicine in Japan, and is marketed under the names Consave® or Epiless®, after it received regulatory approval for the treatment of dogs with idiopathic generalized or focal-onset epilepsy in 2015. In Japan, ZNS is also used in dogs for the

management of seizures of other etiologies such as structural epilepsy, at the veterinarian's discretion. Zonisamide is also used in the management of feline epilepsy. Currently, ZNS is not licensed for use in dogs or cats in North America or Europe, and it is generally used as a second- or third-line ASD. Only a few published studies have evaluated the clinical efficacy of ZNS in veterinary medicine, and these are limited to small case series or anecdotal reports.

Zonisamide as monotherapy has been evaluated in two studies involving a total of 63 dogs with newly diagnosed idiopathic epilepsy (IE).[22,23] Chung et al. reported the results of an open-label trial of ZNS in 10 dogs with IE that manifested as generalized seizures. Dogs were administered ZNS at a dose of 5–15 mg/kg every 12 hours. Six dogs (60%) were considered responders, with a ≥50% reduction in monthly seizure frequency compared to that before the initiation of ZNS, and a follow-up time of 12–36 months. Four of these dogs achieved seizure freedom.[22] Another open-label trial of ZNS monotherapy in 53 dogs with IE was reported by Nomura et al.[23] Dogs were administered ZNS at a dose of 2.7–14.4 mg/kg every 12 hours and followed up for 12 weeks. Forty dogs (76%) had a ≥50% reduction in seizure frequency compared to pretreatment, and 29 (55%) of these dogs achieved seizure freedom.

Zonisamide as add-on therapy has also been investigated in two open-label trials, which included a total of 22 dogs with IE that were refractory to PB +/- other ASDs.[24,25] Most of these dogs had generalized seizures. Adjunctive treatment with ZNS resulted in a ≥50% reduction in seizure frequency compared to that before the initiation of ZNS in 58–80% dogs, and seizure freedom in 17–20% of dogs at follow-up (range, 8–71 weeks; mean, 24.6 weeks).[24,25] The study by Dewey et al. included 12 dogs with IE that were poorly controlled despite adequate standard ASD therapy (i.e., PB +/- KBr +/- other ASDs). The dogs were administered ZNS at a dose of 5–11 mg/kg every 12 hours to achieve serum drug concentrations of approximately 10–40 µg/mL. Seven dogs (58%) were considered responders, with a ≥50% reduction in seizure frequency compared to before the initiation of ZNS, with a follow-up time of 8–71 weeks. Two of these dogs achieved seizure freedom.[24] In the open-label trial by von Klopmann et al., 10 dogs with IE that were poorly controlled despite treatment with PB +/- KBr were administered ZNS at a dose of 10 mg/kg every 12 hours. Monthly seizure frequency was reduced by ≥50% in 8 dogs (80%) with

ZNS administration compared to baseline, and 2 dogs achieved seizure freedom over the follow-up period of 4 months. However, in 3 of these 8 dogs, subsequent seizure control worsened again after 10 to 17 months of treatment.[25] As with other ASDs, such as PB and levetiracetam (LEV), ZNS may show a transient maximal efficacy, the so-called "honeymoon effect", in some individuals. One of the authors undertook a review of medical records from dogs in which ZNS was administered for at least 6 months either as monotherapy or as add-on therapy for IE, to determine the long-term effects of treatment. A diagnosis of IE was made based on a minimum Tier 1 level of confidence according to the International Veterinary Epilepsy Task Force (IVETF) guidelines, with the exception that serum bile acids and ammonia were not measured and urinalysis not performed in all dogs. Additional neurodiagnostic tests were performed in some dogs, including MRI of the brain in 10 dogs, cerebrospinal fluid analysis in 5 dogs and electroencephalography in 9 dogs. In the total of 31 dogs, the median duration of follow-up was 3 years (range, 6–68 months). Twenty four of the 31 dogs (77.4%) were judged to be well controlled (≥50% reduction in seizure frequency compared to baseline, with this pattern maintained for at least two-thirds of the evaluation period) and 7 dogs became seizure free for at least 12 months (seizure free rate, 22.6%). Five dogs experienced adverse effects (AEs) that were all transient and not considered severe (a portion of this data is reported in the study by Yoshioka et al.[26]).

In the American College of Veterinary Internal Medicine (ACVIM) consensus statement on seizure management in dogs, ZNS monotherapy received a low recommendation based on the limited evidence to support its efficacy, whereas its use as add-on therapy received a moderate recommendation, suggesting it is most likely to be an effective treatment based on the available data.[2] A systematic review of published studies evaluating therapy in dogs with IE concluded there was overall insufficient evidence for recommending the use of ZNS as either monotherapy or add-on therapy[27]. Additional published data involving larger numbers of dogs are needed to further substantiate the efficacy of ZNS is dogs.

The published data on the use of ZNS as an ASD in cats only includes experimental studies,[15] anecdotal reports and a description of its use in a review article.[28,29] This limited information suggests that ZNS may be effective in the treatment of feline epilepsy. A systematic review of ASDs in cats assessed the level of evidence for ZNS's efficacy as weak based on the

paucity of published data.[30] Additional clinical studies are warranted to evaluate its efficacy in cats.

CLINICAL USE

Dosing

The recommended oral starting dose for ZNS as maintenance therapy in dogs is:

- 2.5–5.0 mg/kg every 12 hours
  or
- 5.0–7.5 mg/kg every 12 hours when coadministered with PB

This dosing is based on data from 53 dogs that were administered ZNS monotherapy for IE. For the more than 90% of dogs that were considered responders, the mean ZNS dose was 4.8 mg/kg every 12 hours (range, 2.7–8.6 mg/kg every 12 hours) and the mean trough plasma ZNS concentration was 18.9 µg/mL (range, 8.0–48.0 µg/mL).[23] A similar starting dose of 3–7 mg/kg every 12 hours has been recommended by others.[31] In dogs with a history of severe epileptic seizures, or if seizures are anticipated to be severe (e.g., dogs with neoplasia, intracranial hemorrhage, etc.), the authors usually initiate therapy with a higher dose of 5 mg/kg or above. After initial dosing, the maintenance dose can be increased incrementally by approximately 2.5–5.0 mg/kg at 1- to 4-week intervals up to a maximum of 10 mg/kg every 12 hours if necessary, based on seizure control and AEs.

If ZNS is coadministered with PB or other hepatic microsomal enzyme inducers, a dosage increase is required.[31,32] Zonisamide is primarily metabolized by CYP enzymes in the liver,[33] which are induced by PB.[34] A PK study demonstrated that coadministration with PB enhances ZNS clearance in dogs.[12] In another study, dogs administered ZNS alone or ZNS and PB in combination were retrospectively evaluated, focusing on epileptic seizure control as well as ZNS dose and serum concentrations. Among 25 dogs that experienced a decrease in seizure frequency after ZNS initiation, the median ZNS dose in dogs receiving ZNS alone was 6 mg/kg every 12 hours (range, 3.0–12.3 mg/kg every 12 hours), compared to 9 mg/kg every 12 hours (range, 8–13.7 mg/kg every 12 hours) for those

administered ZNS and PB in combination. However, the mean serum ZNS concentrations were the same between groups (19.7 vs 20.5 µg/mL).[35] The findings from this study suggest that for dogs coadministered PB, approximately 1.5 times the ZNS dose is necessary to obtain the equivalent serum concentration achieved with ZNS use alone. Accordingly, when adding ZNS to the treatment regimen in a dog that is being administered PB, a 1.5-fold increase in the dose is recommended. In other words, the recommended ZNS starting dose is 5.0–7.5 mg/kg every 12 hours, and subsequent dosage adjustments should be made based on serum ZNS concentrations and seizure control, as serum ZNS concentrations tend to not correlate as well with dosage when coadministered with PB. If needed, the maintenance dose may be increased incrementally by approximately 2.5–5.0 mg/kg at 1- to 4-week intervals based on seizure control and the presence of AEs, until a ZNS trough concentration of 40 µg/mL is reached. Once this maximum targeted trough concentration is obtained, further increases in dosage should not be attempted.

The recommended starting oral ZNS dose in cats is 2.5 mg/kg every 12 hours or 5 mg/kg every 24 hours. A therapeutic range for cats has not been established. The proposed ZNS dose is extrapolated from the human therapeutic range and results of a PK study of cats.[4] Although administration at 5–10 mg/kg every 24 hours has been suggested,[29,31] the authors recommend administering the daily ZNS dose divided into two doses in an attempt to avoid large daily fluctuations in serum concentrations, as well as high peak concentrations that can cause anorexia. It is suggested that ZNS dosing for cats be initiated at 2.5 mg/kg every 12 hours, with a gradual increase of 1–2 mg/kg as necessary up to a maximum dose of 5–10 mg/kg every 12 hours. A dose greater than 20 mg/kg/day is not recommended in cats, based on an experimental study in which daily doses >20 mg/kg or serum/plasma ZNS concentrations >40 µg/mL resulted in gastrointestinal AEs, somnolence and ataxia in 50% of animals.[4] Although CYP3A and other CYP families are expressed in the liver of cats,[36] it is not known whether or not PB induces hepatic microsomal enzymes, and PB induction does not appear to be clinically significant in this species. Consequently, a ZNS dose increase in cats coadministered PB is not indicated.

However, because ZNS is metabolized by the liver, a serum biochemistry profile should be obtained prior to initiating therapy in both

dogs and cats. If abnormalities in hepatic enzymes or parameters that provide an indirect assessment of liver function (albumin, blood urea nitrogen, bilirubin, glucose, cholesterol) are noted, then care should be taken with the use of ZNS, or an alternative ASD should be considered.

Monitoring

Although ZNS reference ranges have not been established for dogs and cats, targeted serum concentrations have been suggested based on extrapolation from human reference ranges, as well as species specific PK studies and clinical use. The targeted range for trough serum or plasma ZNS concentration is 10–40 μg/mL in dogs and 10–35 μg/mL in cats. Care should be taken to avoid hemolysis when collecting blood, because falsely elevated ZNS concentrations from lysed RBCs can occur. A prospective study of 53 dogs administered ZNS as monotherapy found that >90% of responders had a mean trough plasma concentration of 18.9 μg/mL (range, 8.0 to 48.0 μg/mL).[23] When the ZNS trough serum or plasma concentration exceeds 50 μg/mL, the frequency of AEs tends to increase. Consequently, it is advisable to maintain ZNS trough serum or plasma concentrations between 10–40 μg/mL. This is comparable to the human therapeutic range for ZNS,[21,37] which has been suggested for use in dogs as well.[31] In cats, maintaining a ZNS trough serum or plasma concentration <35 μg/mL is recommended in an attempt to avoid loss of appetite. Since considerable interindividual differences exist in the PK of ZNS in dogs, it is the authors' recommendation that an individual optimal dosing regimen is best achieved based on serum/plasma concentrations, therapeutic efficacy, and the presence of AEs after treatment initiation.

Serum or plasma ZNS concentrations reach steady state after 3–5 days in dogs when ZNS is administered at a dose of 5–30 mg/kg every 12 hours.[10,13] Consequently, serum or plasma ZNS concentrations should be measured at least 5 days after treatment initiation or dosage adjustment. Significant differences between ZNS peak and trough concentrations can be seen in some dogs.[24] For routine monitoring, a blood sample should be collected just before the next dose (trough). The dosing and PK variables useful in clinical monitoring of ZNS in dogs and cats are summarized in Table 14.2.

Trough plasma ZNS concentrations show a linear relationship to the amount of drug administered within the dosage range of 10 to 60 mg/kg/day

in dogs,[10,13] making therapeutic drug monitoring easier (see Fig. 14.3). Dose adjustments can be calculated with the following formula:

TABLE 14.2. Summary of dosing and pharmacokinetic variables useful in clinical monitoring of ZNS in dogs and cats.

	Dogs	Cats
Starting oral dose (mg/kg)	2.5–5.0 every 12 hours (monotherapy) 5.0–7.5 every 12 hours (add-on to PB)	2.5 every 12 hours (or 5.0 every 24 hours)
Time to steady state (days)	5	7
Therapeutic range (µg/mL)	10–40	10–35

PB, phenobarbital.

$$\text{New dose} = \text{Current dose} \times \frac{\text{Target serum concentration}}{\text{Current serum concentration}}$$

It is the authors' recommendation that serum ZNS concentrations be measured at approximately 1 to 2 weeks after starting treatment and after a dosage adjustment, and the animal be also evaluated for AEs at this time, with monitoring every 6 to 12 months thereafter (Box 14.1). The maintenance dose should be adjusted individually in accordance with epileptic seizure control, the presence of AEs and serum concentrations. A treatment algorithm with recommendations on ZNS dosing, measuring serum concentrations, and patient monitoring is outlined in Fig. 14.4.

The ACVIM consensus panel and the IVETF recommend the following laboratory tests before ZNS initiation and periodically during ZNS treatment in dogs to monitor for possible AEs:[1,2]

- Hematology
- Serum biochemistry profile including hepatic enzyme activity and electrolytes
- Blood gas analysis

An increase in serum chloride and a decrease in TCO_2 should prompt further investigations for renal tubular acidosis, an idiosyncratic AE reported with ZNS administration in dogs.[2,43]

ADVERSE EFFECTS AND DRUG INTERACTIONS

Type A adverse effects

Zonisamide is well tolerated in dogs. Commonly reported type A AEs include decreased appetite, reduced activity, ataxia, vomiting, diarrhea, and weight loss.[22–25] These signs tend to be mild and transient. Adverse effects were reported in half of dogs administered ZNS as add-on therapy;[24,25] however, in the authors' experience, AEs are much less frequent when ZNS is used as monotherapy.

As is characteristic of type A AEs, the reported clinical signs are dose-related. When these AEs occur, they typically present during the first few days of treatment and subside over time. In rare instances, dose reduction or ZNS discontinuation may be necessary to alleviate AEs.[22,24] A gradual dose escalation to the targeted dose may be preferable, especially when ZNS is coadministered with an ASD that tends to cause sedation, in order to reduce the incidence and severity of AEs. A chronic toxicity study in dogs determined the maximum tolerated dose of ZNS to be 30 mg/kg/day, as this is the dose for which mild AEs (e.g., decrease in appetite) started to appear.[38] Accordingly, 30 mg/kg/day can reasonably be used as a guide for the maximum dose to be administered in the clinical setting.

BOX 14.1. Recommended monitoring for a dog or cat on zonisamide (ZNS).

- Measure trough serum ZNS concentration at the following time points:
  - Approximately 1–2 weeks (specifically, a minimum of 5 days in dogs and 7 days in cats) after initiation of therapy or any dosage adjustment.
  - Every 6–12 months if seizure control is adequate.
  - When therapeutic success is not achieved or maintained (see Chapter 9 for definition of therapeutic success).
  - Anytime adverse effects (AEs) are reported.
- The targeted range for ZNS serum concentrations is 10–40 µg/mL for dogs and 10–35 µg/mL for cats.

- Care should be taken to avoid hemolysis when obtaining blood for ZNS concentration measurement, as falsely elevated serum ZNS concentrations can occur from lysed red blood cells.
- Perform laboratory analyses at 6 to 12-month intervals, or more frequently if AEs are reported, including:
  - Hematology
  - Serum biochemistry profile, including hepatic enzyme activity and electrolytes
  - +/- Blood gas analysis

In a PK study in healthy cats administered ZNS at a dose of 20 mg/kg every 24 hours (or >40 µg/mL serum/plasma ZNS concentration), 50% of cats developed AEs including anorexia, diarrhea, vomiting, ataxia and somnolence.[4] The authors do not recommend administering ZNS to cats at a dose greater than 10 mg/kg every 12 hours or 20 mg/kg every 24 hours, based on the results of this study and their clinical experience. Dividing the daily dose into two administrations and gradually increasing to the targeted dose are advisable to reduce the risk of the patient developing anorexia. In an anecdotal description of ZNS use in cats included in a review article, 1 of 2 cats receiving ZNS (unknown dosing) developed anorexia that necessitated drug discontinuation.[28] Clinical studies are warranted to further evaluate the safety of ZNS in cats.

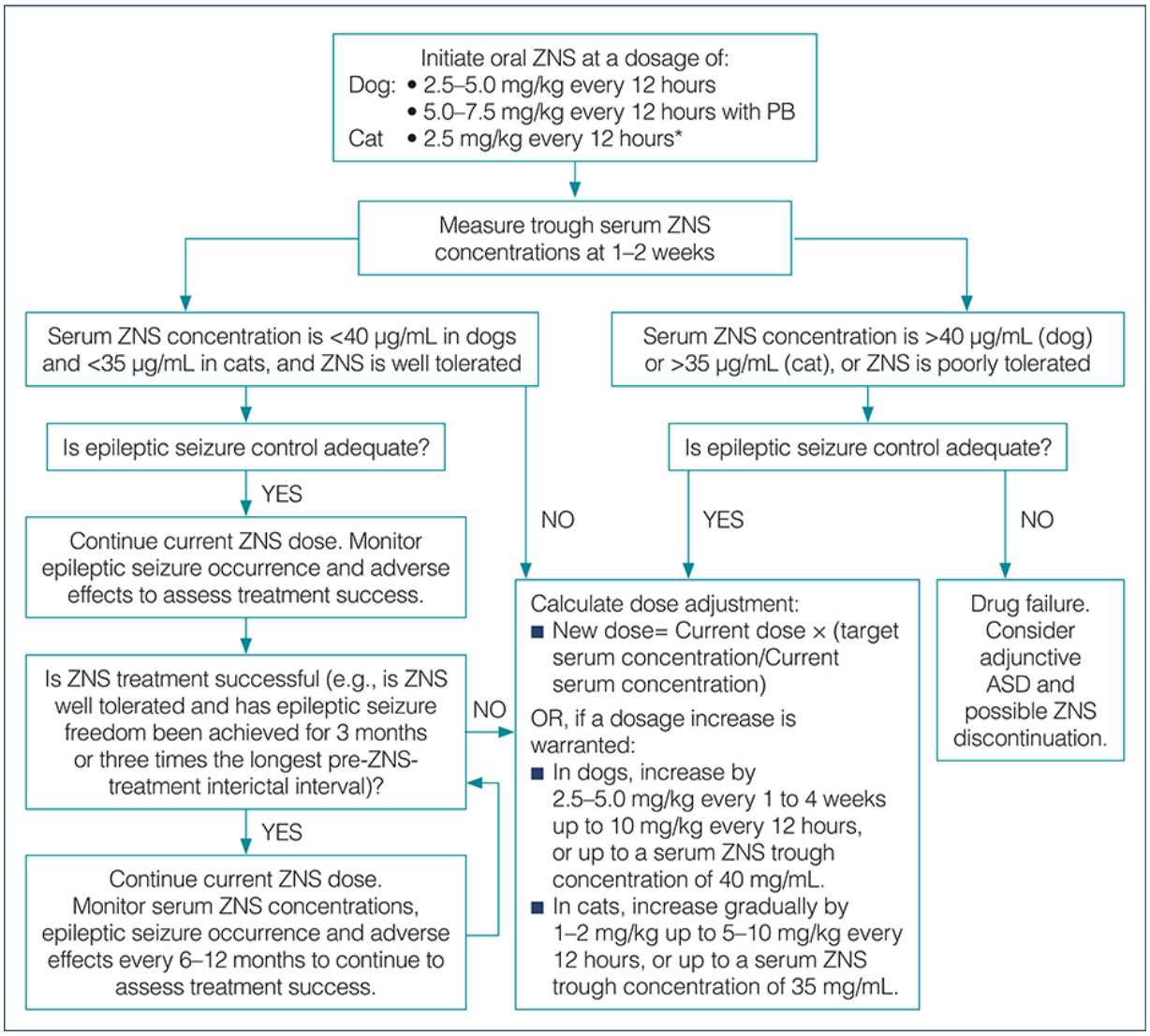


FIGURE 14.4. Algorithm outlining a treatment protocol for zonisamide (ZNS) in dogs and cats based on serum concentrations, degree of seizure control achieved and adverse effects. When ZNS is used in combination with another antiseizure drug such as phenobarbital, serum concentration monitoring, dosing and adverse effects of the other drug should also be factored in the decision-making regarding treatment modulation.
* Every-12-hour dosing is recommended in cats to avoid adverse effects, but administering 5 mg/kg every 24 hours is acceptable if this is not possible.

Type B adverse effects

Rare, type B, AEs reported with the use of ZNS include acute or chronic hepatopathy in 3 dogs;[38–40] erythema multiforme,[42] keratoconjunctivitis sicca (KCS),[24] polyarthropathy,[24] renal tubular acidosis,[43] urinary calculi,[40] and aggressive behavior[44], each in 1 dog; and anticonvulsant hypersensitivity syndrome in 1 cat[45]. Recognition of these rare conditions is important

because full recovery is possible if the drug is discontinued early after the onset of clinical signs.

In 2 dogs with suspected acute idiosyncratic hepatopathy, anorexia and vomiting were seen 10 to 21 days after ZNS initiation. An increase in liver enzyme activities, including a marked AST elevation, was observed. One dog deteriorated and was euthanized despite ZNS discontinuation, while the other dog recovered after ZNS discontinuation and provision of supportive care.[39,40] Chronic liver injury with bile duct proliferation is also reported in 1 dog administered ZNS for 1 year.[41]

In 1 dog, erythema multiforme developed 2 months after ZNS initiation. Significant improvements were seen within 3 days of ZNS discontinuation, with complete resolution of clinical signs after 2 weeks. An idiosyncratic cutaneous adverse drug reaction to ZNS was considered most likely in this case.[42]

Sulfonamide antimicrobials are known to cause various hypersensitivity reactions, including hepatopathy, cutaneous reactions, KCS and polyarthropathy. Zonisamide is chemically related to sulfonamides, but unlike sulfonamide antimicrobials, it does not contain an aromatic amine. The aromatic amine is considered critical in the generation of the immunogenic reaction associated with sulfonamide antimicrobials, by producing nitroso metabolites.[46]

Zonisamide can cause metabolic acidosis due to its inhibition of carbonic anhydrase activity, although its potency in this regard is extremely weak (1/100th that of acetazolamide).[47] Consequently, the exact mechanism for this effect is not yet known. Patients with impaired renal or pulmonary function are at increased risk for metabolic acidosis and, therefore, ZNS should be used with caution in such cases.

Long-term ZNS administration can be associated with renal calculi in approximately 1% of human patients.[48] The exact mechanism for this AE is uncertain. Although ZNS is not contraindicated in patients with a history of renal calculi, in such patients steps should be taken to ensure adequate water consumption, and use of concomitant drugs that act as carbonic anhydrase inhibitors (such as topiramate) and a ketogenic diet should be avoided.[37,48,49] In veterinary medicine, the relation between urolithiasis and ZNS is unclear. Similar precautions as those recommended for humans may be advisable.

As with other ASDs, ZNS can cause behavioral changes. Aggressive behavior episodes associated with an increasing ZNS dose were described in 1 dog, but the dose administered was not reported. The episodes completely resolved within 7 days of ZNS discontinuation.[44]

A cat administered ZNS was reported to develop multiple clinical signs consistent with anticonvulsant hypersensitivity syndrome, including lymphadenopathy, hyperglobulinemia and cytopenia, along with systemic signs of lethargy and anorexia. The first clinical signs were noted 14 days after adding ZNS at a dose of 8 mg/kg every 12 hours to PB and LEV, and the serum ZNS concentration was 49.8 µg/mL 4 days prior to the onset of the clinical signs. It took more than 1 month after ZNS discontinuation for all signs to subside. Anticonvulsant hypersensitivity syndrome to ZNS was suspected to be the cause of this serious condition.[45]

Drug interactions

Phenobarbital

Zonisamide is metabolized by CYP 3A and 2C in humans,[33] and these CYP activities are induced by repeated PB administration in dogs.[34] The PK data available demonstrate that the C_{max}, AUC, $t_{1/2}$ and bioavailability of ZNS are significantly decreased in dogs receiving ZNS concurrently with therapeutic doses of PB,[12] so that the starting ZNS dose should be increased in dogs coadministered PB, as described above. It has been shown that the changes in PK parameters resolve 3 months after PB discontinuation.[12] When a dog administered PB and ZNS polytherapy is switched to ZNS monotherapy, the ZNS dose should be adjusted based on the serum ZNS concentrations obtained at least 3 months after PB discontinuation.

Other drugs

Any drug that induces or inhibits hepatic CYP activity can potentially decrease or increase ZNS serum concentrations. Zonisamide is a weak inhibitor of carbonic anhydrase as well as MAO. Therefore, caution is necessary with concomitant use of other carbonic anhydrase inhibitors, MAO inhibitors, and any drugs metabolized by MAO.

TAKE-HOME MESSAGES

- ✔ Zonisamide is used as both monotherapy and add-on therapy in dogs and cats with epilepsy, although its efficacy is not well established. Additional published data are needed to further substantiate the efficacy of ZNS.
- ✔ Zonisamide is metabolized by the liver and, therefore, alternative ASDs that are not hepatically metabolized are recommended for use in animals with liver dysfunction. If no alternatives are available, ZNS should be used with considerable caution.
- ✔ In dogs, the recommended starting dose for ZNS is 2.5–5.0 mg/kg every 12 hours, and 5.0–7.5 mg/kg every 12 hours when coadministered with PB. The maintenance dose can be gradually increased by approximately 2.5–5.0 mg/kg at 1- to 4-week intervals up to a dose of 10 mg/kg every 12 hours or a maximum ZNS trough serum or plasma concentration of 40 µg/mL if necessary, based on seizure control and AEs.
- ✔ In cats, the recommended starting dose for ZNS is 2.5 mg/kg every 12 hours, with a gradual increase of 1–2 mg/kg as necessary up to a maximum dose of 5–10 mg/kg every 12 hours or a maximum ZNS trough serum or plasma concentration of 35 µg/mL. A reference range for cats has not been established. The proposed ZNS dose is extrapolated from the human reference range and results of a PK study in cats.
- ✔ The targeted range for trough serum or plasma ZNS concentration is 10–40 µg/mL in dogs and 10–35 µg/mL in cats. For routine monitoring, a blood sample to measure serum concentrations should be collected just before the next dose (trough). The maintenance dose is adjusted individually in accordance with seizure control, the presence of AEs and serum concentrations. Dose adjustments can be calculated with the following formula:

  New dose = Current dose × (Target serum concentration/Current serum concentration)
- ✔ The mechanism of action of ZNS is mainly thought to be due to inhibition of both T-type calcium channels and voltage-gated sodium channels. Zonisamide differs from many of the other first-line ASDs

such as PB, KBr and IMP, in that it suppresses excitation while the others enhance inhibition.

- ✔ In general, ZNS is well tolerated in dogs. Commonly reported type A AEs include decreased appetite, reduced activity, ataxia, vomiting, diarrhea, and weight loss. These signs tend to be mild and transient. Anorexia, diarrhea, vomiting, ataxia and somnolence are the most commonly recognized AEs in cats. Dividing the daily dose into two administrations and gradually increasing to the targeted dose are both advisable to reduce the risk of developing anorexia in cats.
- ✔ Rare, type B, AEs reported with the use of ZNS include acute or chronic hepatopathy, and erythema multiforme, keratoconjunctivitis sicca, polyarthropathy, renal tubular acidosis, urinary calculi, aggressive behavior, and anticonvulsant hypersensitivity syndrome. Recognition of these rare conditions is important because full recovery is possible if the drug is discontinued early after the onset of clinical signs.
- ✔ Patients with impaired renal or pulmonary function are at increased risk for renal tubular acidosis, and therefore ZNS should be used with caution in such cases.

REFERENCES

1. Bhatti SFM, De Risio L, Muñana K et al. International veterinary epilepsy task force consensus proposal: Medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015; 11:176.
2. Podell M, Volk HA, Berendt M et al. 2015 ACVIM small animal consensus statement on seizure management in dogs. *J Vet Intern Med.* 2016; 30:477–490.
3. Kwan SY, Chuang YC, Huang CW et al. Zonisamide: Review of recent clinical evidence for treatment of epilepsy. *CNS Neurosci Therapeu*. 2015; 21:683–691.
4. Hasegawa D, Kobayashi M, Kuwabara T et al. Pharmacokinetics and toxicity of zonisamide in cats. *J Feline Med Surg*. 2008; 10:418–421.
5. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. *Seizure*. 2004; 135:S5–S9.
6. Holder JL Jr, Wilfong AA. Zonisamide in the treatment of epilepsy. *Expert Opin Pharmacother*. 2011; 12:2573–2581.

7. Bermejo PE, Anciones B. A review of the use of zonisamide in Parkinson's deisease. *Ther Adv Neurol Disord*. 2009; 2:313–317.
8. Miwa H, Kondo T. T-type calcium channel as a new therapeutic target for tremor. *Cerebellum*. 2011; 10:563–569.
9. Boothe DM and Perkins J. Disposition and safety of zonisamide after intravenous and oral single dose and oral multiple dosing in normal hound dogs. *J Vet Pharmacol Ther*. 2008; 31:544–533.
10. Fukunaga K, Saito M, Muto M, et al. Steady-state pharmacokinetics of zonisamide in plasma, whole blood, and erythrocytes in dogs. *J Vet Pharmacol Ther*. 2010; 33:103–106.
11. Matsumoto K, Miyazaki H, Fujii H et al. Absorption, distribution and excretion of 3-(sulfamoyl[14C]methyl)-1,2-benziosoxazole (AD-810) in rats, dogs and monkeys and of AD-810 in men. *Arzneimittelforschung*. 1983; 33:961–968.
12. Orito K, Saito M, Fukunaga K et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. *J Vet Pharmacol Ther*. 2008; 31:259–264.
13. DS Pharma Animal Health, *Domestic materials*.
14. DS Pharma Animal Health, *Domestic materials*.
15. Ukai M, Hamamoto Y, Yu Y et al. Efficacy of zonisamide on interictal electroencephalography in familial spontaneous epileptic cats. *J Feline Med Surg*. 2018; 20:962–967.
16. Seino S, Okuma T, Miyasaka M et al. Efficacy evaluation of AD-810 (zonisamide). Double-blind study comparing with carbamazepine [in Japanese]. *J. Clin Exp Med*. 1988; 144:275–291.
17. Oguni H, Hayashi K, Fukuyama Y et al. Phase III study of a new antiepileptic AD-810, zonisamide in childhood epilepsy [in Japanese]. *Jpn J Pediatr*. 1988; 41:439–50.
18. Zaccara G, Specchio L. Long-term safety and effectiveness of zonisamide in the treatment of epilepsy: a review of the literature. *Neuropsychiatr Dis Treat*. 2009; 5:249–259.
19. Baulac M, Patten A, Giorgi L. Long-term safety and efficacy of zonisamide versus carbamazepine monotherapy for treatment of partial seizures in adults with newly diagnosed epilepsy: results of a phase III, randomized, double-blind study. *Epilepsia*. 2014; 55:1534–1543.
20. Ohtahara S, Yamatogi Y. Safety of zonisamide therapy: prospective follow-up survey. *Seizure Suppl*. 2004; 1:S50–5; discussion S56.
21. Japanese Society of Neurology. Chapter 3. Medical treatment for adult epilepsy. In: *Clinical Practice Guideline for Epilepsy*. 2018. pp. 25–38.
22. Chung J, Hwang C, Chae J et al. Zonisamide monotherapy for idiopathic epilepsy in dogs. *N Z Vet J*. 2012; 60:357–359.
23. Nomura A, Saito M, Hasegawa D et al. Clinical efficacy and safety of zonisamide monotherapy in dogs with newly diagnosed idiopathic epilepsy. *Proceedings: ACVIM Forum accessed via Veterinary Information Network*; vin.com, 2015.
24. Dewey C, Guiliano R, Boothe D et al. Zonisamide therapy for refractory idiopathic epilepsy in dogs. *J Am Anim Hosp Assoc*. 2004: 40:285–291.
25. Von Klopmann T, Rambeck B, Tipold A. Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. *J Small Anim Pract*. 2007; 48:134–138.
26. Yoshioka R, Saito M, Orito K, et al. Long-term efficacy of zonisamide in dogs with idiopathic epilepsy. *Proceedings: Japanese society of veterinary neurology*. 2008. Available from: https://shinkei.com/.
27. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy--a systematic review. *BMC Vet* Res. 2014; 10:257. doi: 10.1186/s12917-014-0257-9.

28. DEWEY C. Anticonvulsant therapy in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2006; 36:1107–1127.
29. Small Animal Clinical Conference in Epilepsy. *The World of Zonisamide for Veterinary medicine*, Farm Press, 2019.
30. CHARALAMBOUS M, PÁKOZDY Á, BHATTI S et al. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14:64.
31. DE RISIO L. Zonisamide. In: DE RISIO L, PLATT S. *Canine and feline epilepsy,* 1st edition. Oxfordshire, UK: CABI; 2014. pp. 415–425.
32. MUÑANA K. Update seizure management in small animal practice. *Vet Clin North Am Small Anim Pract*. 2013; 3:1127–1147.
33. NAKASA H, NAKAMURA H, ONO S et al. Prediction of drug-drug interactions of zonisamide metabolism in humans from in vitro data. *Eur J Clin Pharmacol*. 1998; 54:177–183.
34. HOJO T, OHNO R, SHIMODA M et al. Enzyme and plasma protein induction by multiple oral administrations of phenobarbital at a therapeutic dosage regimen in dogs. *J Vet Pharmacol Ther*. 2002; 25:121–127.
35. MATSUO E, SAITO M, ORITO K, et al. Therapeutic efficacy of zonisamide in epileptic dogs with/without phenobarbital. *Japanese College of Veterinary Internal Medicine Forum Proceedings*. 2007.
36. OKAMATSU G, KAWAKAMI K, KOMATSU T, et al. Functional expression and comparative characterization of four feline P450 cytochromes using fluorescent substrates. *Xenobiotica*. 2017; 47:951–961.
37. WELTY T. Zonisamide. In: Wyllie E, Gidal B, Goodkin H, Loddenkemper T (eds). *Wyllie's treatment of epilepsy: Principles and Practice*. 7th edition. Philadelphia PA, USA: Wolters Kluwer; 2020. pp. 731–737.
38. SUMITOMO DAINIPPON PHARMA, Domestic materials.
39. SCHWARTZ M, MUÑANA K, OLBY N. Possible drug-induced hepatopathy in a dog receiving zonisamide monotherapy for treatment of cryptogenic epilepsy. *J Vet Med Sci*. 2011; 73:1505–1508.
40. MILLER M, CENTER S, RANDOLPH J et al. Apparent acute idiosyncratic hepatic necrosis associated with zonisamide administration in a dog. *J Vet Intern Med*. 2011; 25:1156–1160.
41. TAKAMI Y, IZAWA T, TANAKA M et al. Hepatocellular necrosis with prominent regenerative reactions in a zonisamide administrated dog. *J Vet Med Sci*. 2020; 82:704–706.
42. ACKERMANN A, FRANK L, MCENTEE M et al. Erythema multiforme associated with zonisamide in a dog. *Vet Dermatol*. 2015; 26:391–392.
43. COOK A, ALLEN A, ESPINOSA D, et al. Renal tubular acidosis associated with zonisamide therapy in a dog. *J Vet Intern Med*. 2011; 25:1454–1457.
44. KANAZONO S, UKAI M, MORI S. Presumptive antiepileptic drug-related abnormal behavior episodes in two dogs. *Sixth Asian Meeting of Animal Medicine Specialties and Asian Small Animal Specialist Veterinary Congress Proceedings*. 2019.
45. COLLINET A, SAMMUT V. Suspected zonisamide-related anticonvulsant hypersensitivity syndrome in a cat. *J Am Vet Med Assoc*. 2017; 251:1457–1461.
46. KHAN D, Knowles S, SHEAR N. Sulfonamide hypersensitivity: fact and fiction. *J Allergy Clin Immunol Pract*. 2019; 7:2116–2123.
47. SUMITOMO DAINIPPON PHARMA, Domestic materials.

48. JANKOVIĆ S. Evaluation of zonisamide for the treatment of focal epilepsy: a review of pharmacokinetics, clinical efficacy and adverse effects. *Expert Opin Drug Metab*. 2020; 16:169–177.
49. ZACCARA G, TRAMACERE L, CINCOTTA M. Drug safety evaluation of zonisamide for the treatment of epilepsy. *Expert Opin Drug Saf*. 2011; 10:623–631.

Other Antiseizure Drugs 15

Kari Foss, Devon Hague

Since the late 1980s and early 1990s, several new antiseizure drugs (ASDs) have been introduced into human medicine for the management of a variety of epilepsies. Systematic reviews have shown that there are little to no studies demonstrating a high level of evidence to support the use of many of these newer ASDs to treat epilepsy in both dogs and cats.[1,2] Currently, there are no studies investigating the pharmacokinetic (PK) properties of some of the newer ASDs, including lacosamide and brivaracetam. Therefore, recommendations for dosing and therapeutic monitoring are unavailable for veterinary patients due to insufficient data. In fact, many of these medications may not be appropriate for use in veterinary patients due to differences in metabolism when compared to humans or potentially toxic side effects. Based on the limited information available, the use of many of the newer ASDs in veterinary patients cannot be recommended at this time. Further information on the ASDs discussed in this chapter is summarized in Tables 15.1 and 15.2.

TABLE 15.1. Clinical properties of newer and/or less commonly utilized antiseizure drugs (ASDs) in dogs.

ASD	PK properties	Efficacy data	Dosing	Adverse effects	Drug interactions
Clorazepate	$t_{1/2}$: 3–6 hours	NA	0.5–2 mg/kg PO every 8–12 hours	Sedation and ataxia, decreased serum albumin and BUN Use caution in patients with hepatic insufficiency	Potential to increase hepatic enzyme induction Use caution in patients on concurrent hepatically metabolized medications
Clonazepam	0.1 mg/kg: $t_{1/2}$: 1–2 hours 2 mg/kg: $t_{1/2}$: 5–6 hours	NA	0.25–0.5 mg/kg PO every 8–12 hours	Sedation and ataxia	Potential to increase hepatic enzyme induction Use caution in patients on concurrent hepatically metabolized medications
Felbamate	$t_{1/2}$: 4–6 hours	Insufficient evidence for use as monotherapy or add-on ASD.	15–20 mg/kg PO every 8 hours	Hepatoxicity, *thrombocytopenia*, *lymphopenia*, KCS	Induces hepatic microsomal P450 enzymes: potential to cause PB toxicity
Gabapentin	50 mg/kg PO once: Oral F 80% 10 mg/kg PO once: ■ $t_{1/2}$: 3.3 hours ■ C_{max}: 9.68 ug/L ■ t_{max}: 1.5 hours 20 mg/kg PO once: ■ $t_{1/2}$: 3.4 hours ■ C_{max}: 12.95 ug/L ■ t_{max}: 1.75 hours	NA for use as monotherapy. Studies favorable for use with PB or KBr, but insufficient evidence for use as add-on ASD.	10–20 mg/kg PO every 6–8 hours	Sedation, ataxia	In people: antacids decrease GI absorption, H2-blockers decrease renal clearance

ASD	PK properties	Efficacy data	Dosing	Adverse effects	Drug interactions
Topiramate	10 mg/kg PO once: ■ $t_{1/2}$: 3.7+0.2 hours ■ C_{max}: 9.2+1.8 ug/mL ■ t_{max}: 2.4+2.5 hours 10 mg/kg PO for 15 days: ■ $t_{1/2}$: 3.8 +0.7 hours ■ C_{max}: 10.3+2.1 ug/mL ■ t_{max}: 2.4+1.1 hours	NA for monotherapy. May be useful add-on with PB and KBr, but insufficient evidence for use as add-on ASD.	5 mg/kg PO every 12 hours; 10–20 mg/kg IV*	Weight loss, sedation in dogs with IE (concurrently on PB or KBr)	Coadministration with PB increases renal excretion and decreases $t_{1/2}$ 4-fold
Pregabalin	4 mg/kg PO once: ■ $t_{1/2}$: 6.90 hours ■ C_{max}: 7.15 ug/mL ■ t_{max}: 1.5 hours	Possible benefit as add-on with PB and/or KBr, but insufficient evidence for use as add-on ASD.	2 mg/kg PO every 8–12 hours, increasing by 1 mg/kg weekly to desired dose	Sedation, ataxia (concurrent administration of PB and KBr)	In people: drug-drug interactions unlikely given no effect on hepatic cytochrome P450 enzymes
Rufinamide	$t_{1/2}$: 9.86 hours (PO)	NA	20 mg/kg PO*; clinical dosing NA	NA	Dogs: no short-term AEs*
Lacosamide	NA	NA	5 mg/kg PO every 12 hours (anecdotal); clinical dosing NA	Dose-dependent ataxia and decreased GI motility	None known
Brivaracetam	NA	NA	NA	NA	In people: hepatic enzyme inducing ASDs may lower plasma concentrations

PK, pharmacokinetic; BUN, blood urea nitrogen; NA, not available; Oral F, oral bioavailability; $t_{1/2}$, half-life; t_{max}, time to peak concentration; PB, phenobarbital; KCS, keratoconjunctivitis sicca; GI, gastrointestinal; IE, idiopathic epilepsy; KBr, potassium bromide; *based on PK studies. Adverse effects (AEs) in italics are categorized as type B; all other AEs are considered type A. Antiseizure drug monitoring is not performed for any of these drugs as targeted serum concentrations have not been established in dogs.

TABLE 15.2. Clinical properties of newer and/or less commonly utilized antiseizure drugs in cats.

ASD	PK properties	Dosing	Adverse effects
Clorazepate	NA	Not recommended for use	*Idiosyncratic hepatotoxicity*
Clonazepam	NA	0.25 mg/kg PO every 12–24 hours	Sedation and ataxia
Gabapentin	5 mg/kg IV: $t_{1/2}$: 3.87 hours	3–8 mg/kg PO every 6–8 hours*; clinical dosing NA	Sedation requiring decreased dosing
	10 mg/kg PO once: Oral F, 94.8% ■ $t_{1/2}$: 2.83–3.63 hours ■ C_{max}: 8–12.42 ug/mL ■ t_{max}: 1.05–1.67hours		
	10 mg/kg PO every 12 hours: ■ $t_{1/2}$: 3.72 12 hours ■ C_{max}: 14.78 ug/mL ■ t_{max}: 1.05 12 hours		
Pregabalin	4 mg/kg PO once: ■ $t_{1/2}$: 10.4±2.6 12 hours ■ C_{max}: 8.3±1.6 ug/mL ■ t_{max}: 2.9±1.2 12 hours	1–2 mg/kg PO every 12 hours*; clinical dosing NA	Severe sedation at 4 mg/kg (reduced dosing recommended)

NA, not available; Oral F, oral bioavailability; $t_{1/2}$, half-life; t_{max}, time to peak concentration; PB, phenobarbital; KCS, keratoconjunctivitis sicca; KBr, potassium bromide; *based on PK studies. Adverse effects (AEs) in italics are categorized as type B; all other AEs are considered type A. Data on efficacy in cats has not been reported with any of these drugs. Antiseizure drug monitoring is not performed for any of these drugs as targeted serum concentrations have not been established in cats.

CLORAZEPATE AND CLONAZEPAM

Clorazepate and clonazepam are both older-generation ASDs in the benzodiazepine class of drugs. They have limited efficacy as maintenance ASDs in dogs, and are more commonly used in the emergency setting, due to their typical short elimination half-life ($t_{1/2}$).[3,4]

Mechanism of action

Benzodiazepines work by binding to γ-aminobutyric acid (GABA) receptors to increase inhibitory neurotransmission (Fig. 15.1). Clorazepate is a prodrug that hydrolyzes in the stomach to the primary active metabolite, nordiazepam.[5] Clonazepam is a benzodiazepine derivative and more potent than diazepam.[5]

Pharmacokinetics

In dogs, clorazepate has a $t_{1/2}$ of 3–6 hours after oral administration and is highly protein bound (85%).[3,4] Clonazepam has a dose-dependent $t_{1/2}$ in

dogs after oral administration, ranging from 1–2 hours for a dose of 0.1 mg/kg, to 5–6 hours for a 2 mg/kg dose.[5] In cats, the PK parameters of these drugs are not well defined.[4]

Dosing

Clorazepate is an oral medication. The recommended dose in dogs is 0.5–1 mg/kg every 8 hours or 2–4 mg/kg every 12 hours.[3,6] Dogs can develop tolerance and dependence with long-term clorazepate administration; consequently, clorazepate is not indicated as a maintenance ASD, as seizure control is not long lasting.[6]

Clonazepam is available in an oral and intravenous (IV) formulation, but the injectable formulation is not available in the United States. The recommended IV clonazepam dose in dogs is 0.05–0.2 mg/kg and may be more efficacious over IV diazepam due to slower development of tolerance.[5] Oral clonazepam dosing in dogs can be administered at 0.5–1 mg/kg every 8–12 hours.[4] Clonazepam has been used for the treatment of focal seizures in cats, at a dose of 0.25 mg/kg orally every 12–24 hours.[3] However, due to the risk of idiosyncratic hepatotoxicity, clorazepate should not be used in cats.

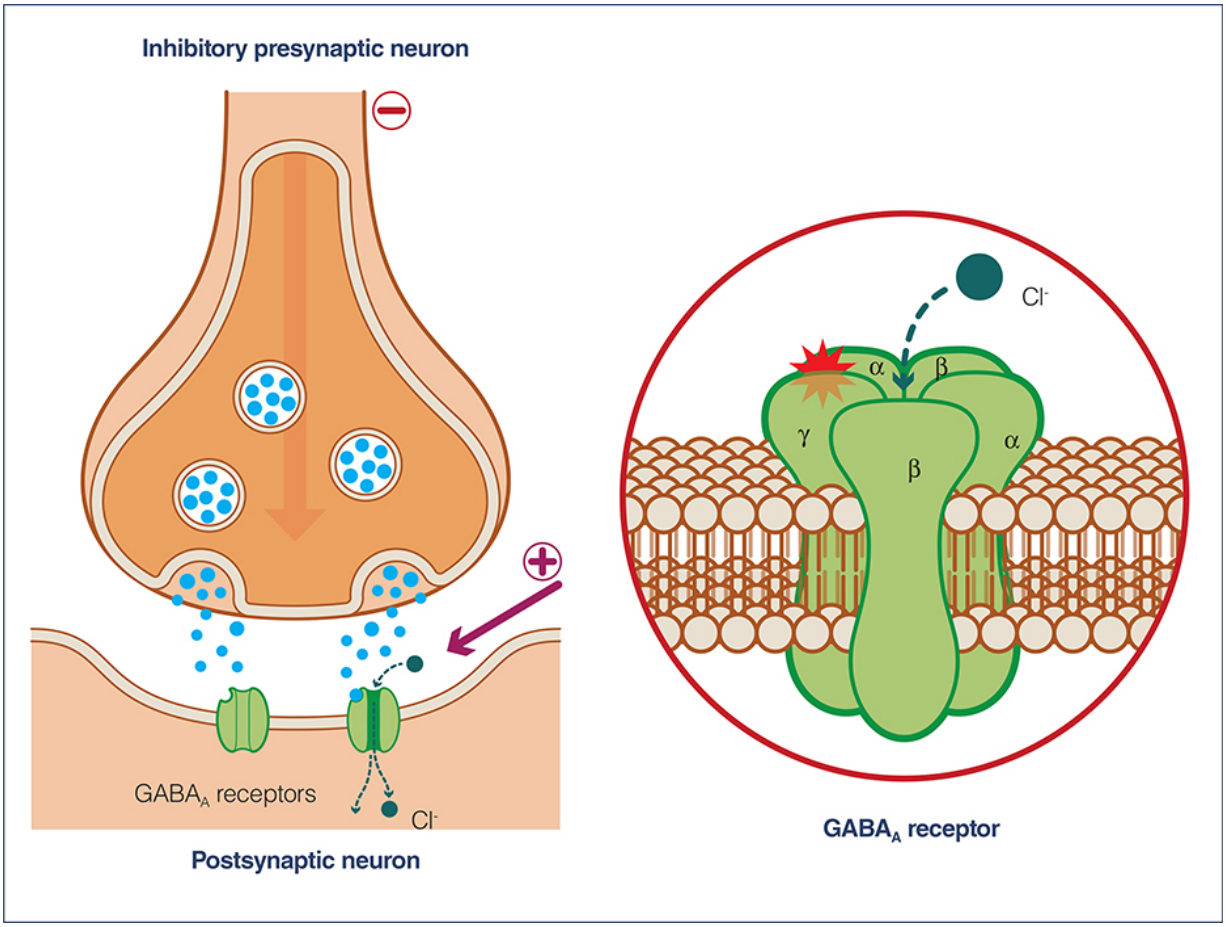


FIGURE 15.1. Mechanism of action of benzodiazepines. Benzodiazepines act to increase inhibitory neurotransmission by binding to γ-aminobutyric acid$_A$ (GABA$_A$) receptors (red star) to enhance the affinity of GABA for its binding site on the receptor, which in turn facilitates the flow of chloride ions across the neuronal cell membrane, hyperpolarizing the postsynaptic neuron.

Clinicians more often choose to use oral clorazepate or clonazepam as pulse therapy to prevent clusters in susceptible dogs.[4] Pulse therapy involves administering an initial oral dose of the medication immediately following a seizure (when the dog is able to swallow) followed by treatment initiation (every 8–12 hours depending on the dose selected) for a 36- to 48-hour period.

Efficacy

When used chronically, clorazepate concentrations can decrease even when the dose is kept constant.[5] Clonazepam (like diazepam) can result in tolerance and hepatic enzyme induction within days to weeks of starting therapy, resulting in poor seizure control. Thus, these medications are more

effective as pulse therapy for short-term emergency use.[3,4] There are no published studies evaluating the efficacy of either of these ASDs in dogs or cats with epilepsy.

Adverse effects

Sedation and ataxia are type A adverse effects (AEs) seen with oral benzodiazepines. These effects can worsen when patients are administered additional ASDs, such as phenobarbital (PB).[6] Based on the potential for increased hepatic enzyme induction when using benzodiazepines, caution should be utilized in patients coadministered medication that is hepatically metabolized, or with hepatic insufficiency.[3,4] In one study of epileptic dogs administered oral clorazepate at 2 mg/kg every 12 hours for 3 weeks, significant decreases in serum albumin and urea nitrogen were observed, although all values stayed within the reference range.[5]

Drug interactions

Due to the potential for clorazepate to increase PB concentrations, measuring serum PB concentrations is recommended at 2 and 4 weeks after clorazepate initiation whenever these two drugs are used concurrently.[5,6]

FELBAMATE

Felbamate was first approved for use in humans with epilepsy in 1993, but it is not commonly used because of the potential for idiosyncratic, life-threatening AEs. It is considered a last resort ASD in dogs with idiopathic epilepsy (IE), due to the limited evidence to support its efficacy.[1,7] Additionally, the drug has limited availability and is typically very expensive, due to the high risk of toxicity in people.[1]

Mechanism of action

Felbamate exerts its antiepileptic effect by potentiating GABA-receptor chloride currents and inhibiting NMDA (N-methyl-D-aspartate) receptor–mediated activity (Fig. 15.2).[7,8]

Pharmacokinetics

In dogs, felbamate has a very short $t_{1/2}$ (4–6 hours) and reaches steady state after 20–30 hours.[8] Felbamate is metabolized through hydroxylation and conjugation by the hepatic cytochrome P450 system and is eliminated in the urine.[8] Differences in hepatic metabolism can result in variable and fast metabolism in some dogs.[8]

Dosing

The recommended oral starting dose in dogs with IE is 15–20 mg/kg every 8 hours.[5,8] While some references infer doses of up to 50–75 mg/kg every 8 hours, there are no published studies evaluating the efficacy or toxicity at doses above 100 mg/kg every 8 hours.[4,5,7,8] Due to the drug's very short $t_{1/2}$, dosing every 6 hours may be necessary.[8]

Based on the limited data available on the use of felbamate in dogs and its potential for severe toxicity in people, performing hematology and serum biochemistry prior to initiating therapy, then monthly for the first 6 months, and every 3–6 months thereafter is recommended.[7,8]

Efficacy

A retrospective study of 6 dogs with focal seizures due to IE that were administered felbamate at an initial oral dose of 50–120 mg/kg/day reported a reduction in seizure frequency in all dogs and seizure freedom in 2 dogs, with a follow-up period of 2–22 months.[8] In another study, 12 out of 16 dogs with drug-resistant epilepsy showed a reduction in seizure activity with the addition of felbamate to their ASD regimen of PB and potassium bromide (KBr).[9]

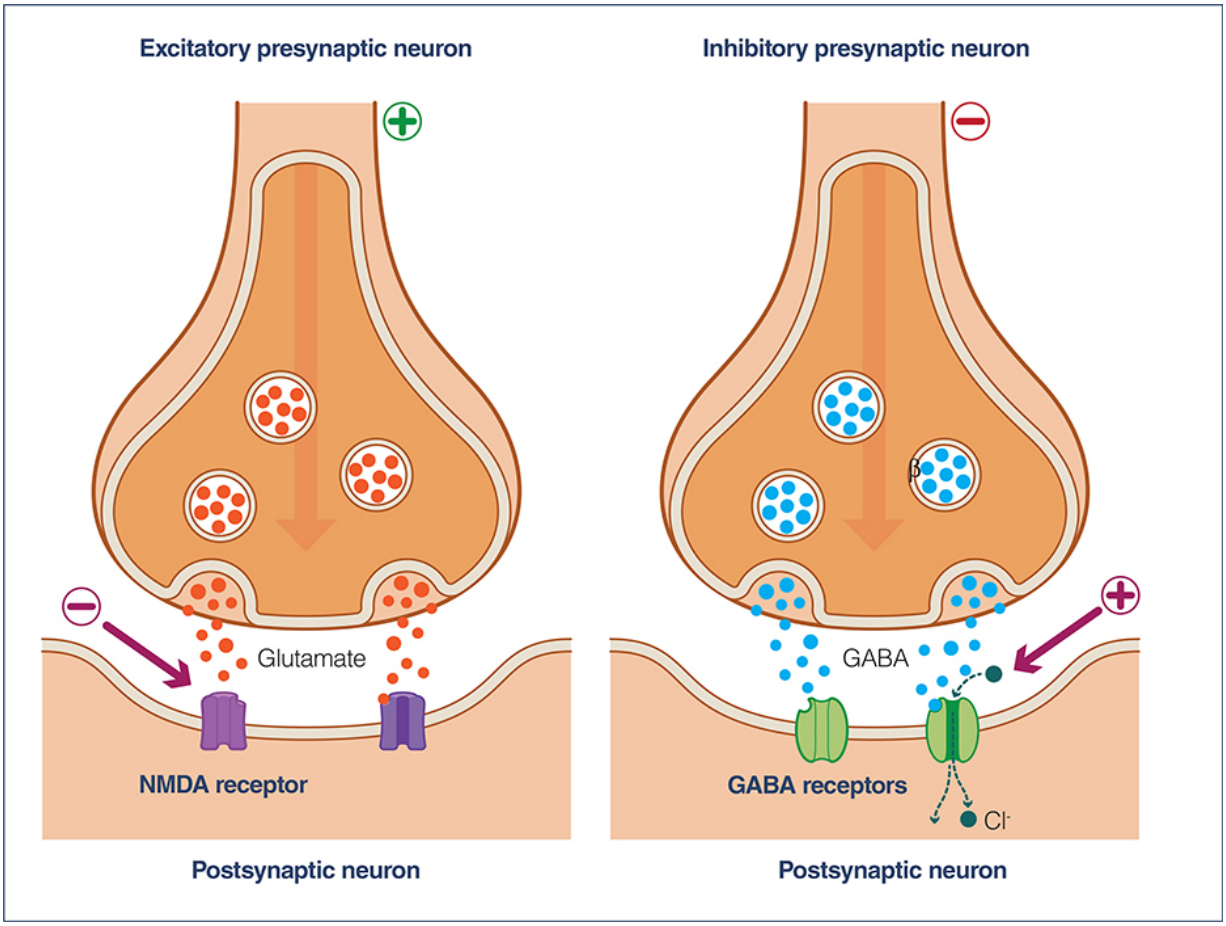


FIGURE 15.2. Mechanism of action of felbamate. Felbamate is thought to exert its effect by increasing conductance through γ-aminobutyric acid (GABA) mediated chloride channels, thereby increasing inhibitory neurotransmission, and by inhibiting the N-methyl-D-aspartate (NMDA) channels, thereby decreasing excitatory neurotransmission.

Adverse effects

Non-life-threatening blood dyscrasias (type B AE) were reported in 2/6 epileptic dogs treated with felbamate (thrombocytopenia and lymphopenia between 3 and 13 months after initiating therapy, respectively). Keratoconjunctivitis sicca has also been reported in dogs.[4,8] In small-breed dogs administered (unspecified) high doses of felbamate, generalized tremors have also been reported as a type A AE.[4] As in humans, felbamate causes minimal sedation in dogs.[4]

Felbamate inhibits hepatic microsomal cytochrome P450 enzymes; thus, it has the potential to cause PB toxicity, by inhibiting its metabolism and increasing serum PB concentrations.[4,7,9] In people, felbamate can cause a fatal aplastic anemia and hepatic failure.[4,7,8] Felbamate-associated

hepatotoxicity can also occur in dogs, with anecdotal reports of reversal of hepatic dysfunction after drug discontinuation.[4,9]

GABAPENTIN

Gabapentin is a cyclic GABA analog that is structurally related to GABA and was approved in 1993 for use as an add-on ASD for the treatment of focal seizures with and without secondary generalization in humans. Gabapentin has been used in dogs with drug-resistant IE.[10,11] It is more commonly used in the treatment of neuropathic pain syndromes in animals and humans.[12]

Mechanism of action

The mechanism of action of gabapentin is not completely understood. While structurally similar to GABA, it does not specifically affect the GABA neurotransmitter system. The proposed mechanism of action involves selective inhibition of voltage-gated calcium channels containing the α2δ-1 subunit (Fig. 15.3).[10]

Pharmacokinetics

The $t_{1/2}$ of gabapentin in dogs is 3–4 hours, and the drug is hepatically metabolized to N-methyl-gabapentin.[13] The oral bioavailability is 80% in dogs, and maximum plasma concentrations increase proportionally with dosing.[13] The $t_{1/2}$ in cats is similar to that in dogs, ranging from 2–5 hours following IV or oral dosing.[12,13] Repeated oral dosing in cats does not alter the drug's PK properties and bioavailability after a single oral dose is 94.8%.[12]

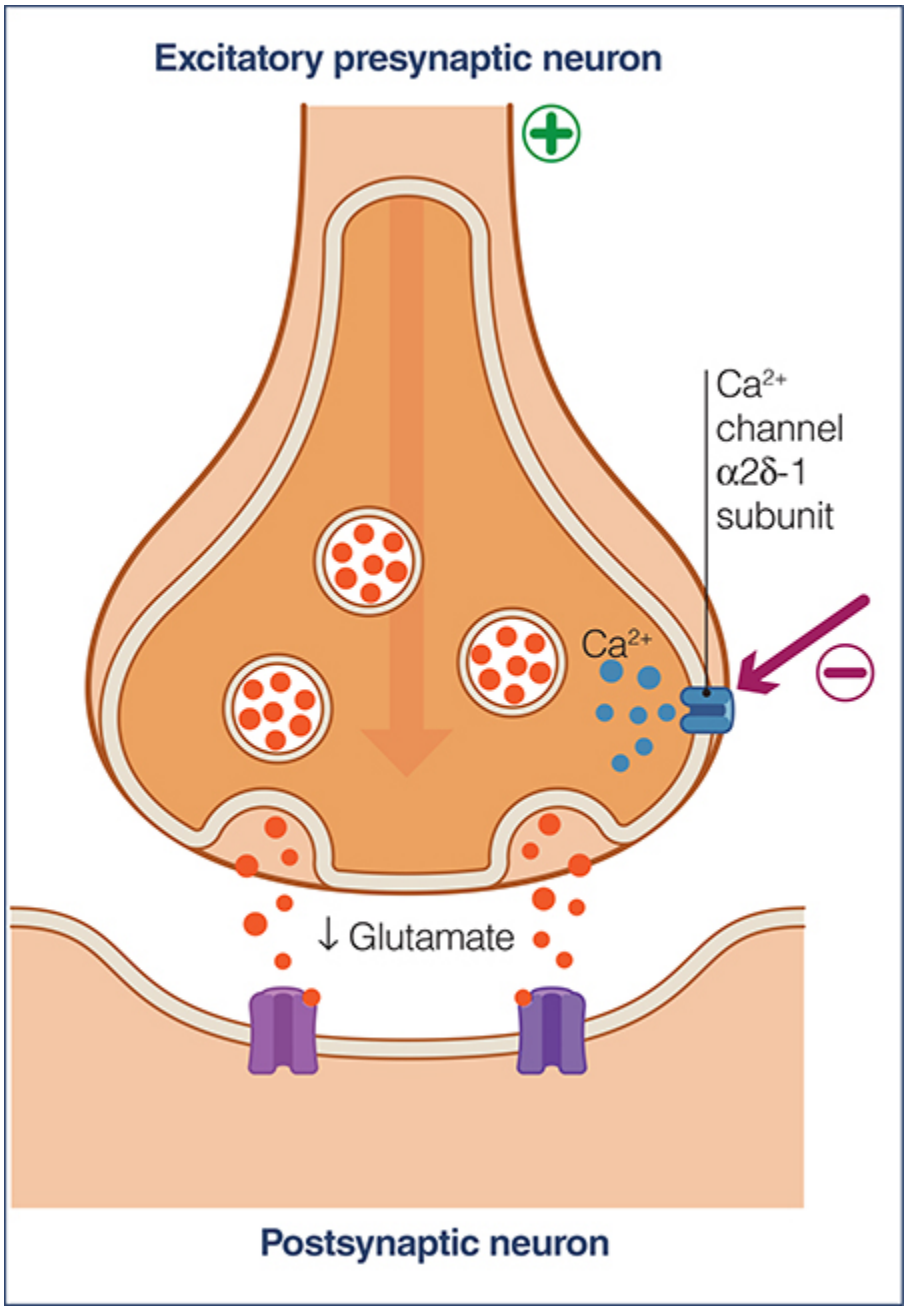


FIGURE 15.3. Mechanism of action of gabapentin and pregabalin. Both gabapentin and pregabalin are proposed to exert their effect by binding to the α2δ-1 subunit of the voltage gated calcium channels, thereby altering calcium currents and inhibiting the presynaptic release of excitatory neurotransmitters.

Dosing

The recommended dosing in dogs is 10–20 mg/kg orally every 8 hours, as this maintains serum concentrations of 2 ug/mL (the reported therapeutic concentration in people) for up to 12 hours.[14]

In cats, the suggested oral dose is 8 mg/kg every 6 hours, but doses of 3 mg/kg every 6 hours were able to maintain a plasma concentration of 2 ug/mL.[12,13] Therefore, dosing of 3–8 mg/kg every 6 hours is recommended in cats based on PK studies. There is no published information on the clinical use of gabapentin in cats with epilepsy.

Efficacy

In one open-label study evaluating gabapentin as add-on therapy to PB and KBr in dogs with IE, 17 dogs received oral gabapentin at a dosage of 35–50 mg/kg/day divided every 8–12 hours over 4 months. While the interictal period was increased and the postseizure recovery time was decreased, no significant reduction in overall epileptic seizure frequency was noted.[15] In another open-label study, 11 dogs with PB and KBr-resistant IE were administered oral gabapentin at a dosage of 10 mg/kg every 8 hours for 3 months. In this population, the number of epileptic seizures per week and the number of days with any epileptic seizure activity in a one-week period were significantly decreased.[11]

Adverse effects

Adverse effects in humans include sedation, dizziness, headache, nausea, and obesity.[16] In dogs, sedation and ataxia have been reported.[11,15] In cats, mild to moderate sedation was noted up to 2 hours after IV administration. Oral dosing appeared to be well tolerated.[13]

Drug interactions

In people, antacids reduce gabapentin's gastrointestinal absorption and H_2 receptor blockers decrease its renal clearance.[16]

TOPIRAMATE

Topiramate is a sulfamate-substituted monosaccharaide and newer-generation ASD that was approved in the US in 1996 as monotherapy and adjunctive treatment of primary generalized seizures and focal seizures in

humans. It is derived from the naturally occurring monosaccharide D-fructose and contains a sulfamate functionality.[18]

Mechanism of action

Topiramate exerts its antiepileptic effects through several mechanisms: blockage of voltage-dependent sodium channels, enhancement of GABA neuroinhibition, antagonism of AMPA and kainite subtype glumatate receptors currents, and effects on voltage-activated Ca^{2+} channels (Fig. 15.4). It also demonstrates minimal inhibition of carbonic anhydrase isoenzymes, though this unlikely contributes to its anticonvulsant activity.[18]

Pharmacokinetics

In healthy Beagles administered a single oral 40 mg/kg dose of topiramate, peak plasma concentrations occurred at 0.6–3.8 hours and oral bioavailability ranged from 27 to 59%.[19] In a study involving dogs with naturally occurring epilepsy, the oral bioavailability was reported to range from 62 to 102%.[20] Topiramate is eliminated mostly unchanged in the urine of dogs. However, significant biliary excretion following topiramate administration was also noted.[19]

Dosing

A daily oral dose of 5 mg/kg every 12 hours administered to dogs with drug-resistant IE was well tolerated.[21] Increased topiramate clearance is found in the presence of enzyme-inducing drugs in both humans and dogs. Dogs on an enzyme inducer, such as PB, may require higher doses in order to achieve target plasma concentrations of 20–30 μg/mL.[20]

Efficacy

In a prospective, open-label, noncomparative study of topiramate administered at a dose of 5 mg/kg orally every 12 hours to dogs with drug-resistant IE, 5/10 dogs were classified as responders (≥50% decrease in seizure frequency compared to pretreatment) over a 6-month follow-up period, with a mean decrease in epileptic seizure frequency of 66%. Three of the 5 dogs remained responders over an additional follow-up period of 3–9 months. These findings suggest that topiramate may be useful as an add-on medication to PB and KBr in canine IE.[21]

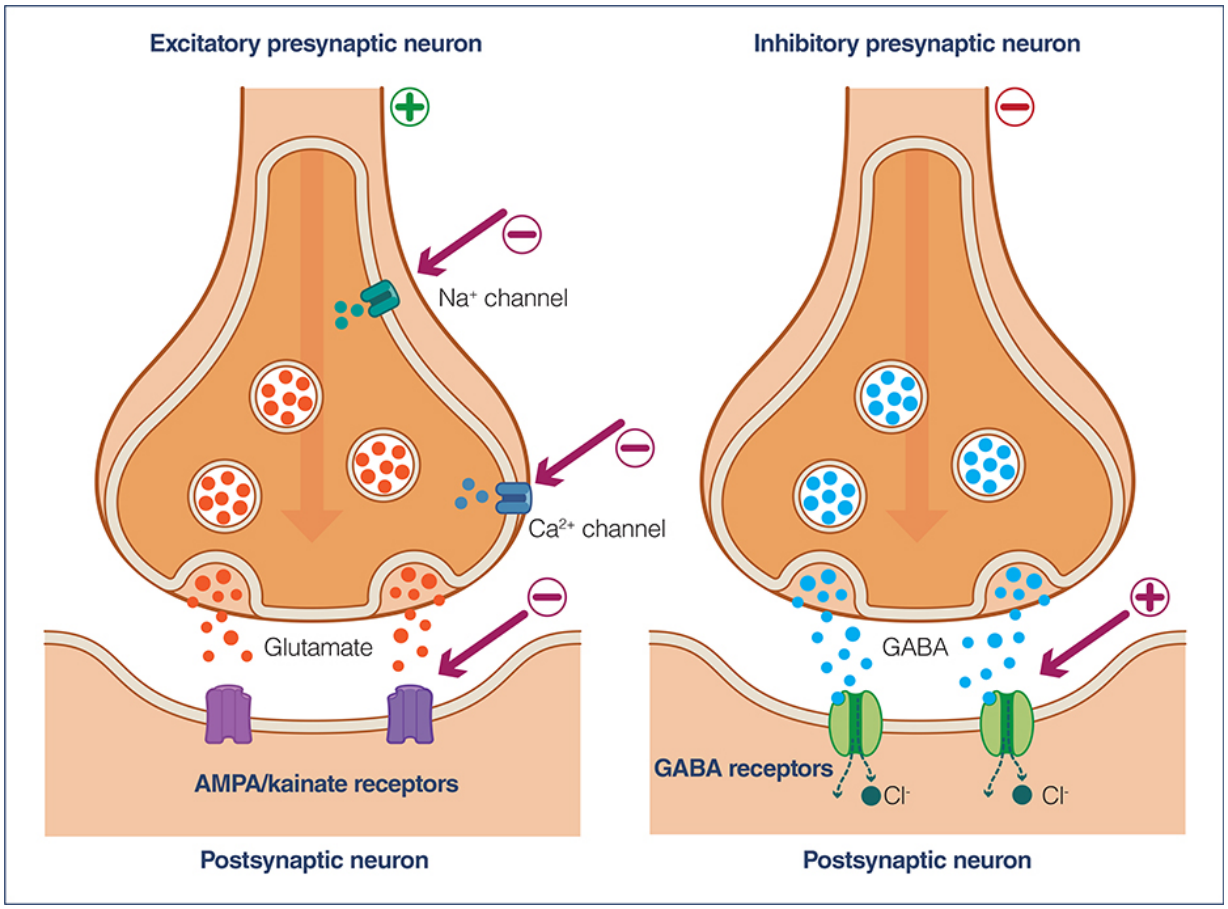


FIGURE 15.4. Mechanism of action of topiramate. Topiramate exerts its effect by decreasing excitatory neurotransmission via blocking of voltage dependent sodium and calcium channels, and antagonism of AMPA/kainite subtype glutamate receptors. It also increases inhibitory neurotransmission by enhancing GABA receptor activity.

Adverse effects

Adverse effects in people are mostly central nervous system (CNS)-related and include fatigue, somnolence, headache, psychomotor slowing, confusion, memory impairment, etc. Other AEs are weight loss, diarrhea, decreased appetite, metabolic acidosis, and nephrolithiasis.[18]

No AEs were noted in healthy Beagles administered topiramate orally at a dose of 10–15 mg/kg/day for 15 days or in epileptic dogs receiving a single IV 10–20 mg/kg dose.[19,20] In a study evaluating oral topiramate as an add-on to PB and KBr in dogs with IE, 7/9 dogs experienced weight loss and severe sedation, leading to topiramate discontinuation in 1 dog.[21]

Drug interactions

In dogs, PB coadministration resulted in a 5.6-fold greater clearance and an approximate 4-fold shorter $t_{1/2}$ of topiramate.[20]

PREGABALIN

Pregabalin is structurally similar to gabapentin and was approved in the US in 2005. It is currently licensed for the treatment of focal epilepsies, neuropathic pain, fibromyalgia, and anxiety disorders in adults.[16] Its use as a treatment for seizures in dogs and its PK properties in cats have been investigated.[17,22]

Mechanism of action

The mechanism of action of pregabalin is similar to that of gabapentin, which interacts with the α2δ-1 subunit of voltage-gated calcium channels (Fig. 15.3). However, pregabalin has an increased binding affinity for this subunit, suggesting that it may be more potent than gabapentin.[17,22]

Pharmacokinetics

Similarly to gabapentin, pregabalin is also metabolized to its N-methyl metabolite in dogs, and a single oral dose of 4 mg/kg exceeded the reported minimal therapeutic concentration in people of 2.8–8.2 mg/mL for ~11 hours with a $t_{1/2}$ of 7 hours, and a time to peak concentrations of 1.5 hours.[23] A single 4 mg/kg oral dose of pregabalin in healthy cats reached concentrations considered to be therapeutic. The time to peak plasma concentration was around 2.9 hours.[17]

Dosing

In cats, a single oral dose of 4 mg/kg can lead to profound sedation; therefore, 1–2 mg/kg every 12 hours dosing has been recommended based on a PK study.[17] An oral dose of 3–4 mg/kg every 8 hours in dogs caused AEs (worsening ataxia, etc). Therefore, an oral starting dose of 2 mg/kg every 8–12 hours is recommended, increasing by 1 mg/kg/week until the desired dose is obtained. Increased hepatic enzymes (ALP, ALT) were noted

in 6/11 dogs administered pregabalin. As such, monitoring liver enzymes in patients is recommended.[22]

Efficacy

In an open-label noncomparative study of dogs with PB and KBr-resistant IE, 9/11 dogs were reported to have a significant reduction in epileptic seizure frequency after oral administration of pregabalin at a dosage of 3–4 mg/kg every 8 hours for 3 months. Of those dogs, 7 were considered responders with a mean and median seizure reduction of 64% and 58%, respectively.[22]

Adverse effects

Adverse effects in people include dizziness and somnolence. Dry mouth, edema, and blurred vision have also been reported.[22] Sedation and ataxia were noted in 10/11 dogs with IE administered pregabalin as add-on therapy to PB and KBr, and signs persisted for the course of the 3-month study.[22,23] Cats can experience severe sedation when administered pregabalin at 4 mg/kg, and therefore a dose of 1–2 mg/kg every 12 hours is recommended.[17]

Drug interactions

In humans, pregabalin has no effect on hepatic cytochrome P450 enzymes. Therefore, drug–drug interactions due to inhibition of the metabolism of other agents by pregabalin are unlikely.[23]

RUFINAMIDE

Rufinamide is a triazole derivative structurally unrelated to any other ASD. It was approved in 2008 for the treatment of seizures associated with Lennox–Gastaut syndrome in humans >4 years of age and focal seizures with and without secondary generalization.[24]

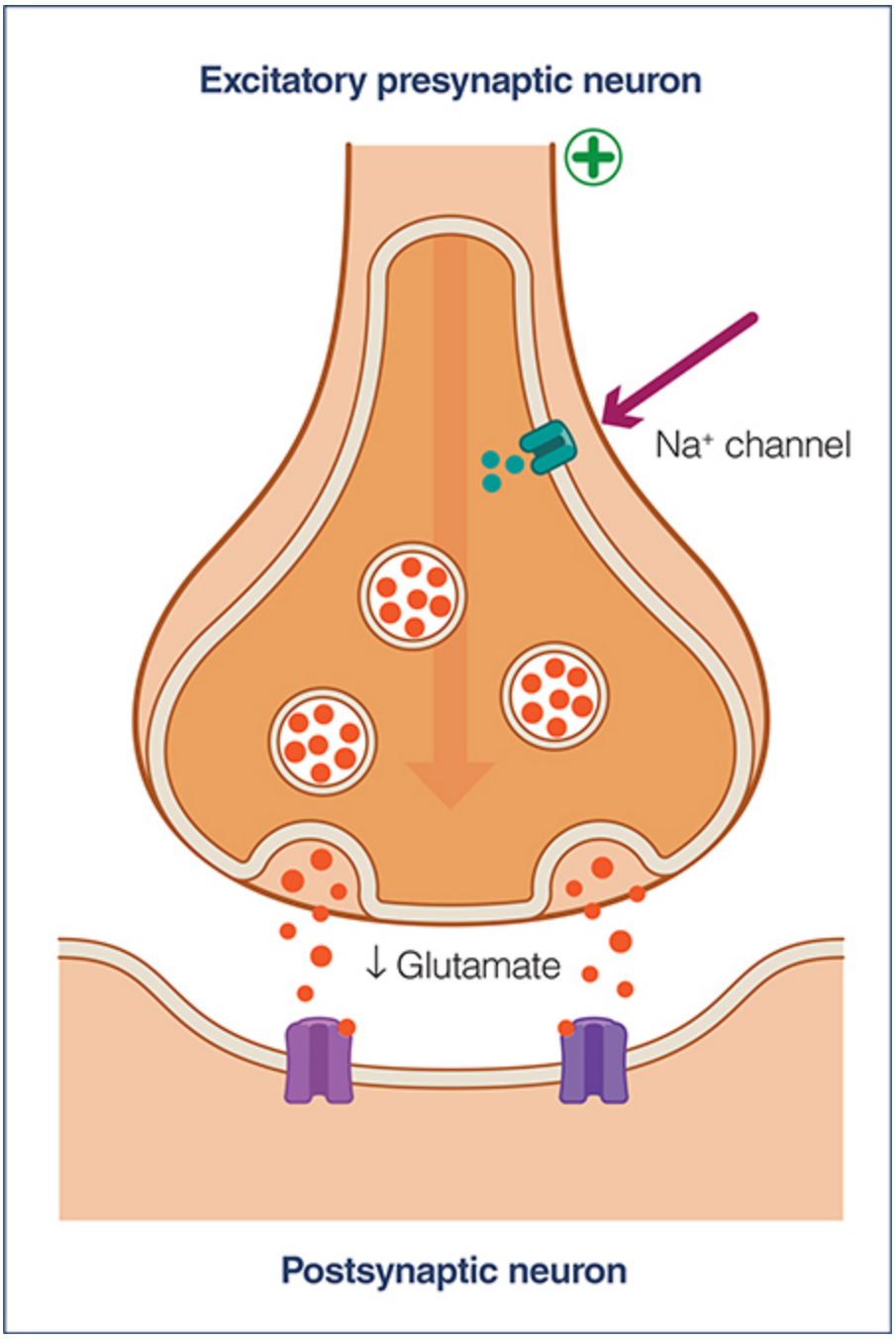


FIGURE 15.5. Antiseizure mechanism of action for rufinamide and lacosamide. Although both of these drugs exert an effect by acting on presynaptic voltage-gated sodium channels, lacosamide is unique in that it enhances slow inactivation of these channels, whereas rufinamide and other ASDs are thought to influence the fast inactivation.

Mechanism of action

Rufinamide limits sodium-dependent action potentials, thus stabilizing neuronal membranes (Fig. 15.5). Rufinamide does not show measurable

binding to neurotransmitter receptors; therefore, it is not thought to exert its effects via these receptor–ligand pathways.[24]

Pharmacokinetics

In people, oral rufinamide is 70% absorbed when administered with food. It is 34% protein-bound and metabolized via hepatic hydrolysis of the carboxamide group by carboxylesterases, forming an inactive metabolite, of which 2–4% is excreted unchanged in the urine and feces. It does not affect the hepatic cytochrome P450 system.[24]

Following a single oral 20 mg/kg dose, the mean $t_{1/2}$ in dogs was 9.86 hours and mean plasma concentrations were 19.6 ug/mL, exceeding the reported therapeutic concentration in people of 15 ug/mL.[25]

Dosing

Dosing has not been established for either dogs or cats with epilepsy.

Efficacy

Based on results of randomized controlled trials in humans, rufinamide may be more effective in reducing seizure frequency by at least 50% when used as an add-on in drug-resistant focal epilepsy compared to other ASDs.[26] There are no reports on its efficacy as an ASD in dogs or cats.

Adverse effects

Adverse effects in humans include headache, dizziness, somnolence, vomiting, nausea, fatigue, and diplopia.[24,26] In addition, a dose-dependent shortening of the QT interval has been reported in humans.[24] No short-term AEs were noted with administration of rufinamide to healthy dogs.[25] Electrocardiography did not reveal any changes to the QT interval or other abnormalities.[25]

Drug interactions

Rufinamide has no effect on the hepatic cytochrome P450 system, resulting in a low potential for drug–drug interactions. However, PB, primidone, phenytoin, and carbamazepine can increase its clearance by up to 25% in humans.[24,27]

LACOSAMIDE

Lacosamide is another newer generation ASD that was initially approved in 2008 for the adjunctive treatment of focal onset seizures in adults. There is limited information on its use in veterinary patients.

Mechanism of action

Lacosamide's mechanism of action may involve decreasing neuronal excitation by inactivation of slow voltage-gated sodium channels (see Fig. 15.5) and binding to a collapsin response mediator protein-2 (CRMP2).[3,28]

Pharmacokinetics

The PK features of lacosamide have not been studied in dogs or cats. In people, oral lacosamide is absorbed quickly and eliminated through the kidneys, and does not interact with other ASDs.[3,28]

Dosing

An anecdotally reported, oral starting dose of lacosamide in dogs is 5 mg/kg every 12 hours, although there is no published data to support this. In the emergency setting, a dose of 3 mg/kg IV over 15 minutes in dogs has been proposed, though not studied.[3,28]

Efficacy

The effectiveness of lacosamide in reducing epileptic seizures in dogs and cats is unknown. In people, lacosamide is efficacious as an add-on treatment for drug-resistant epilepsy.[28]

Adverse effects

Dose-dependent ataxia and reduced gastrointestinal motility have been anecdotally reported with chronic administration of lacosamide in dogs.[3]

Drug interactions

There are no clinically relevant drug–drug interactions identified with lacosamide.[3]

BRIVARACETAM

Brivaracetam is structurally similar to levetiracetam and was approved in 2016 as mono- or add-on therapy for focal seizures in humans ≥4 years of age.[29–31]

Mechanism of action

Brivaracetam binds to the SV2A ligand with a 10- to 30-fold higher affinity for this receptor than levetiracetam (see Chapter 12, Fig. 12.1). It also inhibits voltage-dependent sodium currents and reverses the inhibitory effects of negative modulators on GABA and glycine induced currents.[31]

Pharmacokinetics

There are no published studies on the PK properties of brivaracetam in dogs or cats. In humans, brivaracetam has nearly complete oral bioavailability and exhibits low protein binding.[30] Its $t_{1/2}$ is 7–8 hours, and it is metabolized by hydrolysis of the acetamide group, producing a carboxylic acid metabolite that is 34% renally excreted. It also undergoes hydroxylation via CYP2C19 (part of the hepatic cytochrome P450 system), forming inactive metabolites. Eight to 11% of the metabolite is excreted unchanged in the urine.[29,31]

Dosing

A recommended dose in dogs and cats has not been established. Studies in humans have demonstrated a favorable efficacy and safety profile at doses of 50–200 mg/kg/day.[33]

Efficacy

Brivaracetam has been shown to be efficacious in people with focal seizure activity with or without secondary generalization. In rodent models, it provided protection against focal and secondary generalized seizures and was found to be more potent than levetiracetam in preventing secondary generalization.[31] Its efficacy as an ASD in dogs or cats has not been established.

Adverse effects

The most frequently reported AEs in humans include somnolence, fatigue, dizziness, nasopharyngitis, nausea, and headache.[29,31] Adverse effects in dogs and cats are unknown.

Drug interactions

Brivaracetam has a low potential for drug interactions, although increased plasma concentrations may occur when given with inhibitors of CYP2C19. Hepatic enzyme-inducing ASDs may slightly decrease the drug's plasma concentrations in humans.[30,31]

TAKE-HOME MESSAGES

- ✔ Several new ASDs have been introduced for the treatment of epilepsy in humans since the late 1980s, and have subsequently been finding use in veterinary medicine. However, there is currently a low level of evidence to support their use in veterinary patients.
- ✔ Data on the efficacy and tolerability of these medications in canine and feline patients has yet to be reported.
- ✔ Therapeutic monitoring is not routinely performed in humans administered these newer ASDs, and reference ranges have not been established in dogs and cats.
- ✔ Many newer ASDs may not be appropriate for use in canine and feline patients given differences in drug metabolism and the potential for toxicities.
- ✔ Based on the lack of available information, the use of these newer ASDs in veterinary medicine is not recommended at this time; rather, currently established ASDs should be selected for use.

REFERENCES

1. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy – a systematic review. *BMC Vet Res*. 2014; 10(1):257.

2. Charalambous M, Pakozdy A, Bhatti SFM, Volk HA. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14(1):64.
3. Podell M. Antiepileptic Drug Therapy and Monitoring. *Top Companion Anim Med*. 2013;28(2): 59–66.
4. Dewey CW. Anticonvulsant therapy in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2006; 36(5):1107–1127, vii.
5. Boothe DM. Anticonvulsant therapy in small animals. *Vet Clin North Am Small Anim Pract*. 1998; 28(2):411–448.
6. Thomas WB. Idiopathic epilepsy in dogs. *Vet Clin North Am Small Anim Pract*. 2000; 30(1):183–206, vii.
7. Bhatti SFM, De Risio L, Muñana K et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. *BMC Vet Res*. 2015; 11(1):176.
8. Ruehlmann D, Podell M, March P. Treatment of partial seizures and seizure-like activity with felbamate in six dogs. *J Small Anim Pract*. 2001; 42(8):403–408.
9. Dayrell-Hart B, Tiches D, Vite C. Efficacy and safety of felbamate as an anticonvulsant in dogs with refractory seizures. *J Vet Intern Med*. 1996; 10(3):174.
10. Kelly K. Gabapentin. *Neuropsychobiology*. 1998; 38(3):139–44.
11. Platt SR, Adams V, Garosi LS et al. Treatment with gabapentin of 11 dogs with refractory idiopathic epilepsy. *Vet Rec*. 2006; 159(26):881–4.
12. Adrian D, Papich MG, Baynes R et al. The pharmacokinetics of gabapentin in cats. *J Vet Intern Med*. 2018; 32(6):1996–2002.
13. Siao KT, Pypendop BH, Ilkiw JE. Pharmacokinetics of gabapentin in cats. *Am J Vet Res*. 2010; 71(7):17–821.
14. Kukanich B, Cohen RL. Pharmacokinetics of oral gabapentin in greyhound dogs. *Vet J*. 2011; 187(1):133–135.
15. Govendir M, Perkins M, Malik R. Improving seizure control in dogs with refractory epilepsy using gabapentin as an adjunctive agent. *Aust Vet J*. 2005; 83(10):602–608.
16. Jacob S, Nair AB. An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. *Drugs RD*. 2016; 16(4):303–316.
17. Esteban MA, Dewey CW, Schwark WS et al. Pharmacokinetics of single-dose oral pregabalin administration in normal cats. *Front Vet Sci*. 2018; 5:136.
18. Sachdeo RC. Topiramate. Clinical profile in epilepsy. *Clin Pharmacokinet*. 1998; 34(5):335–46.
19. Streeter AJ, Stahle PL, Holland ML et al. Pharmacokinetics and bioavailability of topiramate in the beagle dog. *Drug Metab Dispos Biol Fate Chem*. 1995; 23(1):90–93.
20. Vuu I, Coles LD, Maglalang P et al. Intravenous topiramate: pharmacokinetics in dogs with naturally occurring epilepsy. *Front Vet Sci*. 2016; 3:107. doi: 10.3389/fvets.2016.00107.
21. Kiviranta A-M, Laitinen-Vapaavuori O, Hielm-Björkman A, Jokinen T. Topiramate as an add-on antiepileptic drug in treating refractory canine idiopathic epilepsy. *J Small Anim Pract*. 2013; 54(10):512–520.
22. Dewey CW, Cerda-Gonzalez S, Levine JM et al. Pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy. *J Am Vet Med Assoc*. 2009; 235(12):1442–1449.

23. Salazar V, Dewey CW, Schwark W et al. Pharmacokinetics of single-dose oral pregabalin administration in normal dogs. *Vet Anaesth Analg*. 2009; 36(6):574–580.
24. Hakimian S, Cheng-Hakimian A, Anderson GD, Miller JW. Rufinamide: a new anti-epileptic medication. *Expert Opin Pharmacother*. 2007;8(12): 1931–1940.
25. Wright HM, Chen AV, Martinez SE, Davies NM. Pharmacokinetics of oral rufinamide in dogs. J *Vet Pharmacol Ther*. 2012; 35(6):529–533.
26. Panebianco M, Prabhakar H, Marson AG. Rufinamide add-on therapy for drug-resistant epilepsy. *Cochrane Database Syst Rev*. 2020; 11(11):CD011772.
27. Hsieh DT, Thiele EA. Efficacy and safety of rufinamide in pediatric epilepsy. *Ther Adv Neurol Disord*. 2013; 6(3):189–198.
28. Weston J, Shukralla A, McKay AJ, Marson AG. Lacosamide add-on therapy for partial epilepsy. *Cochrane Database Syst Rev*. 2015; (6):CD008841.
29. Kappes JA, Hayes WJ, Strain JD, Farver DK. Brivaracetam: an adjunctive treatment for partial-onset seizures. *J Clin Pharmacol*. 2017; 57(7):811–817.
30. Moseley BD, Chanteux H, Nicolas J-M et al. A review of the drug−drug interactions of the antiepileptic drug brivaracetam. *Epilepsy Res*. 2020; 163:106327.
31. Stephen LJ, Brodie MJ. Brivaracetam: a novel antiepileptic drug for focal-onset seizures. *Ther Adv Neurol Disord*. 2018;11:1756285617742081.
32. Zhu L, Chen D, Chen T et al. The adverse event profile of brivaracetam: A meta-analysis of randomized controlled trials. *Seizure*. 2017; 45:7–16.
33. Klein P, Diaz A, Gasalla T, Whitesides J. A review of the pharmacology and clinical efficacy of brivaracetam. *Clin Pharmacol Adv Appl*. 2018; 10:1–22.

Cannabidiol in Canine Epilepsy

16

Stephanie McGrath

The *Cannabis sativa* plant is composed of over 100 phytocannabinoids, the cannabinoid compounds found naturally in the plant. The two most recognized and studied cannabinoids are cannabidiol (CBD), a nonpsychotropic cannabinoid, and Δ-9-tetrahydrocannabinol (THC), a psychotropic cannabinoid. Studies have established that CBD has anticonvulsive properties in vitro and in vivo in murine seizure models.[1–4] Additionally, a number of human clinical trials studying the effect of CBD on epilepsy have been reported in the literature.[5–11] Although the results of early human clinical trials were promising, they were mostly small studies, unblinded, not randomized, and often had incomplete datasets.[5–6] However, recently, a series of randomized clinical trials studying the efficacy, safety and tolerability of oral CBD for drug-resistant seizures in humans have been performed.[7–11] The results of this research led to the first plant-derived cannabinoid medication to receive regulatory approval in the US and Europe for the treatment of seizures associated with two severe pediatric forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome. Subsequently, the first veterinary study assessing the effect of CBD on seizure frequency in dogs with refractory idiopathic epilepsy (IE) was published.[12] Although the results were encouraging, the study emphasized the need for larger controlled clinical trials in veterinary medicine to assess efficacy, dosing and safety more accurately.

MECHANISM OF ACTION

Although various mechanisms have been proposed for CBD's anticonvulsive effects, the exact mechanism of action remains unknown. Cannabinoid-specific receptors have been identified as part of the endocannabinoid system, the two most studied being cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). THC binds to CB1 receptors in the central nervous system (CNS), activating voltage-gated calcium channels and enhancing potassium channel conduction, which, in turn, modulates neuronal activity.[13] However, CBD does not appear to have a high affinity for CB1 or CB2 receptors, making this mode of action unlikely.[13] Given the demonstrated effectiveness of CBD in animal seizure models, past mechanistic research has investigated CBD's effect on maintaining neuronal function, including membrane potential maintenance, regulation of neurotransmitter release, and postsynaptic calcium modulation. Specifically, studies have proposed a variety of anticonvulsive mechanisms of CBD that may involve binding to members of the transient receptor potential channels, thereby leading to decreased glutamate (a major excitatory neurotransmitter);[14,15] activating 5-hydroxytryptophan 1A receptors;[16] and inhibiting adenosine reuptake.[17] Recent research has more specifically focused on the ability of CBD to reduce neuronal excitability through its effects on the modulation of calcium channels (TRPV1) and sodium channels, antagonism at G protein-coupled receptors (GPR55), and inhibition of adenosine transport.[18]

TRPV1

Transient receptor potential vanilloid type 1 (TRPV1) receptors are ubiquitous in the CNS and are thought to play a role in epilepsy through their effect on calcium channel modulation and the ability to regulate neuronal activity via the release of the excitatory neurotransmitter glutamate.[19–20] It has been shown that TRPV1 is overexpressed in the brains of epileptic patients, and, given its effect on cortical excitability, TRPV1 likely plays an important role in epilepsy.[21–22] There is evidence that CBD readily stimulates TRPV1 receptors and quickly desensitizes them.[14,23] The effect of CBD on TRPV1 receptors with regard to epilepsy was evaluated in an acute model of generalized seizures in TRPV1 knock-out mice compared to wild-type littermates.[24] Deletion of the TRPV1 gene resulted in a diminished response to CBD in mice, which greatly contributed to the

concept that TRPV1 may be an important target in the anticonvulsive action of CBD.[24]

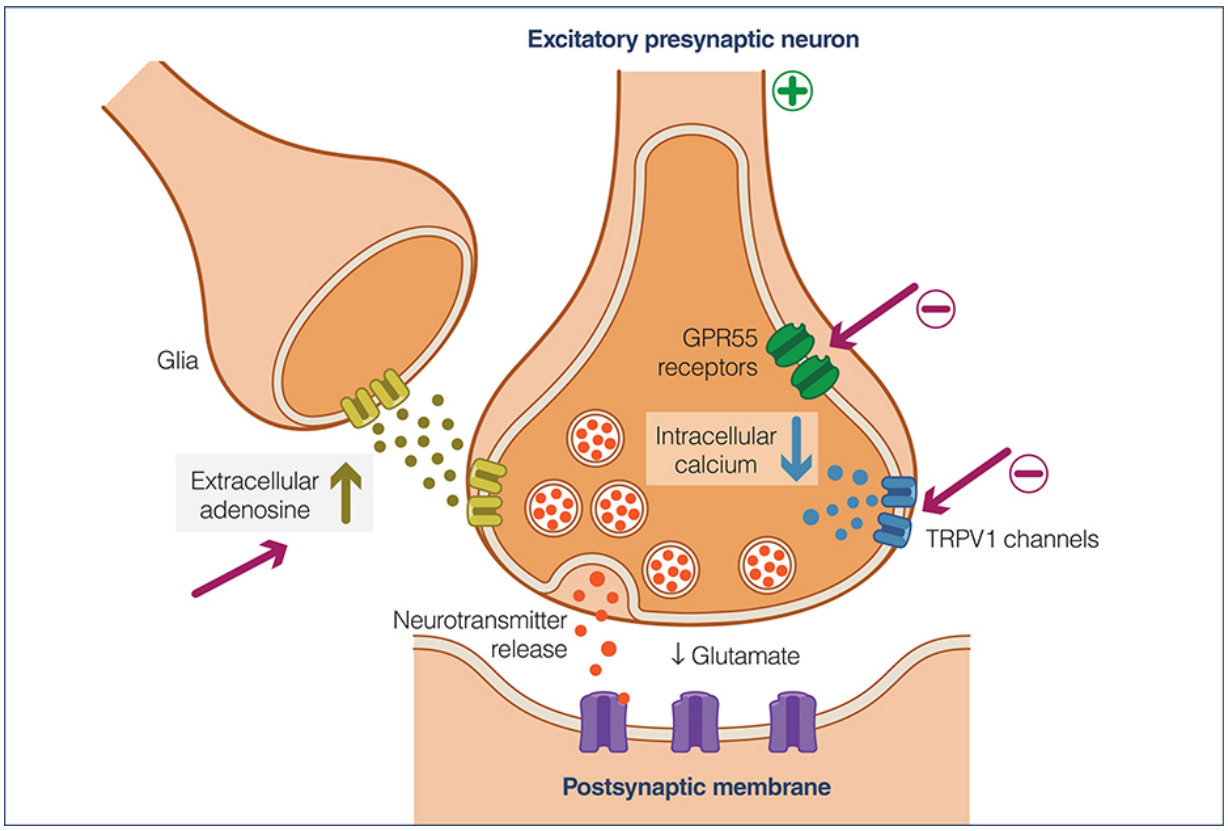


FIGURE 16.1. Mechanism of action of cannabidiol. Cannabidiol is proposed to exert its anticonvulsive effect by decreasing excitatory neurotransmission via modulation of calcium channels through stimulation of transient receptor potential vanilloid type 1 (TRPV 1) receptors and antagonism of G protein–coupled receptors (GPR55), and inhibition of neurotransmitter release through effects on adenosine transport.

GPR55

A class of G protein-coupled receptors, known as GPR55 receptors, have been shown to be increased in the hippocampus of epileptic patients.[25] By enhancing calcium release from inositol triphosphate-gated intracellular stores, GPR55 receptors cause an increase in intracellular calcium concentration, which is hypothesized to, in turn, modulate neuronal excitability and transmission.[24,26,27] It appears that CBD has the ability to block a potent GPR55 agonist, lysophosphatidylinositol (LPI), thereby restoring neuronal excitatory/inhibitory balance in seizure models. An in vitro study demonstrated the ability of CBD, administered at a concentration of 1 μM to human cells, to successfully antagonize GPR55

receptors in both epileptic and nonepileptic conditions,[25] making GPR55 a promising target in CBD epilepsy research.

Adenosine

Adenosine is considered an endogenous anticonvulsant and potent neuromodulator.[28–29] Adenosine is released after neuronal depolarization and, via actions with 7-transmembrane G protein-coupled receptors, mediates synaptic activity and inhibits neurotransmitter release.[18,30] Cannabidiol has been shown to increase extracellular adenosine and inhibit adenosine reuptake.[31–33] Given the inherent anticonvulsant properties of adenosine and the demonstrated effect of CBD on adenosine release and reuptake, it is postulated that CBD may play an important role in the modulation of epileptic seizures via this mechanism.

Sodium channels

Voltage-gated sodium channels (VGSC) have also been proposed as a potential target for CBD's anticonvulsant effects. Aberrant VGSC activity (resurgent currents) has been thought to contribute to certain forms of epilepsy. Resurgent currents may be dysregulated in epilepsy, causing channels to re-open during the repolarization phase of the action potential, which, in turn, heighten neuronal excitability.[34] This alteration in VGSC activity may be an important target in epilepsy treatment. Patel et al. described CBD's mechanistic interaction with VGSCs to decrease seizure activity, making aberrant VGSC resurgent currents a promising target.[34] Another study described CBD's ability to inhibit VGSC function.[35] However, there are concerns that the concentrations of CBD used in these preliminary studies are not clinically achievable,[18] making the relevance questionable.

A number of clinical trials have demonstrated anticonvulsive properties of CBD; however, the exact mechanism of action of CBD's anticonvulsive effects remains elusive. Although other targets, outside the scope of this review, have been identified, and even more may be discovered, several targets have come to the forefront of the current research focus. Taking into account the results of mechanistic studies, as well as achievable doses, the three main mechanisms contributing to CBD's ability to temper neuronal excitation in seizure patients, are TRPV1 receptor desensitization, GPR55 receptor antagonism, and adenosine reuptake inhibition.

PHARMACOKINETICS

A number of recent pharmacokinetic (PK) analyses have been performed in companion animals, utilizing a variety of product types (CBD isolate: pure CBD without other cannabinoids; full-spectrum CBD: CBD plus a variety of other cannabinoids, including THC; and broad-spectrum CBD distillate: CBD plus a variety of other cannabinoids, without THC), formulations (oral oil tinctures, soft chews, topical creams, and oral capsules), and dosages. A summary of the PK studies conducted so far can be found in Table 1.

Dogs

CBD-dominant pharmacokinetic studies

Bartner et al. published one of the first canine PK studies, evaluating a full-spectrum hemp product administered via three delivery methods (oral CBD-infused oil, oral CBD-infused capsules, and CBD-infused transdermal cream applied to the pinnae).[36] Two single doses (5 mg/kg and 10 mg/kg) were given to healthy research dogs, randomly assigned to dosing groups of five dogs. Of the three formulations, the CBD-infused oil had the highest maximum concentration (C_{max}), longest elimination half-life ($t_{1/2}$), and greatest systemic exposure (represented by the area under the curve, AUC). Specifically, the PK data for the 5 mg/kg and 10 mg/kg doses of oral CBD-infused oil showed a $t_{1/2}$ of 199.7 +/- 55.9 minutes and 127.5 +/- 32.2 minutes, respectively; a C_{max} of 625.3 +/- 164.3 ng/mL and 845.5 +/- 262.2 ng/mL, respectively; and an AUC of 135.6 +/- 46.3 min·ug/mL and 297.6 +/- 112.8 min·ug/mL, respectively.

In another study, 4 research dogs were orally administered a full-spectrum hemp-derived CBD oil (50/50% mix of CBD/CBDA with additional minor cannabinoids and terpenes) at single doses of 1 mg/kg and 4 mg/kg of CBD, with a 2-week washout period between each dosing protocol.[37] The PK analysis showed a median $t_{1/2}$ of 4.2 hours for both doses, a C_{max} of 102.3 ng/mL (60.7–132.0 ng/mL) for the 1 mg/kg dose and 590.8 ng/mL (389.5–904.5 ng/mL) for the 4 mg/kg dose, and an AUC of 367 h·ng/mL (183–437 h·ng/mL) for the 1 mg/kg dose and 2658 h·ng/mL (1753–3048 h·ng/mL) for the 4 mg/kg dose. A similar PK study performed using oral soft chews (50/50% mix of CBD/CBDA) dosed at 1 mg/kg CBD

revealed a much shorter $t_{1/2}$ of 1.0 +/- 0.2 hours, a higher C_{max} of 301 +/- 63 ng/mL, and a much higher AUC of 1297 +/- 210 h·ng/mL.[38] The apparent wide variation in $t_{1/2}$, C_{max} and systemic exposure among dogs is a consistent finding in the published canine PK studies. The discrepancies may arise from the variety of forms of CBD used (oil/oil bases, chew, cream), CBD type (full-spectrum, isolate, broad-spectrum), fed versus fasted administration, individual metabolism, and other factors.

CBD/THC combination pharmacokinetic studies

A study investigating the PK parameters of a cannabis oil composed of both THC and CBD in healthy Labrador Retrievers evaluated a dose of 1.5 mg/kg THC plus 0.0375 mg/kg CBD, in both fasted and fed dogs.[39] For both the fasted and fed dogs, the results for THC showed a median $t_{1/2}$ of 1.74 (0.80–3.5) hours and 1.86 (0.86–3.01) hours, respectively; a C_{max} of 24.34 (9.2–77.1) ng/mL and 7.10 (3.6–11.4) ng/mL, respectively; and an AUC of 69.94 (20.26–95.43) h·ng/mL and 24.00 (7.84–58.65) h·ng/mL, respectively. No detectable plasma CBD was found at any time point. Of note, the fasted dogs in this study had a higher C_{max} and AUC, as compared with the fed dogs. Given the highly lipophilic nature of THC, it is expected that THC has greater bioavailability in the fed dogs. To this effect, previous studies in humans and rodents demonstrated that cannabinoids were absorbed faster and achieved a higher C_{max} and AUC in a fed state.[40] The authors postulated that the olive oil base was sufficient to increase the THC bioavailability in the fasted state, whereas in the fed state, the meal may have sequestered the phytocannabinoids, altering their PK profile. Therefore, based on the results of this study, a high-fat meal (or oil base) may be sufficient to activate intestinal lymphatic transport and lead to higher cannabinoid systemic exposure and C_{max}.

TABLE 16.1. Summary of cannabidiol product pharmacokinetic data in dogs.

Study	Cannabinoids	Product type	Dose (mg/kg)	CBD half-life (h)	CBD C_{max} (ng/mL)	CBD AUC (hr·ng/mL)
Bartner et al. (2018)	CBD-dominant	Oil	5	3.3	625	2259
		Capsule		1.6	346	1633
		Transdermal cream		ND	74	195
	CBD-dominant	Oil	10	2.1	846	4965
		Capsule		1.9	578	2716
		Transdermal cream		ND	278	500
Gamble et al. (2018)	CBD-dominant	Oil	1	4.2	102	367
			4	4.2	591	2658
Deabold et al. (2019)	CBD-dominant	Soft chews	1	1	301	1297
Lebkowska-Wieruszewska et al. (2019)	THC:CBD	Oil	1.5 mg/kg THC; 0.0375 mg/kg CBD (fasted)	1.7	24	70
			1.5 mg/kg THC; 0.0375 mg/kg CBD (fed)	1.9	7	24
Fernández-Trapero et al. (2020)	THC:CBD	Sublingual spray	8.1 mg/kg THC; 7.5 mg/kg CBD	ND	10	95
Chicoine et al. 2020	THC:CBD	Oil	0.1 mg/kg THC; 2 mg/kg CBD	2.5	213	759
			0.25 mg/kg THC; 5 mg/kg CBD	2.6	838	2935
			0.5 mg/kg THC; 10 mg/kg CBD	2.3	1868	7239

CBD, cannabidiol; THC, Δ-9-tetrahydrocannabinol; C_{max}, maximum concentration; AUC, area under the curve.

Another study investigated the pharmacokinetics of Sativex®, a formulated cannabis extract developed as an oromucosal spray, administered to healthy dogs using a single or multiple doses of 8.1 mg/kg THC and 7.5 mg/kg CBD via sublingual delivery.[41] The single dose PK analysis showed a C_{max} of 18.5 ng/mL for THC and 10.5 ng/mL for CBD and a time to C_{max} of 2 hours. The AUC was 94.9 h·ng/mL for THC and 60.4 h·ng/mL for CBD. The dogs were subsequently treated with the same dose daily for a 14-day period. A similar THC/CBD PK profile was demonstrated, but with a time to C_{max} of 1 hour. Interestingly, the plasma levels of CBD and THC after multiple doses showed a progressive elevation, the concentration values pre- and postdose tending to converge. This was apparently due to an increase in the pre-dose plasma concentration after about a week of daily administration. The authors suggest this trend could be due to the accumulation of phytocannabinoids in fat and other

organs, allowing them to undergo a progressive, slow release when plasma levels start diminishing. Lastly, a recent study evaluated the PK of various oral doses of a cannabis extract containing a 1:20 ratio of THC:CBD in 13 healthy research dogs.[42] The doses administered were "low" (2 mg/kg CBD; 0.1 mg/kg THC), "medium" (5 mg/kg CBD; 0.25 mg/kg THC), and "high" (10 mg/kg CBD; 0.5 mg/kg THC). The PK analysis of CBD showed a $t_{1/2}$ of 2.5 h, 2.6 h, 2.3 h, a C_{max} of 213 ng/mL, 838 ng/mL, and 1868 ng/mL, and an AUC of 759 h·ng/mL, 2935 h·ng/mL, 7239 h·ng/mL for the low, medium, and high doses, respectively. The $t_{1/2}$ of approximately 2 h is similar to the results obtained in previous studies. The C_{max} for the low dose is consistent with previous reports; however, with the medium and high doses, the C_{max} appears to increase in a dose-dependent (nonlinear) manner. Although this nonlinear increase in C_{max} was not observed in all studies, it is worth noting, especially if higher doses are considered in a clinical setting.

Cats

A single dose PK evaluation was performed in 6 healthy research cats that were administered a 2 mg/kg dose of CBD-infused fish oil (50/50% mix of CBD and CBDA), equivalent to 1 mg/kg CBD.[38] The PK data showed a mean $t_{1/2}$ of 1.5 +/- 0.1 hours, a Cmax of 43 +/- 9 ng/mL, and an AUC of 164 +/- 29 h·ng/mL. Given the $t_{1/2}$, Cmax and AUC were considerably lower than in their canine counterparts, it appears that cats may absorb and metabolize CBD differently than dogs.

Overall, from the various PK studies, it appears that PK processes in dogs and cats are dynamic and may be affected by the frequency and degree of drug exposure. Many extrinsic factors, including dose, route of administration, vehicle (tincture, capsule, edible, transdermal cream, inhalant), and fed/fasted conditions, as well as intrinsic factors, such as rates of absorption and individual metabolism, can substantially influence drug concentrations. Appreciating this wide variation is important and monitoring CBD blood concentrations will likely be critical when considering dosing ranges for pets and when setting up controlled clinical trials.

EFFICACY

In 2018, the FDA approved the first plant-derived cannabidiol product, Epidiolex®, for the treatment of refractory seizures secondary to two severe forms of pediatric epilepsy, Lennox-Gastaut syndrome and Dravet syndrome. The drug was approved for similar use in Europe in 2019, under the name Epidyolex®. Several open-label and placebo-controlled clinical trials demonstrated the effectiveness of various doses of Epidiolex® (an oral 99% pure oil-based CBD product) in reducing median monthly seizure frequency in both children and adults with refractory forms of epilepsy. A double-blind, placebo-controlled trial evaluating the effect of 20 mg/kg/day of adjunctive CBD administered to children with Dravet syndrome showed a median monthly seizure frequency reduction of 38.9%, as compared with a 13.3% reduction in the placebo group.[7] An open-label trial assessing the effect of adjunctive CBD on seizure frequency in patients with severe, intractable, treatment-resistant epilepsy showed that oral doses up to 25 or 50 mg/kg/day were effective in reducing median monthly seizures by 36.5%.[8] And, finally, a phase 3, double-blind, placebo-controlled trial investigated the effect of add-on CBD therapy at a dose of 20 mg/kg/day on the frequency of drop seizures associated with treatment-resistant Lennox-Gastaut syndrome.[11] The patients in the treatment group showed a median percentage reduction in monthly drop seizure frequency of 43.9%, compared with a reduction of 21.8% in the control group. Interestingly, a separate study, specifically evaluating the association of plasma concentrations of CBD and seizure control, showed that higher plasma levels of CBD were associated with greater seizure improvement.[43] The study also demonstrated a positive linear correlation between CBD dosage (range, 5–50 mg/kg/day) and plasma level (range, 7.1–1200 ng/mL). These pivotal trials, along with several other studies, provided convincing evidence of CBD's anticonvulsive effects, prompting the approval of the first medication containing a purified drug substance derived from cannabis to be used for certain forms of epilepsy.

In contrast to the human field of medicine, the research evaluating the effects of CBD on canine epilepsy is still scant. A single pilot study assessing the effects of CBD in client-owned dogs with naturally occurring intractable IE was recently published. This randomized, double-blind, placebo-controlled study compared the effects of CBD on seizure frequency

in dogs that were experiencing uncontrolled seizure activity, defined as two or more epileptic seizures per month, while receiving at least one standard antiseizure drug (ASD). The dogs in the treatment group were administered a CBD-dominant hemp oil, along with their prescribed conventional treatment.[12] Sixteen dogs completed the study. The 9 dogs in the treatment group received 2.5 mg/kg oral CBD-dominant oil every 12 hours in addition to their standard ASD therapy, and the 7 dogs in the control group received the same volume of a disguised placebo oil in addition to their standard ASD therapy, for a study period of 12 weeks. Conventional ASD therapy was comprised of phenobarbital, potassium bromide, levetiracetam, and zonisamide, either alone or in various combinations. Eight of 9 (89%) dogs in the treatment group and 3 of 7 (43%) dogs in the control group experienced a reduction in average monthly seizure frequency when compared to the reported seizure frequency for the 16 weeks prior to study enrollment. A significant reduction in the group median for mean seizure frequency in the treatment group (33%), as compared with the placebo group (0%) was demonstrated. However, a "responder" was defined as a dog that experienced at least a 50% reduction in mean seizure frequency during the treatment phase, as compared with the baseline period; there was no difference in number of "responders" between the treatment group and the placebo group. Throughout the study, plasma CBD concentrations were measured every 4 weeks. Of note, the plasma concentrations were negatively correlated with seizure frequency, meaning that the dogs that attained higher CBD plasma concentrations displayed a greater reduction in seizure frequency. Overall, the conclusion of the study was that although the results were encouraging, additional research assessing a larger population of dogs is needed to determine the efficacy of CBD as an ASD in companion animals.

CLINICAL USE

There is still a scarcity of information available regarding effective dosing for canine IE. The search for developing a dosing regimen, identifying a target range for therapeutic blood concentrations, and a better understanding of breed, sex, and individual response to CBD is underway. As outlined in

previous sections, several human epilepsy clinical trials and one canine IE clinical trial have been published in peer-reviewed journals, the human studies successfully culminating in the approval of the first plant-based CBD medication for epilepsy. The canine pilot study tested the effect of 5 mg/kg/day on IE in client-owned dogs.[12] The CBD was administered as an oil at a concentration of 100 mg/mL at a dose of 2.5 mg/kg orally every 12 hours for a 3-month period. Although the results of the study were encouraging, more information is necessary prior to recommending a clinical dosing range. However, based on the PK data available for dogs and cats, daily dosing every 12 hours is proposed. However, regardless of an eventual consensus on a dosing range for CBD for canine diseases, given the variability in individual absorption and metabolism of CBD, ascertaining a therapeutic range by monitoring CBD blood concentrations will likely be critical in its use in veterinary medicine.

ADVERSE EFFECTS AND DRUG INTERACTIONS

The safety profile of CBD in dogs is still under investigation. Preliminary studies have shown adverse effects (AEs), such as elevations in hepatic enzymes; however, long-term studies have not been performed. Therefore, the safety of chronic use and the significance of the hepatic enzyme increases are still unknown. In one study, healthy research dogs were randomly divided into groups of 5 dogs and administered 5 or 10 mg/kg/day CBD-dominant products delivered via oral oil, oral capsules, or transdermal cream for 6 weeks.[44] Adverse effects included diarrhea, which occurred in all dogs at various timepoints, and an elevated serum alkaline phosphatase (ALP), which occurred only in the dogs receiving the oral CBD forms. The diarrhea was mild and self-limiting. Postprandial bile acid concentrations were measured and showed no alterations, making short-term hepatic dysfunction in this cohort of dogs unlikely. Overall, the study showed that short-term oral and transdermal CBD was well tolerated, when administered for a period of six weeks.

In a study assessing the effects of CBD on osteoarthritis in dogs, the first arm of the study evaluated the safety of administering CBD-infused soft

chews to 4 healthy research dogs.[37] The dogs were dosed with 1 mg/kg CBD soft chews every 12 hours for 84 days. Adverse effects included loose stool and vomiting, at an occurrence of 3.3% and 0.45%, respectively. At this dose, there were no hematological or serum biochemistry changes outside the reported reference range for any dog during the study period, supporting the apparent short-term safety profile of oral CBD.

A study investigating the safety of escalating oral doses of CBD and THC, alone and in combination, in healthy research dogs, showed that CBD alone was better tolerated than THC and CBD/THC in combination.[45] Five treatment groups (n = 4/group) received one of the following regimens of escalating doses/volumes: CBD-dominant oil, THC-dominant oil, CBD/THC (1.5:1) dominant oil, sunflower oil placebo, and medium chain triglyceride (MCT) oil placebo. The CBD-dominant oil was administered to a maximum dose of approximately 62 mg/kg, the THC-dominant oil to a maximum dose of approximately 49 mg/kg, and the CBD/THC oil to a maximum dose of approximately 12 mg/kg CBD/8 mg/kg THC. The sunflower and MCT oil were given orally to maximum volumes of 45 mL and 35 mL. Adverse events were observed in all dogs, most of which were mild, including diarrhea, vomiting, lethargy, and ataxia. The dogs administered CBD-dominant oil did not experience any moderate or severe AEs. The dogs receiving THC-dominant oil or CBD/THC oil combination had moderate to severe AEs, including ataxia, hypothermia and lethargy, at certain doses. The primary laboratory change was an increase in hepatic enzymes in some of the dogs. One dog in the CBD-dominant oil group and 1 dog in the CBD/THC oil group experienced 2.9- and 3.6-fold increases in ALP, respectively. No other significant abnormalities were noted. This study offers the first controlled scientific comparison of the tolerability of CBD and CBD/THC oils, and demonstrated that CBD oil (without THC) was better tolerated.

In another study evaluating oral doses of CBD combined with THC in dogs, dogs were administered three different doses of 1:20 THC:CBD, either as a single dose or as multiple doses.[42] For the single dose phase, dogs were administered a low dose (2 mg/kg CBD; 0.1 mg/kg THC), a medium dose (5 mg/kg CBD; 0.25 mg/kg THC), or a high dose (10 mg/kg CBD; 0.5 mg/kg THC). Five of 6 dogs in the high dose group developed neurological signs, including hyperesthesia and ataxia. The severity of the clinical signs in the high-dose group appeared to be closely associated with

their CBD/THC plasma concentrations, meaning the dog with the lowest plasma concentrations had no apparent neurological signs and the dog with the highest plasma concentrations had the most obvious signs. During the second phase, only the medium dose was used, each dog receiving a total of five consecutive doses given every 12 hours. The AEs noted in this phase were infrequent and minor, the main neurological sign being hyperesthesia (6/12 dogs). The study concluded that dogs tolerated the low and medium doses of CBD/THC well, but substantial neurological signs were observed in dogs receiving the high dose. Further, the occurrence and severity of the clinical signs seemed to be associated with the plasma concentrations.

As CBD is often used as adjunctive therapy, drug interaction studies are imperative in understanding its safety profile. Unfortunately, to date, little research has been done in veterinary medicine to better elucidate this issue. Given CBD's inhibitory effect on cytochrome enzymes, it has the potential to affect the hepatic metabolism of many commonly used drugs, most notably ASDs. Several studies in human medicine have shown that CBD can alter the serum concentrations of several ASDs, including clobazam, zonisamide, and topiramate.[46–47] Specifically, by inhibiting certain enzymes associated with the cytochrome P450 system, CBD seems to cause an increase in certain drugs that are primarily metabolized by the liver. The interactions associated with clobazam, in particular, were substantial enough to potentially warrant a dose adjustment when used in conjunction with CBD.[46] Since ASDs used in veterinary medicine undergo hepatic metabolism, such as phenobarbital, zonisamide, and topiramate, drug–drug interaction studies are critical to the future use of CBD for treating epileptic patients and monitoring of ASD serum concentrations is strongly advisable in the meantime.

TAKE-HOME MESSAGES

- ✔ Three main mechanisms of CBD's effect on seizure activity include:
  - ✔ TRPV1 receptor desensitization
  - ✔ GPR55 receptor antagonism
  - ✔ Adenosine reuptake inhibition
- ✔ The efficacy of CBD as a treatment for IE in dogs is currently under investigation.

- ✔ To date, a clinical dosing range has not been established for dogs and cats, although twice-daily (every 12 hours) dosing appears to be appropriate based on PK analyses.
- ✔ Monitoring CBD blood concentrations is critical when considering dosing ranges for pets.
- ✔ Monitoring liver enzymes and function is imperative, at least until longer term safety studies are available.
- ✔ Cannabidiol functions as an inhibitor of cytochrome P450 enzymes, and this can potentially cause an increase in serum concentrations of hepatically metabolized ASDs, such as phenobarbital and zonisamide. Until more information is available on such drug–drug interactions, it is advisable to monitor serum concentrations of hepatically metabolized ASDs when administered concurrently with CBD.

REFERENCES

1. Consroe P, Wolkin A. Cannabidiol – Antiepileptic drug comparisons and interactions in experimentally induced seizures in rats. *J Pharmacol Exp Ther*. 1977; 201:26–32.
2. Consroe P, Benedito MA, Leite JR et al. Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice. *Eur J Pharmacol*. 1982; 83:293–298.
3. Jones NA, Hill AJ, Smith I et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther*. 2010; 332:569–577.
4. Jones NA, Glyn SE, Akiyama S et al. Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures. *Seizure*. 2012; 21:344–352.
5. Cunha JM, Carlini EA, Pereira AE et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology*. 1980; 21:175–185.
6. Devane WA, Hanus L, Breuer A et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*. 1992;258:1946–1949.
7. Devinsky O, Cross JH, Laux L et al. Trial of cannabidiol for drug-resistant seizures in the Dravet síndrome. *N Engl J Med*. 2017; 376:2011–2020.
8. Devinsky O, Marsh E, Friedman D et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016; 15:270–278.
9. Devinsky O, Patel AD, Cross JH et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut síndrome. *N Engl J Med*. 2018; 378:1888–1897.
10. Devinsky O, Verducci C, Thiele EA et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav*. 2018; 18:1525–1550.

11. Thiele E, Marsh ED, French JA et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2018; 391:1085–1096.
12. McGrath S, Bartner LR, Rao S et al. Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *J Am Vet Med Assoc*. 2019; 254:1301–1308.
13. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav*. 2017; 70(Pt B):313–318.
14. De Petrocellis L, Ligresti A, Moriello AS et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol*. 2011; 163:1479–1494.
15. Sylantyev S, Jensen TP, Ross RA, Rusakov DA. Cannabinoid- and lysophosphatidylinositol-sensitive receptor GPR55 boosts neurotransmitter release at central synapses. *Proc Natl Acad Sci.* 2013; 110:5193–5198.
16. Campos AC, Ferreira FR, Guimarães FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: Possible involvement of 5HT1A receptors. *J Psychiatr Res.* 2012; 46:1501–1510.
17. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: A mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci.* 2006; 103:7895–7900.
18. Gray RA, Whalley BJ. The proposed mechanisms of action of CBD in epilepsy. *Epileptic Disord*. 2020; 22(S1):10–15.
19. Ligresti A, Moriello AS, Starowicz K et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther*. 2006; 318:1375–87.
20. Xing J, Li J. TRPV1 receptor mediates glutamatergic synaptic input to dorsolateral periaqueductal gray (dl-PAG) neurons. *J Neurophysiol*. 2007; 97:503–11.
21. Mori F, Ribolsi M, Kusayanagi H et al. TRPV1 channels regulate cortical excitability in humans. *J Neurosci*. 2012; 32(3):873–879.
22. Sun FJ, Guo W, Zheng DH et al. Increased expression of TRPV1 in the cortex and hippocampus from patients with mesial temporal lobe epilepsy. *J Mol Neurosci*. 2013; 49(1):182–193.
23. Bisogno T, Hanus L, De Petrocellis L et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol*. 2001;134:845–852.
24. Gray RA, Stott CG, Jones NA et al. Anticonvulsive properties of cannabidiol in a model of generalized seizure are transient receptor potential vanilloid 1 dependent, *Cannabis and Cannabinoid Res*. 2020; 5(2):145–149.
25. Rosenberg E, Bazelot M, Salah A et al. Cannabidiol (CBD) exerts antiepileptic actions by targeting the LPI-GPR55 lipid signaling system potentiated by seizures, abstract, *American epilepsy society*, 2018.
26. Devinsky O, Cilio MR, Cross H et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014; 55:791–802.
27. Rimmerman N, Kozela E, Levy R et al. Cannabinoid signaling through non-CB1, non-CB2 GPCR targets in microglia. In: Abood ME, Sorense RG, Stella N (eds.).

EndoCANNABINOIDS: Actions at Non-CB1/CB2 Cannabinoid Receptors. Springer: New York; 2013. pp. 143–171.

28. Dunwiddie TV, Endogenously released adenosine regulates excitability in the in vitro hippocampus. *Epilepsia*. 1980; 21(5):541–548.
29. Weltha L, Reemmer J, Boison D. The role of adenosine in epilepsy. *Brain Res Bull*. 2019; 151:46–54.
30. During MJ, Spencer DD. Adenosine: a potential mediator of seizure arrest and postictal refractoriness. *Ann Neurol*. 1992; 32:618–24.
31. Mijangos-Moreno S, Poot-Aké A, Arankowsky-Sandoval G et al. Intrahypothalamic injection of cannabidiol increases the extracellular levels of adenosine in nucleus accumbens in rats. *Neurosci Res*. 2014; 84:60–63.
32. Liou GI, Auchampach JA, Hillard CJ et al. Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor. *Invest Ophthalmol Vis Sci*. 2008; 49:5526–5531.
33. Boison D. The biochemistry and epigenetics of epilepsy: focus on adenosine and glycine. *Front Mol Neurosci*. 2016; 9:26.
34. Patel RR, Barbosa C, Brustovetsky T et al. Aberrant epilepsy-associated mutant Nav1.6 sodium channel activity can be targeted with cannabidiol. *Brain*. 2016; 139:2164–2181.
35. Ghovanloo MR, Shuart NG, Mezeyova J et al. Inhibitory effects of cannabidiol on voltage-dependent sodium currents. *J Biol Chem*. 2018; 293(43):16546–15558.
36. Bartner LR, McGrath S, Rao S et al. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Can J Vet Res*. 2018; 82:178–183.
37. Gamble LJ, Boesch JM, Frye CW et al. Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic Dogs. *Front Vet Sci*. 2018; 23(5):165.
38. Deabold KA, Schwark WS, Wolf L, Wakshlag JJ. Single-dose pharmacokinetics and preliminary safety assessment with use of cbd-rich hemp nutraceutical in healthy dogs and cats. *Animals (Basel)*. 2019; 9(10):832.
39. Łebkowska-Wieruszewska B, Stefanelli F, Chericoni S et al. Pharmacokinetics of Bedrocan®, a cannabis oil extract, in fasting and fed dogs: An explorative study. *Res Vet Sci*. 2019; 123:26–28.
40. Zgair A, Wong JC, Lee JB et al. Dietary fats and pharmaceutical lipid excipients increase systemic exposure to orally administered cannabis and cannabis-based medicines. *Am J Transl Res*. 2016; 8(8):3448–3459.
41. Fernández-Trapero M, Pérez-Díaz C, Espejo-Porras F et al. Pharmacokinetics of Sativex® in dogs: towards a potential cannabinoid-based therapy for canine disorders. *Biomolecules*. 2020; 10(2):279.
42. Chicoine A, Illing K, Vuong S et al. Pharmacokinetic and safety evaluation of various oral doses of a novel 1:20 THC:CBD cannabis herbal extract in dogs. *Front Vet Sci*. 2020; 7:583–404.
43. Szaflarski JP, Hernando K, Bebin EM et al. Higher cannabidiol plasma levels are associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. *Epilepsy Behav*. 2019; 95:131–136.
44. McGrath S, Bartner LR, Rao S et al. A report of adverse effects associated with the administration of cannabidiol in healthy dogs. *J Am Holistic Vet Med Assoc*. 2018; 52:34–38.

45. VAUGHN D, KULPA J, PAULIONIS L. Preliminary investigation of the safety of escalating cannabinoid doses in healthy dogs. *Front Vet Sci*. 2020; 7:51.
46. GASTON TE, BEBIN EM, CUTTER GR et al. Interactions between cannabidiol and commonly used antiepileptic drugs, *Epilepsia*. 2017; 58(9):1586–1592.
47. GEFFREY AL, POLLACK SF, BRUNO PL, THIELE EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015; 56(8):1246–1251.

Dietary Management of Canine Epilepsy

17

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Many dog owners are unsatisfied with conventional antiseizure drugs (ASDs) typically prescribed for canine epilepsy. Medications have adverse effects (AEs), and approximately a third of dogs with idiopathic epilepsy (IE) do not respond to ASD therapy with a meaningful reduction in seizure frequency (i.e., a ≥50% reduction from baseline). Like human epilepsy, when canine epilepsy does not respond to two tolerated and appropriately chosen ASD trials, it is classified as drug-resistant. Dietary therapy is considered an accepted treatment for certain epileptic syndromes in humans, and this has fostered a growing interest into its potential use in the management of dogs with drug-resistant epilepsy.

This chapter describes the known impairments in energy metabolism in "epileptic" brain areas from rodent chronic epilepsy models as well as dogs and humans with epilepsy. These impairments are thought to lead to energy deficits, and thereby justify the use of auxiliary brain fuels to provide energy to brain cells. Energy is crucial for regular brain functions, homeostasis, and preventing seizure generation. The chapter will provide a summary of the biochemistry and anticonvulsant effects of ketogenic diets and medium chain triglycerides (MCTs) in humans, rodents, and dogs, and finally, discuss their proposed anticonvulsant mechanisms. More details about all of these topics can be found in the cited reviews and books.[1–16]

PATHOPHYSIOLOGY AND MECHANISM OF ACTION

Glucose as the main regular brain fuel

The brain has a high demand for energy, and therefore requires a continuous supply of fuel for it to function normally. In healthy mammals, glucose is the predominant fuel source used by the brain in the fed state. Glucose is taken up into cells where it is phosphorylated by hexokinase in the cytosol to produce glucose-6-phosphate, which is then broken down via the subsequent steps of glycolysis to yield 2 pyruvate, 2 ATP and 2 NADH. Pyruvate can also be turned into lactate and excreted from the brain through oxidation of one NADH molecule in the cytosol. To yield additional energy, pyruvate is further metabolized in mitochondria. Compared to the oxidative metabolism of glucose-derived carbons in mitochondria, very little ATP is produced from the cytosolic metabolism of glucose.

Various tools are used by researchers and physicians to assess rates of glucose metabolism within specific areas of the brain. The cerebral metabolic rate of glucose (CMR_{GLC}) is, in a clinical context, most commonly measured by ^{18}fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) (see Chapter 6 for further discussion of PET). FDG is a radioactive glucose analogue that, like glucose, can be taken up into the brain and phosphorylated by hexokinase to produce FDG-6-phosphate. However, this metabolite gets almost completely trapped at this stage of glycolysis. This is because in FDG, the 2-hydroxyl group found in glucose that is required for further glycolysis is replaced by ^{18}F. Thus, the intensity of FDG-PET signals, indicated by the amount of radiation produced by FDG and FDG-6-phosphate, reflects the rate of glucose uptake and hexokinase activity. Since hexokinase is the rate-limiting enzyme of glycolysis, FDG-PET is therefore considered to reveal the rate of overall activity of glucose metabolism via glycolysis in tissues.

Brain areas with low FDG-PET signals are thought to have low glucose utilization, and/or be “hypometabolic”. Epileptogenic foci exhibit reduced FDG-PET signals during interictal periods compared to healthy brain areas, even when these areas have normal morphology and few structural alterations.[17] This indicates that brain glucose metabolism can be impaired in brain areas that are thought to generate seizures. In addition to FDG-PET,

this has been shown using ^{14}C-deoxyglucose autoradiography and by tracing the metabolism of ^{13}C-glucose in the brains of rodent chronic seizure models.[7,17]

Glycolysis and other biochemical pathways produce pyruvate, which can enter mitochondria and be oxidatively decarboxylated by pyruvate dehydrogenase (PDH) to yield acetyl coenzyme A (acetyl-CoA). To yield energy, acetyl-CoA enters the tricarboxylic acid (TCA) cycle and can produce 1 ATP, 1 $FADH_2$ and 4 NADH. When oxygen is available, each $FADH_2$ and NADH can then, via the electron transport chain, produce an additional 2 ATP and 3 ATP, respectively. Therefore, during aerobic metabolism, the majority of ATP is generated in mitochondria via oxidative phosphorylation involving the TCA cycle, the electron transport chain and ATP synthase (complex V).

In epileptic brain areas, oxidative glucose metabolism can be impaired and contribute to seizures by promoting energy imbalance[7,15] (see the *Metabolism, biochemical and other protective effects of brain fuels derived from fats* section). This is based on data collected in rodent models of chronic epilepsy and in humans. Rodent models show signs of reduced cytosolic and mitochondrial glucose metabolism, which is expected to reduce the production of ATP via oxidative phosphorylation. There is also evidence that oxidative glucose metabolism and mitochondrial function are perturbed in the brains of humans with epilepsy.[7] The electron transport chain has also been shown to be functionally and structurally altered in "epileptic" brain tissue in both rodent models and humans.[3,7,18] These biochemical alterations have been shown to promote oxidative stress, which may reduce the activity of the TCA cycle, as many of the key enzymes of this important cycle, including PDH, are vulnerable to inhibition by oxidation.

Taken together, glucose metabolism can be impaired in epileptogenic brain areas. Specifically, it appears that 1) glycolysis is reduced and 2) TCA cycle activity can be lowered, due to an impaired entry of glucose-derived carbons and decreased PDH activity. Also, glucose-derived carbons are important building blocks for amino acids and lipids. Thus, the perturbations in the epileptic brain may have profound consequences for brain structural integrity and repair.

Proposed mechanism of seizure generation via energy shortage

Data collected by FDG-PET and similar other techniques that quantify CMR_{GLC} indicate that the use of blood-derived glucose as a fuel in epileptogenic foci can be lower in humans, canines, and rodents (reviewed in Han et al[15]). This, combined with the fact that epileptic areas have a high demand for energy, even interictally (evidenced by the presence of interictal spikes in electroencephalograms, which denote high electrical activity in between seizures), renders it likely that some epileptogenic foci are in an energy deficit. This is problematic, since at rest and during synaptic activity, energy is crucial to sustain ion and neurotransmitter balances in the central nervous system (CNS). The function of the sodium–potassium ATPase and glutamate transporters, which maintain stable neuronal membrane potentials and normal synaptic activity, requires a large amount of the total brain energy consumed. Energy deficits in epileptogenic foci are likely to reduce the activities of the sodium–potassium ATPase and glutamate transporters, as well as other important transporters, which can promote neuronal hyperexcitability, and in turn, epileptic seizures. This is supported by a study in rats, which found that epileptiform activity was induced when brain glycolysis was blocked by chronic administration of 2-deoxyglucose, modeling "chronic hypometabolism" in the brain.[19] In addition, many genetic metabolic disorders cause epileptic seizures. For instance, many individuals with a deficiency in glucose transporter 1 (GLUT1), the glucose transporter responsible for most of the glucose uptake into the brain, experience epileptic seizures.

Metabolism, biochemical and other protective effects of brain fuels derived from fats

Energy deficits in "epileptic" brain areas warrant the use of auxiliary fuels. Both the medium chain fatty acids, octanoic acid and decanoic acid, and C4 ketone bodies are such auxiliary fuels (Fig. 17.1), as they are taken up and metabolized by human, canine, and rodent brains in mitochondria.[7,11,15,16]

The fats found in "standard" dog food mostly contain long chain fatty acids, defined as being greater than 12 carbons in length. Medium chain fatty acids, containing between 6 and 12 carbons, are rarer in natural dog foods. Coconut oil and palm kernel oil are very rich in dodecanoic acid, which is also called lauric acid (C12). Commercially available MCTs, which can be produced from coconut oil or other fat sources, typically contain 30–70% octanoic and 30–70% decanoic acids (C8 and C10 fatty

acids, also called caprylic and capric acid, respectively) and smaller amounts of dodecanoic acid. The characteristics of medium chain fatty acids and MCTs are summarized in Box 17.1. In the gastrointestinal tract, long chain and medium chain fat sources are cleaved by lipases to produce long and medium chain fatty acids. The complicated uptake and transport of long chain fatty acids via the lymph to the liver is summarized in a simplified fashion in Figure 17.2. In contrast, medium chain fatty acids are thought to diffuse directly into the blood and then travel to the liver and other tissues, as shown in the same figure. When blood glucose levels are low, such as during fasting or while consuming a ketogenic diet, the liver uses long and medium chain fatty acids as well as amino acids to produce C4 ketone bodies, namely acetoacetate and β-hydroxybutyrate (BHB). Ketone bodies enter and exit cells via monocarboxylate transporters and can replace glucose as brain fuel when blood glucose levels are low.[7,16] Medical ketogenic diets are typically very high in long chain fats, often are calorie restricted, and can sometimes be supplemented with MCTs (see below).

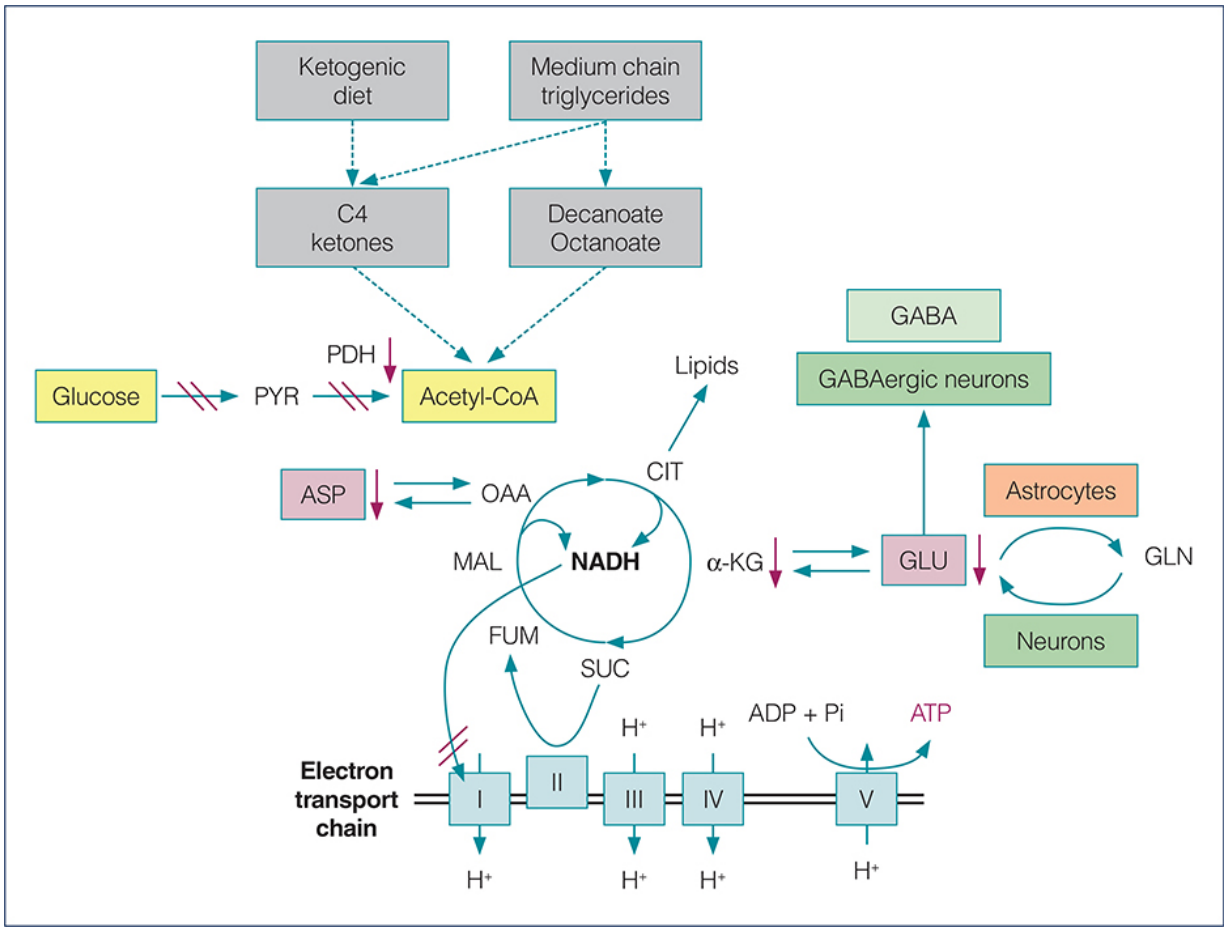
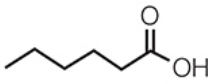
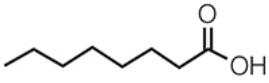
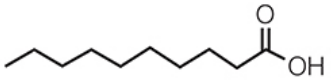
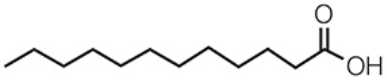


FIGURE 17.1. Changes in brain cell energy metabolism in epilepsy. Normally, oxidative glucose metabolism in mitochondria generates the greatest amount of ATP in brain cells, namely via the tricarboxylic acid (TCA) cycle and the electron transport chain. This figure shows perturbations found in epileptogenic areas in rodent models, dogs and humans with epilepsy.[7,15] Red arrows and double lines indicate reductions in metabolite levels, glucose uptake and activities of hexokinase or pyruvate dehydrogenase (PDH). These impairments can lead to reduced ATP production. Metabolic management approaches for epilepsy are highlighted with grey background and their metabolic effects are indicated. C4 ketone bodies are provided by ketogenic diets and medium chain triglycerides. Additionally, medium chain triglycerides produce medium chain fatty acids and their anions, decanoate and octanoate. C4 ketones and medium chain fatty acids directly produce acetyl coenzyme A (acetyl-CoA) and do not require PDH for entry into the TCA cycle.
α–KG, α-ketoglutarate; ASP, aspartate; CIT, citrate; FUM, fumarate; GABA, γ-aminobutyric acid; GLN, glutamine; GLU, glutamate; MAL, malate; OAA, oxaloacetate; PYR, pyruvate; SUC, succinate.

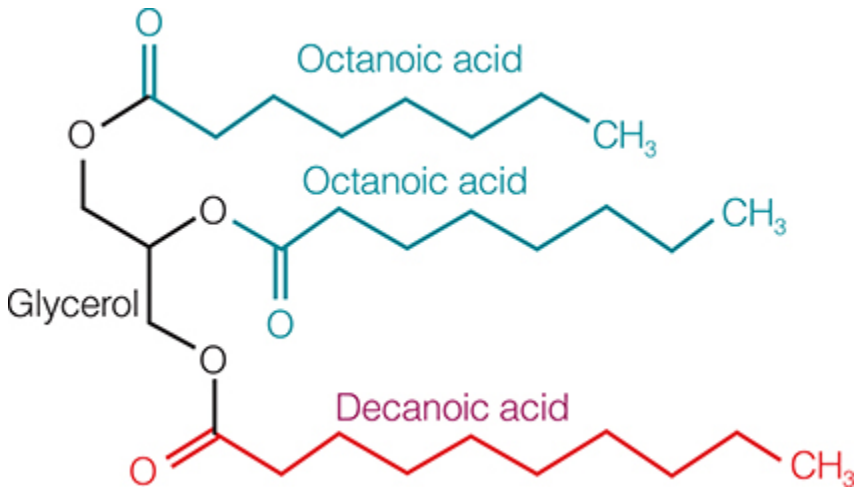
Medium chain triglycerides can also be added to standard ("nonketogenic") food to provide quick and sustained energy independent from insulin action. This approach produces octanoic and decanoic acids as well as ketone bodies in the liver. Unlike C4 ketone bodies, medium chain fatty acids directly diffuse into cells and organelles in their uncharged acid forms. In aqueous solutions, they occur in their anionic forms, octanoate and decanoate, and in blood they are bound to albumin. It appears that ketone bodies are metabolized by both neurons and astrocytes, while in vivo, medium chain fatty acids appear to be metabolized mostly in astrocytes.[7,16,20]

BOX 17.1. Characteristics of medium chain fatty acids and medium chain triglycerides.

- The **medium chain fatty acids** (MCFAs) are listed below:

Carbon chain length	Systematic name	Common name	Chemical structure
6	Hexanoic acid	Caproic acid	
8	Octanoic acid	Caprylic acid	
10	Decanoic acid	Capric acid	
12	Dodecanoic acid	Lauric acid	

- **Medium chain triglycerides** (MCTs) are comprised of glycerol molecules attached (esterified) to three medium chain fatty acids, ranging between six and 12 carbons in length. An example of an MCT is shown on the right.
- The MCFAs octanoic and decanoic acid and their triglycerides have been reported to have some anticonvulsant activity.
- Commercially produced MCT oils contain high amounts of octanoic and decanoic acids, and sometimes smaller amounts of dodecanoic acid.
- Good natural sources of dodecanoic acid include coconut oil and palm kernel oil, but there is limited research on the utility of dodecanoic acid as an anticonvulsant. Coconut oil also contains small amounts of octanoic and decanoic acids, but this is not comparable to the levels found in commercially produced MCT oils.
- Medium chain triglycerides are an ideal means to provide high amounts of octanoic and decanoic acids to the body as it avoids the direct administration of free acids or their salts (which in high amounts are toxic).



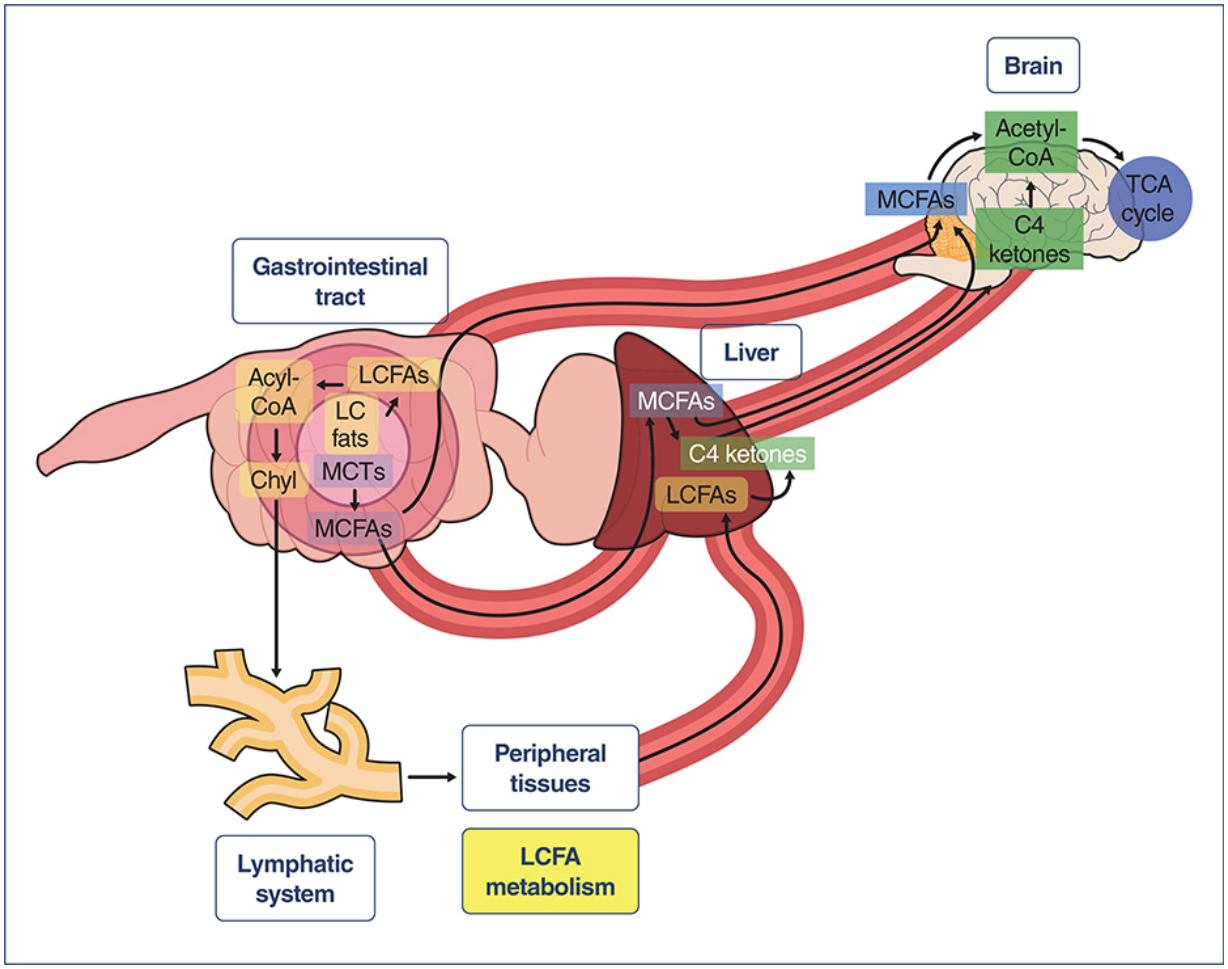


FIGURE 17.2. Metabolism of long chain fats and medium chain fats. In the small intestine, lipases produce long chain fatty acids from long chain fats, which are then transported to the intestinal mucosa. There, fatty acids are metabolized to acyl-coenzyme A, which then forms triglycerides (the primary component of chylomicrons). In the form of chylomicrons, long chain fatty acids can be transported through the whole body via the lymphatic system. Some long chain fatty acids are metabolized in peripheral tissues while others enter the liver. Medium chain triglycerides are digested by lipases to medium chain fatty acids and leave the intestinal tract via the portal vein or other veins providing blood directly to the heart. Thus, medium chain fatty acids reach organs faster than lipids derived from long chain fats. C4 ketone bodies are formed during the hepatic metabolism of fatty acids, which leave and enter cells in liver, brain and other organs via monocarboxylate transporters. In contrast to long chain fatty acids, medium chain fatty acids diffuse into cells. Medium chain fatty acids and C4 ketones are both metabolized to acetyl-coenzyme A, which enters the tricarboxylic acid cycle to produce energy.

Acyl-CoA, acyl-coenzyme A; acetyl-CoA, acetyl-coenzyme A; Chyl, chylomicrons; LCFAs, long chain fatty acids; LC fats, long chain fats; MCFAs, medium chain fatty acids; MCTs, medium chain triglycerides; TCA, tricarboxylic acid.

"PHARMACOLOGY AND PHARMACOKINETICS" OF KETOGENIC DIETS AND MEDIUM CHAIN TRIGLYCERIDES

For medications to be effective in treating epilepsy, it is important to maintain blood concentrations of the active drug or drug metabolites in the therapeutic window over time. However, when using ketogenic diets, opinions regarding biologically relevant concentrations of C4 ketone bodies in blood vary. Similarly, the needed frequency of dosing for MCTs and the ideal blood concentrations for anticonvulsant effects of medium chain fatty acids are unknown. On the other hand, both medium chain fatty acids and C4 ketone bodies are metabolized rapidly, and their mechanisms of action appear to be based on such fast metabolism in the "epileptic" brain to provide additional energy, so that blood concentrations may be irrelevant for antiseizure effects. In addition, the exact daily schedule of consuming ketogenic meals or supplementing MCTs may vary as long periods between moderately sized meals favor moderate C4 ketone production by the liver. However, as add-on MCT treatment may not require caloric restriction or ketone formation, MCT doses and the frequency of dosing need to be determined.

In addition to providing brain fuels, C4 ketone bodies and both octanoic and decanoic acids contribute to γ-aminobutyric acid (GABA) synthesis.[20] Also, ketogenic diet feeding[1,4] and decanoic acid[21] have antioxidant effects and can protect mitochondria. Mitochondria are important for energy metabolism and many other important physiological functions and there is evidence that mitochondrial protection and antioxidant defense mechanisms are important contributors to anticonvulsant activity.[6] Both ketogenic diets and decanoic acid can activate the peroxisome proliferator-activated receptor γ2, PPARγ2, a transcription factor that can promote mitochondrial biogenesis and has antioxidant effects (reviewed in Han et al[15]). At very high concentrations, decanoic acid also blocks AMPA receptors[22], although such concentrations are unlikely to be reached in the mammalian brain.

More studies are needed to fully understand the physiological and protective effects of MCTs, as they typically contain both octanoic and decanoic acids.

EFFICACY

Efficacy of ketogenic diets, medium chain triglycerides and medium chain fatty acids in rodent seizure models

Anticonvulsant effects of ketogenic diets, medium chain fatty acids and MCTs of various compositions have been observed in several rodent models. In these studies, efficacy in different laboratories and diet compositions can vary, e.g., with different "control diets", fat sources, caloric restriction or 6:1 vs. 4:1 ketogenic diets used. Higher ketogenic ratios and caloric restriction seem to have the most robust anticonvulsant effects in rodent seizure models.[1,23] Many researchers have reported on the efficacy of ketogenic diets in several acute seizure and chronic epilepsy models in rats and mice.

In contrast to ketogenic diets, MCTs and medium chain fatty acids have only been tested in acute seizure models in mice and ex vivo (reviewed in Han et al[15]). Anticonvulsant effects of octanoic and decanoic acids as well as their triglycerides (trioctanoin or tricaprylin and tridecanoin or tricaprin, respectively) were found in several studies using the 6 Hz model, a mouse model of psychomotor epilepsy.[21,24–26] Efficacy in this model is thought to reveal efficacy of treatments against human focal (unaware) seizures.[2] This is important because new ways to manage focal seizures in people are most urgently needed, as these types of seizures are often drug-resistant. Medium chain fatty acids and MCTs had little to no effect on seizure susceptibility when evaluated in the maximal electroshock model and models using $GABA_A$ receptor channel blockers to induce seizures. These models can indicate efficacy of treatments in people against acute tonic-clonic seizures and generalized unaware seizures in humans, respectively.[2] Medium chain triglycerides have not been assessed in chronic rodent seizure models in which disturbed brain metabolism is present. This is important to note because antiseizure effects in chronic models are currently considered the best evidence for efficacy of new epilepsy treatments.[2,27]

Medical ketogenic diets and medium chain triglycerides used for human epilepsies

For centuries, fasting has been known to reduce seizure occurrence in people. To mimic this effect, a medical ketogenic diet was developed 100

years ago. This original “classic” ketogenic diet contains four parts of weight in fat and one part per weight of proteins and carbohydrates together (4:1 ratio), resulting in a diet from which about 90% of energy intake is derived from fat. For the original ketogenic diet, dietitians teach people with epilepsy and/or their caregivers to weigh out foods to be consumed, and a vitamin supplement is given. Caloric intake is carefully determined and sometimes even restricted. Over the years, medical ketogenic diets have evolved considerably, and different versions of medical ketogenic diets are now used to treat epilepsy in infants, children, and adults. Some ketogenic diets include MCTs, which are an excellent source of ketone bodies in this diet context and allow patients to consume higher amounts of carbohydrates and protein. To increase compliance, tolerability and palatability of the diet, the proportion of fat is sometimes lowered, to 3:1 or even 2:1 ratios of fat vs. proteins and carbohydrates. Alternatively, a modified Atkins Diet can be used, which maintains a seizure-reducing effect in some individuals. Another option is the low glycemic index diet, which aims to minimize postprandial spikes in blood sugar, and has been shown to reduce seizures in some human patients with refractory epilepsy.[9]

Currently, ketogenic diets are first-line treatments for infantile spasms and seizures occurring with genetic disorders where glucose metabolism is perturbed, such as in glucose transporter 1 deficiency syndrome (GLUT1DS) or pyruvate dehydrogenase complex deficiency. Several clinical trials have tested ketogenic diets in adults and children with other types of epilepsy, after two ASDs failed, and there is evidence that this metabolic approach can reduce seizures.[8] A Cochrane systematic review of these studies published in 2020 concluded that certainty of evidence for the anticonvulsant effects of ketogenic diets is low for children and very low for adults.[13] Additional controlled studies and personalized medicine are expected to provide improved guidance for the use and efficacy of ketogenic diets for individuals with epilepsy, as well as their caregivers and clinicians. Successful reduction of seizures with ketogenic diets seems to depend on sustained blood sugar concentrations in the lower normal range, in addition to increased blood ketone concentrations. This physiological state favors brain use of C4 ketone bodies as fuels. There is anecdotal evidence that while on ketogenic diets, patients have breakthrough seizures after eating sugary treats.

The therapeutic benefits of MCTs by themselves in the context of "regular/nonketogenic diets" have been explored in several metabolic and neurological disorders in humans.[11,14] Evidence from clinical trials is overall encouraging and indicates that incorporating MCTs into regular diets has the potential to improve diabetes mellitus, obesity, and brain function in certain disease contexts.[14] One major advantage of MCTs is that there are none of the negative neurocognitive effects that are associated with the use of many ASDs in humans. Also compared to high fat ketogenic diets, major negative cardiovascular effects appear to be absent when using MCTs with dietitian support. Several small clinical trials indicate that the approach of add-on MCTs is feasible for individuals with epilepsy, with about two thirds of patients tolerating this treatment, and some children and adults achieving improved control of seizures.[15,28] More clinical trials are urgently needed to determine the most effective MCT compositions, the best tolerated formulations and the types of epilepsies that respond best.

Ketogenic diet and medium chain triglyceride-containing food for dogs

Little is known about dietary intervention for the treatment of epilepsy in dogs. Dogs evolutionarily consume mostly meat and much fewer carbohydrates than humans, so from our human perspective, it is difficult to know what constitutes a ketogenic diet for a dog. There is a single report, published only in abstract form, describing the results of a randomized, double-blinded, placebo-controlled trial evaluating the effectiveness of a high-fat, low carbohydrate diet compared to a control diet in reducing seizure frequency in dogs with drug resistant IE. After a 3- to 6-month baseline period during which all dogs were fed a control diet, 17 dogs were randomized to be fed either the ketogenic diet or a control diet for 6 months, with 12 dogs completing the study (6 in each group). No difference in seizure frequency between the treatment and control groups was identified, although dogs fed the ketogenic diet had significantly higher serum concentrations of the ketone body BHB compared to the control group. Three of 9 dogs on the ketogenic diet developed pancreatitis.[29]

Three clinical trials[30–32] have tested the efficacy of add-on MCTs to commercial dog food and were summarized in 2021.[15] They are shown in Table 17.1. These studies all tested add-on MCTs for 3 months and included a relatively small number of dogs with IE. The study populations were

diverse, containing dogs of a variety of breeds aged between 6 months and 12 years and with body weights between 4 and 65 kg. Law et al. performed a randomized, double-blinded, placebo-controlled crossover study evaluating the effectiveness of an MCT diet in the treatment of IE in 21 dogs.[30] The study included dogs diagnosed with IE based on an International Veterinary Epilepsy Task Force (IVETF) Tier 2 level of confidence, that were being administered at least one ASD and had experienced a minimum of 3 seizures in the 3 months prior to enrollment. Dogs were randomized to be fed either the test MCT diet or a control diet (with no added MCTs and lard used as a fat substitute) for a 3-month period, after which time each dog was switched to the alternate diet for an additional 3 months. There was no alteration in ASD therapy during the course of the study, and no significant changes in serum concentrations of phenobarbital (PB) or bromide between the placebo and MCT-containing diet. A significantly lower seizure frequency was reported when dogs were fed the test diet compared to the control diet (2.31/month vs 2.67/month, $p = 0.020$). Three dogs (14%) became seizure free, and 7 dogs (33%) experienced a ≥50% reduction in seizure frequency on the test diet. Six dogs (29%) showed an overall increase in seizure frequency while fed the MCT diet. No significant difference was reported in ataxia, sedation and quality of life between the test and control diet, based on a visual analog score completed by the owners at 3 and 6 months. While being fed the MCT-containing diet, vomiting was reported in 5 dogs and diarrhea in 2 dogs; on the control diet, vomiting was reported in 4 dogs and diarrhea in 4 dogs. There was a small increase in 2-hour postprandial (~30%) serum BHB levels in dogs fed the test diet compared to the control diet.

TABLE 17.1. Summary of clinical trials evaluating the efficacy of medium chain triglycerides (MCTs) in the treatment of idiopathic epilepsy in dogs.

	Law et al., 2015[29]	Berk et al., 2020[30]	Molina et al., 2020[31]
Study design			
Number of dogs (n)	21	28	21
Trial type	Randomized, double-blinded, crossover	Randomized, double-blinded, crossover	Open-label, single-arm
Placebo	Lard	Olive oil	No placebo
MCT formulation	Diet	Dietary supplement	Diet
MCT amounts	5.5% (w/w%)/10% (E%)	9% (E%)	6.5% (w/w%)
Frequency of seizures			
Seizure freedom, n (% of dogs)	3 (14%)	2 (7%)	2 (10%)
≥50% Reduction	7 (33%)	3 (11%)	7 (33%)
<50% Reduction	5 (24%)	12 (43%)	7 (33%)
No change or increase	6 (29%)	11 (39%)	5 (24%)
Days with seizures			
Seizure freedom, n (% of dogs)	3 (14%)	2 (7%)	2 (10%)
≥50% Reduction	4 (19%)	2 (7%)	7 (33%)
<50% Reduction	10 (48%)	13 (46%)	7 (33%)
No change or increase	4 (19%)	11 (39%)	5 (24%)

w/w%, percentage of MCT in the diet based on weight of MCT oil vs total feed; E%, amount of MCT consumed as a percentage of total energy intake.

A similarly designed randomized, double-blinded, placebo-controlled, crossover study was subsequently performed in 28 dogs with a diagnosis of IE, in which the dogs' existing diets were supplemented with a 9% metabolic energy-based amount of MCT oil or control (olive) oil for 3 months, followed by a switch to the alternative treatment for an additional 3 months.[31] Similarly to the previous study, dogs were recruited based on a diagnosis of IE with an IVETF Tier 2 level of confidence, with a minimum of 3 seizures in the 3 months prior to enrollment while being treated with at least one ASD. Two dogs were being treated with imepitoin (IMP) only, while the remainder were on combination therapy with 2 (n = 9) or 3 (n = 17) ASDs, with PB, potassium bromide (KBr), levetiracetam (LEV), and IMP most commonly prescribed. Seizure frequency was determined to be significantly lower with the MCT supplement compared to the control (2.51/month vs 2.67/month, p = 0.02). With the MCT supplement, 2 dogs (7%) became seizure free and 3 dogs (11%) had a ≥50% reduction in seizure frequency. Eleven dogs (39%) had no response to MCT supplementation with either no change (n = 3) or an overall increase (n = 8) in seizure frequency. There was a significant reduction in serum PB

concentrations during the MCT supplementation (30.04 ± 7.81 g/mL) compared to the control period (32.78± 7.91 g/mL; p = 0.03), but no changes in bromide concentrations were observed during the course of the study. Two dogs developed gastrointestinal signs while on the MCT supplement, one with diarrhea and another with vomiting, both of which resolved without further effects. After 90 days of MCT supplementation, there were small increases in preprandial (~15%) and 2 hours postprandial (~20%) serum BHB levels compared to the control diet.

Molina et al. performed an open-label, uncontrolled, single-arm diet trial involving 21 dogs with an IVETF Tier 1 diagnosis of IE.[32] To be included, dogs had to have ≥3 seizures in the 3 months prior to enrollment while being treated with at least one ASD. Dogs were transitioned over 7 days to a commercially available MCT-containing diet (Purina NeuroCare™) and followed up for 12 weeks. Fourteen dogs were being treated with PB either alone or in combination with KBr, LEV or IMP. Five dogs were being administered IMP alone. Two dogs were being administered a combination of PB, LEV and topiramate. A significant reduction in seizure frequency was reported during feeding of the MCT diet compared to a retrospective baseline (1.7/month vs. 2.5/month, p = 0.04). Two dogs (10%) became seizure free, and 7 dogs had a ≥50% reduction in seizure frequency, while 5 dogs (24%) had no change (n = 1) or an increase (n = 4) in seizure frequency while on the MCT diet. Serum concentrations of PB, with or without bromide, were reported for 9 dogs, with no change noted between the end of the study and baseline.

In a recent case study, a moderately ketogenic diet was custom designed by an expert in ketogenic diets for a dog that had drug resistance to PB to KBr and experienced weekly seizures. The dog was switched from a white fish/white potato diet to a diet containing fatty lamb, pumpkin, and a blend of virgin coconut oil and MCT as macronutrients. No seizures were reported for 33 weeks, except for two breakthrough seizures when not eating for two days in the absence of its owner.[33]

Taken together, these studies suggest that MCTs and moderately ketogenic diets have potential to help manage IE in dogs. These dietary therapies may be efficacious in improving seizure control in dogs with drug-resistant IE, and appear to be treatments that are well tolerated with minimal AEs. Currently there is insufficient evidence to recommend this form of therapy in dogs with IE; however, based on the apparent safety of

dietary therapy, it may be a reasonable option to trial in dogs with drug-resistant IE. It is suggested that similar guidelines for treatment success to those recommended with the use of ASDs (outlined in Chapter 9) be utilized when initiating dietary therapy. Diets including MCT seem to also benefit other health issues in dogs, some of which can be associated with epilepsy. As in people, overall metabolism as well as functions of the CNS seem to be improved, including cognitive impairments, and conditions similar to dementia.

MANIPULATIONS OF MACRONUTRIENTS – PRACTICAL CONSIDERATIONS FOR THE TREATMENT OF DOGS WITH EPILEPSY

It is important to note that when contents of fats, carbohydrates and protein are manipulated, such as by ketogenic diets and/or supplementing MCTs, involvement of dietitians, nutritionists and/or other trained specialists is absolutely necessary to ensure adequate nutrition and control of body weight as well as growth in children or young animals. In people, ketogenic diets can lead to AEs such as lethargy, hunger, and constipation, as well as kidney stones and bone fractures in the long term.

Supplementing MCT appears to be a more straightforward strategy but requires eating to satiety and/or reduction of other macronutrients to avoid weight gain. This is not always a problem, as in some people and probably also dogs, MCTs can increase short and long-term satiety and/or reduce appetite. Care needs to be taken when newly introducing MCT oil, as it is well-known to lead to gastrointestinal AEs, such as diarrhea, stomach cramps, bloating and sometimes constipation in humans, especially when used in high amounts. Thus, MCTs, especially when in oil form, need to be slowly introduced and titrated up gradually. Different formulations of MCTs may have fewer gastrointestinal AEs, e.g., MCTs emulsified with other foods or powder formulations where MCTs are bound to fiber or silica. However, it can be very difficult for the consumer to assess the content of commercially available MCT formulations. Some products marketed as ketogenic MCT powders or bars contain MCTs bound to the carbohydrate

maltodextrin, which is not compatible with ketogenic diets. Finally, as MCTs reduce eating of "other natural foods," it is important to ensure that adequate amounts of essential amino acids, polyunsaturated fatty acids as well as vitamins and minerals are provided. Thus, specialists with training in dog nutritional requirements would be needed to teach dog owners how to design and use ketogenic diets and/or MCTs. These diets could be tailored to patients and their families and electronic resources can be developed to aid with shopping for adequate products and feeding. As a more straightforward option for owners with epileptic dogs, commercial dog food containing MCTs is available and/or is being developed in several countries.

In summary, more research is needed, but the dietary treatments described appear to be a promising addition to ASDs in the management of IE. Medium chain triglycerides with the preparations and the dosage used in the few canine IE clinical trials have shown efficacy in improving seizure control in some dogs with drug-resistant IE.

TAKE-HOME MESSAGES

- ✔ Medium chain triglycerides appear to be generally safe when administered at up to 15% of energy intake and are not associated with the severe AEs that can be seen with ASDs.
- ✔ There is some evidence to suggest that providing ~10% of energy intake in the form of MCTs, either as a component of a commercial feed or as a supplement to an adjusted diet, can reduce seizure frequency in some dogs with drug-resistant IE. However, more evidence on their efficacy is needed. Medium chain triglyceride powders marketed for humans are not recommended for canines with IE, as they often contain carbohydrates.
- ✔ When using MCT as an add-on treatment to regular dog food, a nutritionist or specialist should be consulted.
- ✔ Administering large quantities of MCT oil to dogs can lead to gastrointestinal AEs. This can be avoided by slow introduction of MCT oil over several weeks and mixing or emulsifying with other foods.

- ✔ When administering MCT oil, other foods need to be reduced to avoid weight gain while ensuring that adequate amounts of essential amino acids, polyunsaturated fatty acids as well as vitamins and minerals are provided. A reduction in foods containing refined carbohydrates may be necessary. More data are needed in dogs to determine the best tolerated and most effective MCT doses, compositions, and formulations and which types of IE may respond best to this treatment. In addition, MCT could also be offered as an adjunctive treatment to ASDs to owners of dogs with drug-resistant IE, provided they understand that more research is required in this field.
- ✔ In dogs with IE receiving MCT either as a component of a commercial feed or as a supplement to an adjusted diet for 3 months without improvement of seizure control, it can be assumed that MCT are unlikely to be helpful and could be discontinued.

Disclosure

Karin Borges has received consulting fees from Nestlé Purina PetCare in the past and has been independent during the time of writing.

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REFERENCES

1. Bough KJ, Rho JM. Anticonvulsant mechanisms of the ketogenic diet. *Epilepsia*. 2007; 48(1):43–58.
2. Smith M, Wilcox KS, White HS. Discovery of antiepileptic drugs. *Neurotherapeutics*. 2007; 4(1):12–17.
3. Kudin AP, Zsurka G, Elger CE, Kunz WS. Mitochondrial involvement in temporal lobe epilepsy. *Exp Neurol*. 2009; 218(2):326–332.
4. Masino SA, Rho JM. Mechanisms of ketogenic diet action. In: Noebels J, Avoli M, Rogawski M, Olsen R, Delgado-Escueta A (eds.). *Jasper's basic mechanisms of the epilepsies*. 4th ed. New York: Oxford University Press; 2012. pp. 1001–1022.
5. Masino, S. (ed.). *Ketogenic diet and metabolic therapies: expanded roles in health and disease*. New York: Oxford University Press; 2016.
6. Pearson-Smith JN, Patel M. Metabolic dysfunction and oxidative stress in epilepsy. *Int J Mol Sci*. 2017; 18(11):2365.
7. McDonald T, Puchowicz M, Borges K. Impairments in oxidative glucose metabolism in epilepsy and metabolic treatments thereof. *Front Cell Neurosci*. 2018; 12:274.
8. Liu H, Yang Y, Wang Y et al. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. *Epilepsia Open*. 2018; 3(1):9–17.
9. Rezaei S, Harsini S, Kavoosi M et al. Efficacy of low glycemic index treatment in epileptic patients: a systematic review. *Acta Neurol Belg*. 2018; 118(3):339–349.
10. Kossof EH, Turner Z, Cervenka MC, Barron BJ. *Ketogenic diet therapies for epilepsy and other conditions*. 7th ed. New York: Springer Publishing; 2020.
11. Cunnane SC, Trushina E, Morland C et al. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. *Nat Rev Drug Discov*. 2020; 19(9):609–633.
12. Barker-Haliski M, Steve White H. Validated animal models for antiseizure drug (ASD) discovery: Advantages and potential pitfalls in ASD screening. *Neuropharmacology*. 2020; 167:107750.
13. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev*. 2020(6).
14. Huang L, Gao L, Chen C. Role of medium-chain fatty acids in healthy metabolism: a clinical perspective. *Trends Endocrinol Metab*. 2021; 32(6):351–366.
15. Han FY, Conboy-Schmidt L, Rybachuk G et al. Dietary medium chain triglycerides for management of epilepsy: New data from human, dog, and rodent studies. *Epilepsia*. 2021; 62(8):1790–1806.
16. Morris AA. Cerebral ketone body metabolism. *J Inherit Metab Dis*. 2005; 28(2):109–121.
17. O'Brien TJ, Newton MR, Cook MJ et al. Hippocampal atrophy is not a major determinant of regional hypometabolism in temporal lobe epilepsy. *Epilepsia*. 1997; 38(1):74–80.
18. Kunz WS, Kudin AP, Vielhaber S et al. Mitochondrial complex I deficiency in the epileptic focus of patients with temporal lobe epilepsy. *Ann Neurol*. 2000; 48(5):766–773.
19. Samokhina E, Popova I, Malkov A et al. Chronic inhibition of brain glycolysis initiates epileptogenesis. *J Neurosci Res*. 2017; 95(11):2195–2206.
20. Andersen JV, Westi EW, Jakobsen E et al. Astrocyte metabolism of the medium-chain fatty acids octanoic acid and decanoic acid promotes GABA synthesis in neurons via elevated glutamine supply. *Mol Brain*. 2021; 14(1):132.
21. Tan KN, Carrasco-Pozo C, McDonald TS et al. Tridecanoin is anticonvulsant, antioxidant, and improves mitochondrial function. *J Cereb Blood Flow Metab*. 2017; 37(6):2035–2048.

22. Chang P, Augustin K, Boddum K et al. Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain*. 2015; 139(2):431–443.
23. Samala R, Willis S, Borges K. Anticonvulsant profile of a balanced ketogenic diet in acute mouse seizure models. *Epilepsy Res*. 2008; 81(2):119–1127.
24. McDonald TS, Tan KN, Hodson MP, Borges K. Alterations of hippocampal glucose metabolism by even versus uneven medium chain triglycerides. *J Cereb Blood Flow Metab*. 2014;34(1):153–160.
25. Wlaź P, Socała K, Nieoczym D et al. Acute anticonvulsant effects of capric acid in seizure tests in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015; 57:110–116.
26. Wlaź P, Socała K, Nieoczym D et al. Anticonvulsant profile of caprylic acid, a main constituent of the medium-chain triglyceride (MCT) ketogenic diet, in mice. *Neuropharmacology*. 2012; 62(4):1882–1889.
27. Thomson KE, Metcalf CS, Newell TG et al. Evaluation of subchronic administration of antiseizure drugs in spontaneously seizing rats. *Epilepsia*. 2020; 61(6):1301–1111.
28. Schoeler NE, Orford M, Vivekananda U et al. K.Vita: a feasibility study of a blend of medium chain triglycerides to manage drug-resistant epilepsy. *Brain Commun*. 2021.
29. Patterson E, Muñana K, Kirk CA. Results of ketogenic food trial for dogs with idiopathic epilepsy. *J Vet Int Med*. 2005;19.
30. Law TH, Davies ES, Pan Y et al. A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. *Br J Nutr*. 2015; 114(9):1438–1447.
31. Berk BA, Law TH, Packer RMA et al. A multicenter randomized controlled trial of medium-chain triglyceride dietary supplementation on epilepsy in dogs. *J Vet Intern Med*. 2020; 34(3):1248–1259.
32. Molina J, Jean-Philippe C, Conboy L et al. Efficacy of medium chain triglyceride oil dietary supplementation in reducing seizure frequency in dogs with idiopathic epilepsy without cluster seizures: a non-blinded, prospective clinical trial. *Vet Rec*. 2020; 187(9).
33. Masino SA, Freedgood NR, Reichert HR et al. Dietary intervention for canine epilepsy: Two case reports. *Epilepsia Open*. 2019; 4(1):193–199.

Neurostimulation for Canine Epilepsy

18

Sofie F.M. Bhatti, Marios Charalambous, Luc Van Ham

Despite a plethora of drugs available to treat epilepsy, resistance to combined antiseizure drug (ASD) therapy occurs in approximately one-third of human and canine patients with epilepsy.[1,2] Since epilepsy is associated with an important comorbidity and mortality in people and dogs,[3,4] alternative nonpharmacological treatment strategies are warranted. In humans, epilepsy surgery has convincingly proven superiority over drug therapy if one or two ASDs have failed and an epileptogenic focus can be resected.[5] However, when the combination of surgery and drug therapy fail or surgery is not indicated, neurostimulation is pursued as an alternative therapeutic strategy for drug-resistant epilepsy.

In human epilepsy, neurostimulation-based treatments have gained considerable interest since the approval of vagus nerve stimulation (VNS) in 1997. In neurostimulation, either brain or cranial nerves are stimulated electrically in order to suppress cortical hyperexcitability and subsequently decrease epileptic seizure frequency, duration and severity. Today, VNS,[6] deep brain stimulation (DBS)[7] and responsive neurostimulation (RNS)[8] are approved techniques that are currently used in the management of drug-resistant epilepsy in people. Vagus nerve stimulation and DBS provide stimulation in an open-loop manner, i.e., therapy is delivered according to preprogrammed fixed settings regardless of the individual patient's clinical symptoms or disease characteristics. Responsive neurostimulation requires placement of one or two depth or cortical electrodes located in or over the epileptogenic foci. These electrodes continuously monitor electrical activity of the foci and deliver a brief and mild electrical stimulation in response to

abnormal epileptiform activity so as to suppress epileptic seizures before any seizure manifestations are present, i.e., in a closed-loop fashion.[9] Closed-loop systems may provide more effective and efficient therapy.[9] Vagus nerve stimulation, DBS and RNS are invasive neurostimulation modalities, which means that a surgical procedure is needed to implant the electrodes and other devices. An increasing number of noninvasive/nonsurgical alternatives such as transcutaneous VNS (tVNS),[10] trigeminal nerve stimulation (TNS),[11] transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)[12] are currently being investigated for the management of drug-resistant epilepsy in human epilepsy centers around the world. A serious drawback of these neurostimulation modalities is that there are no standardized guidelines on when or how to use the various techniques and there is no common consensus across epilepsy centers.

The mechanisms of action of neurostimulation differ depending on the targets and stimulation parameters used and are incompletely understood so far. One interesting finding, differing from the outcome following drug therapy or resective surgical treatment, is an increase in efficacy with longer observation periods, which has been reported for several types of neurostimulation.[13–17]

In human epilepsy, low to moderate quality of evidence supports the efficacy and safety of VNS, DBS and RNS in patients with drug-resistant epilepsy. There is very low to moderate quality of evidence that tDCS is effective and well tolerated. Transcutaneous VNS, TMS and TNS appear well tolerated, but there are currently insufficient data to support the efficacy of any of these modalities for drug-resistant epilepsy.[6,18]

Only a limited number of the neurostimulation treatment strategies in humans have been investigated in canine epilepsy. Currently, many dogs with drug-resistant epilepsy are eventually euthanized or die during uncontrollable seizures.[19]

This chapter focuses on VNS and TMS since both neurostimulation techniques have been studied in dogs with idiopathic epilepsy (IE) in recent years.

VAGUS NERVE STIMULATION

Vagus nerve stimulation is defined as an intermittent electrical stimulation of the vagus nerve using an implantable device. The device, which is surgically implanted in the left cervical region, consists of spiral-shaped electrodes that are wrapped around the vagus nerve and a pulse generator or neurostimulator that is implanted below the clavicle (humans) or dorsocranial to the scapula (dogs). Subcutaneously tunneled wires connect the stimulator to the electrodes (Fig.18.1).

This invasive but extracranial type of stimulation was developed in the 1980s and is currently routinely used in human epilepsy centers worldwide. The first vagus nerve stimulator was implanted in 1989. The surgical technique and devices used in dogs are comparable to those in people and have been described in two previous reports[20,21] (Figs. 18.2 and 18.3). A programming wand is used for wireless communication between the stimulator and the programmer[22–24] (Fig. 18.4).

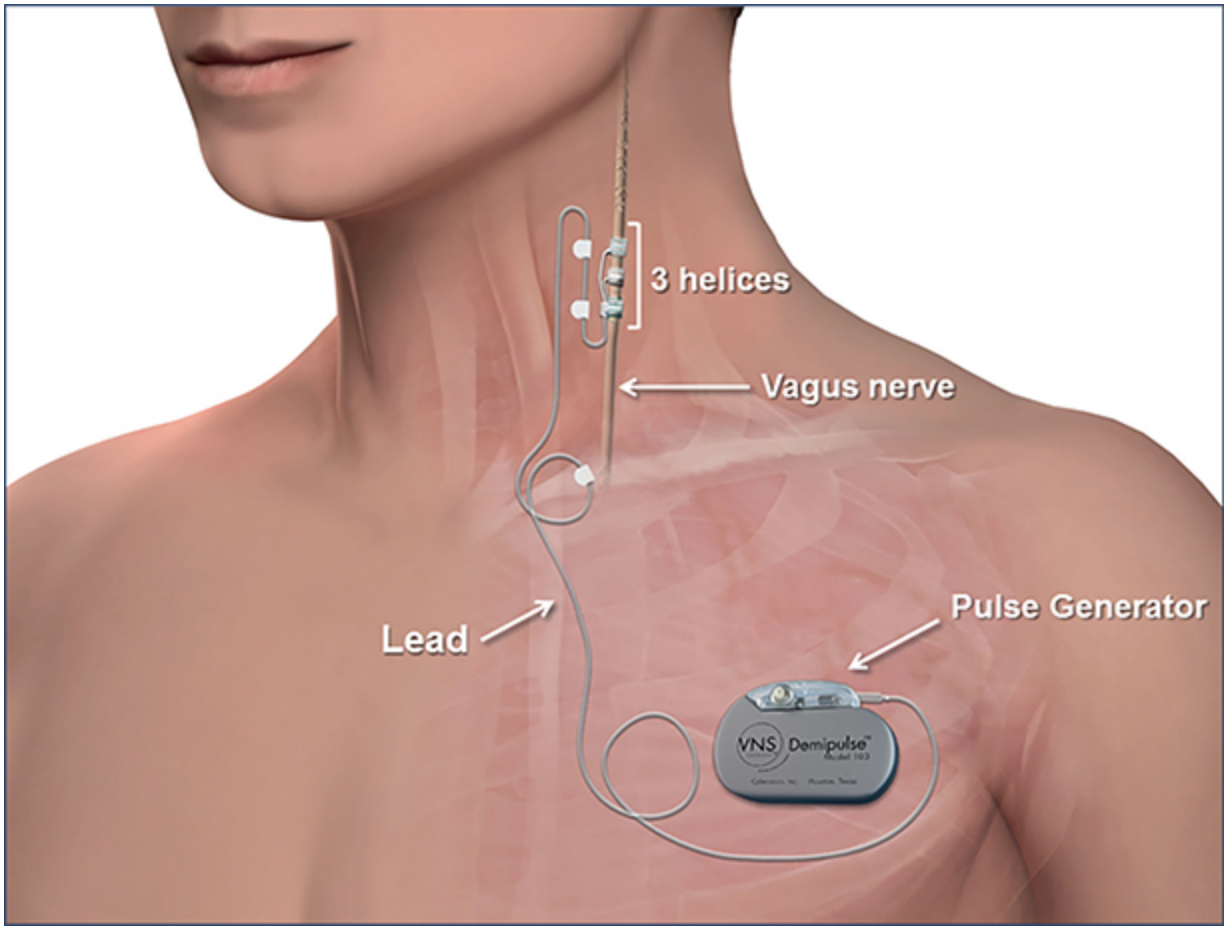


FIGURE 18.1. Illustration of a VNS therapy system (Cyberonics, Inc.) implanted in a person.

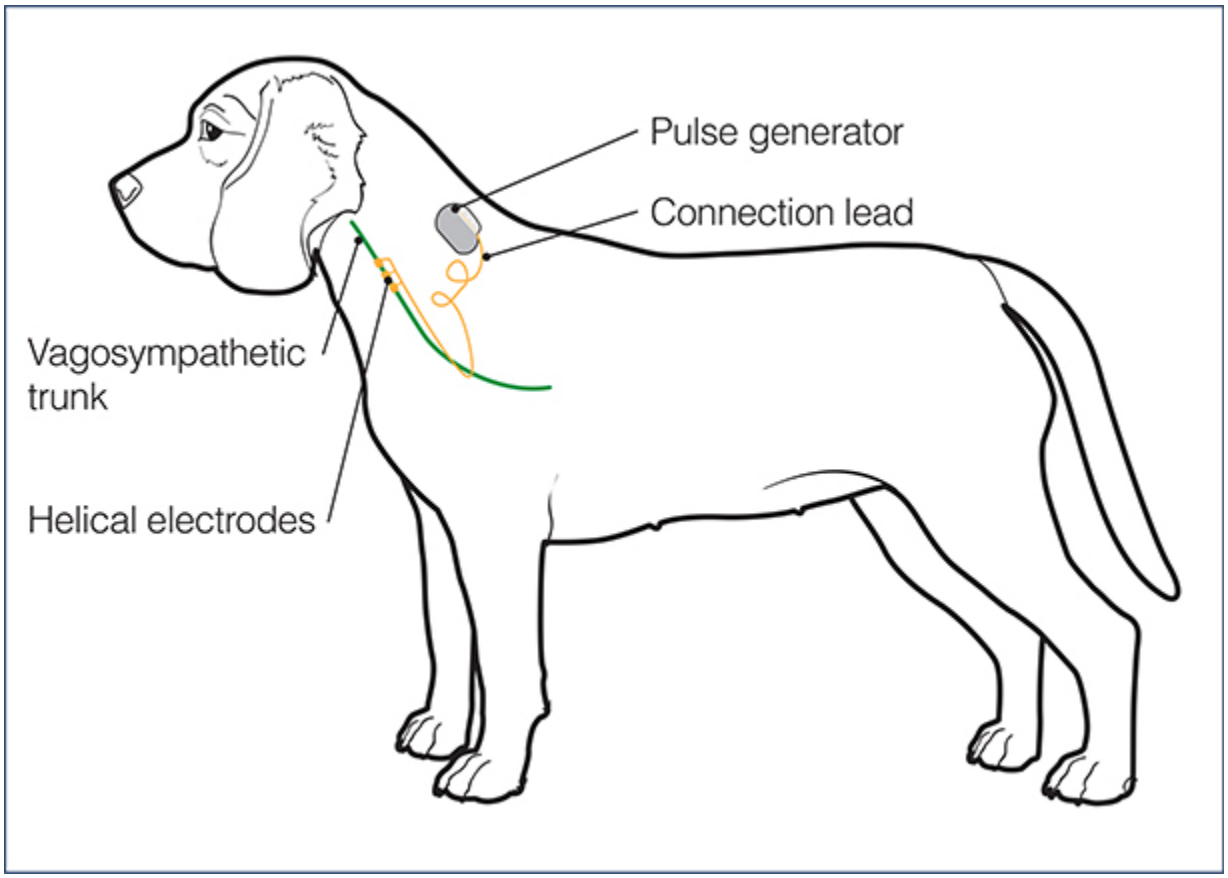


FIGURE 18.2. Schematic representation of a VNS device (in gray and orange) implanted in the left cervical region of a dog. The helical electrodes are wrapped around the left vagosympathetic trunk (green). Note the strain relief loops of the connection lead. The pulse generator is implanted subcutaneously dorsocranial to the scapula.

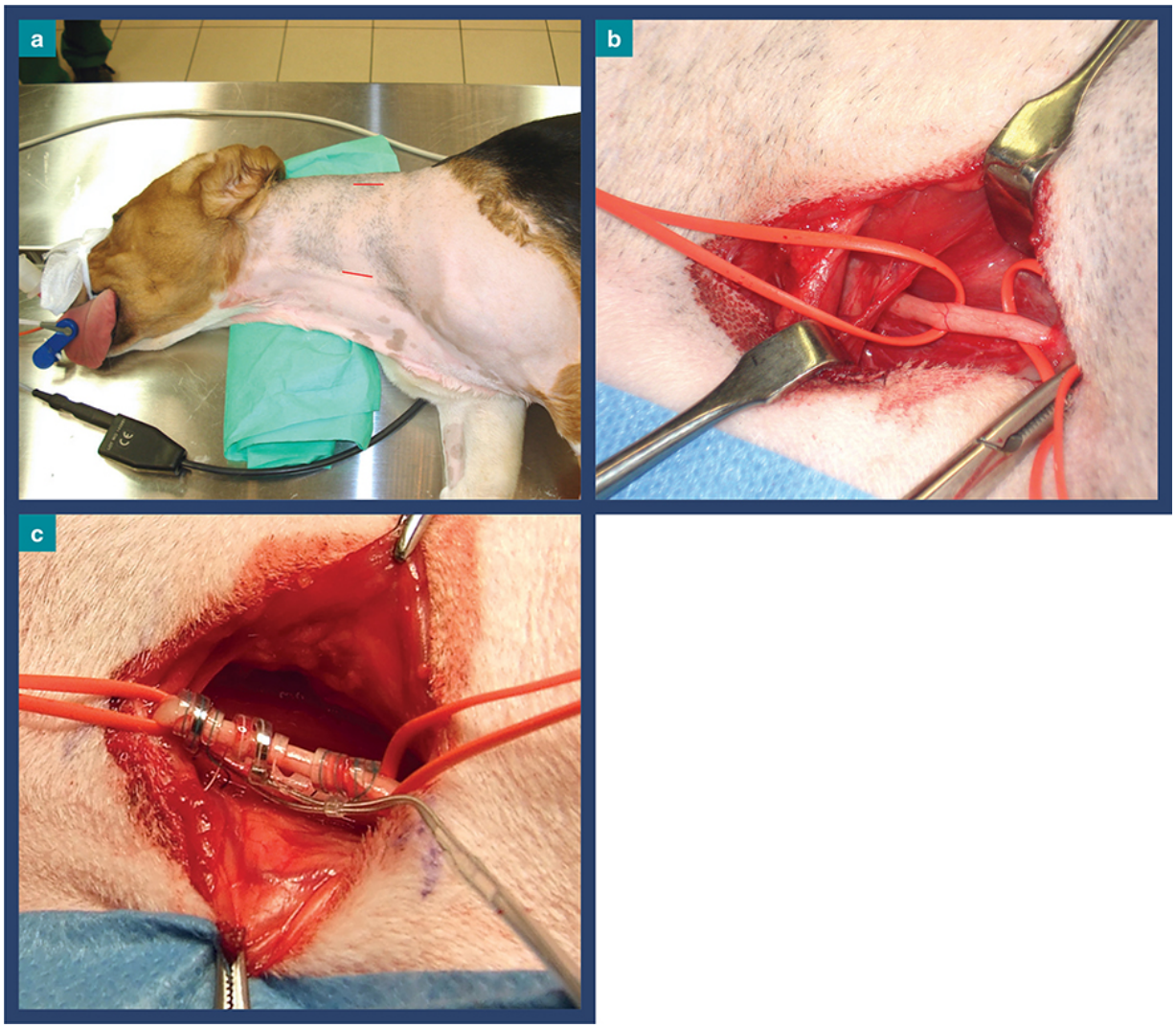


FIGURE 18.3. Surgical procedure for VNS implantation in a dog. a) Location of the ventral and dorsal incisions (marked in red). Two incisions in the left lateral cervical region are made: a dorsal incision for placement of the pulse generator and a ventral incision (4–5 cm separated from the dorsal incision) for placement of the helical electrodes around the left vagosympathetic trunk approximately 0.5 cm dorsal and parallel to the jugular furrow. b) Left vagosympathetic trunk isolated with two vessel loops at the ventral incision site (cranial is left and caudal is right). c) The two helical electrodes and anchor tether placed around the left vagosympathetic trunk at the ventral incision site (cranial is left and caudal is right).



FIGURE 18.4. A dog with an implanted VNS device. A programming wand is used for wireless communication between the stimulator and the programmer.

The vagus nerve is a mixed cranial nerve that consists of approximately 80% afferent fibers originating from the heart, aorta, lungs, and gastrointestinal tract, and approximately 20% efferent fibers that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and the pharynx.[25–27] Afferent fibers primarily project to the nucleus of the solitary tract. In VNS therapy, the electrodes are placed in an orientation (negative pole cranial to the positive pole, Fig. 18.5) that primarily activates afferent cervical vagal fibers but coactivation of the efferent fibers is inevitable.[28]

Given the influence of the efferent fibers of the vagus nerve on the heart, the potential occurrence of cardiac adverse effects (AEs) was a serious initial concern when VNS was introduced as a treatment for drug-resistant epilepsy in humans.[29] Despite this concern, clinically relevant cardiac AEs of VNS have rarely been noticed in humans. To avoid cardiac

complications, the left vagus nerve is usually chosen as it has less cardiac influence than the right nerve both in humans and dogs.[20,30–32] Furthermore, the helices are placed distal to the vagal cardiac branches in humans to avoid stimulation of these fibers during VNS. This is impossible in dogs due to anatomical differences and therefore, dogs might be more sensitive to the cardiac effects of VNS than humans.[20,33] However, VNS studies in ambulatory healthy dogs have not shown significant effects on heart rate variability.[33] In a study by Muñana et al.,[20] surgical implantation of the device in 10 dogs with IE was safe and well-tolerated. During intraoperative impedance testing of the device, transient bradycardia (3/10) or asystole (1/10) was seen. Postoperative AEs were monitored during 6 months after implantation. The most commonly reported complications included Horner syndrome (2/10), seroma formation (2/10), and migration of the pulse generator (1/10).[20] Martlé et al. also reported that implantation of a VNS system in the left cervical region appeared to be safe, feasible and well-tolerated in a cohort of 10 healthy Beagle dogs with a follow-up period of 3 years.[21] Intraoperative complications did not arise. Postoperatively, several complications occurred such as seroma formation (7/10), dysphonia (1/10), Horner syndrome (1/10), twisting (5/10) and traumatic damage of the lead (3/10), and movement of the distal helix (anchor tether) (4/10). Hence, all efforts should be made to prevent seroma formation as this transient complication may also contribute to movement and damage of the system. Regular impedance testing is important as altered impedance values can indicate serious complications requiring surgical revision of the system. Noninvasive, transcutaneous VNS in dogs with IE was found to be safe with mild AEs.[34] Adverse effects occurred in 25% of dogs, with reports of a hoarse bark, limb trembling, lethargy, behavioral changes, and an increase in epileptic seizure frequency.

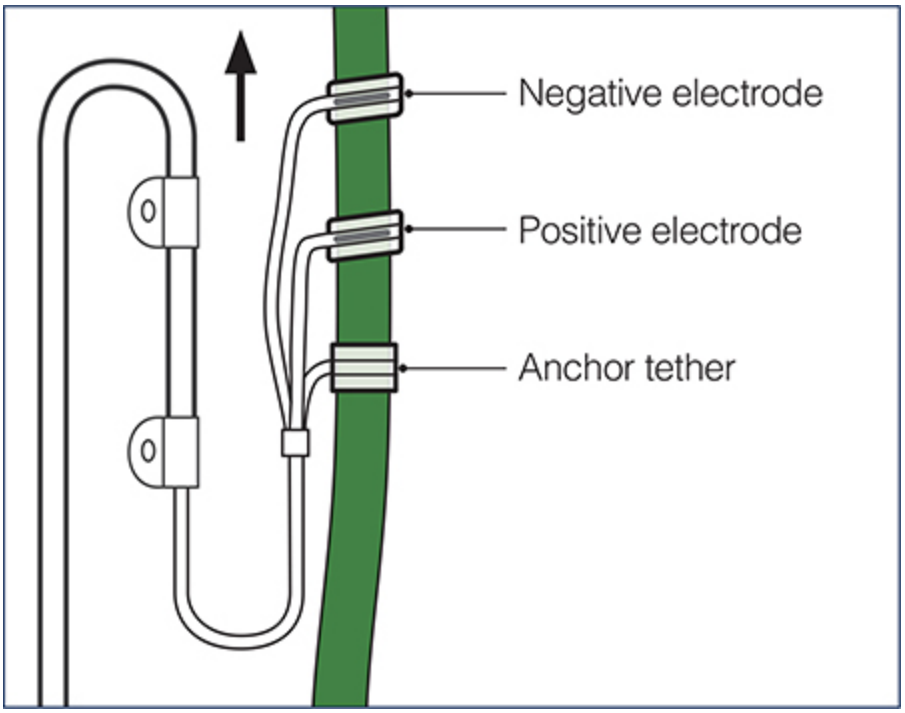


FIGURE 18.5. The electrodes are placed in an orientation (negative pole cranial to the positive pole) that primarily activates afferent cervical vagal fibers (the arrow indicates the cranial direction).

In people, VNS therapy is usually well tolerated and has a low incidence of AEs.[32] The most common AEs in humans and dogs are shown in Boxes 18.1 and 18.2, respectively.

From the extensive body of research on the mechanism of action, it has become clear that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers.[35,36] Unilateral stimulation affects both cerebral hemispheres, as shown in several functional imaging studies.[37,38] Central nervous system structures, such as the thalamus, the locus coeruleus, the nucleus of the solitary tract and limbic structures probably play a functional role in the mechanism of action of VNS.[39–42] The intracranial effect of VNS may be based on regional increases in γ-aminobutyric acid (GABA) concentrations, and on decreased glutamate and aspartate concentrations, or may involve other neurotransmitters that have been shown in the past to have an epileptic seizure threshold-regulating role such as serotonin and norepinephrine.[43–45] Follesa et al. showed an increase in norepinephrine concentration in the prefrontal cortex of the rat brain after acute VNS.[46] An increased norepinephrine concentration after VNS has also been measured in the hippocampus[47] and the amygdala[48] of rats. In adult healthy Beagle dogs, acute VNS reduced regional cerebral blood flow,

evaluated by single photon emission computed tomography (SPECT), in the left frontal and right parietal cortex[49] (see Chapter 6 for further discussion of SPECT) and caused an increase in norepinephrine concentrations in the cerebrospinal fluid.[50] This supports previous findings indicating that VNS influences the locus coeruleus–norepinephrine system.

BOX 18.1. Reported adverse effects of vagus nerve stimulation in humans.

Acute, surgery related	Chronic, often stimulation related	Chronic, not related to stimulation
■ Infection ■ Left vocal-cord paresis ■ Hemorrhage ■ Lower facial weakness ■ Bradycardia and asystole during device test ■ Pain at the implant site ■ Seroma formation ■ Paraesthesia ■ Headache ■ Coughing ■ Voice alteration – hoarseness ■ Nausea	■ Coughing ■ Voice alteration – hoarseness ■ Throat pain ■ Dyspnea – shortness of breath ■ Dyspepsia – vomiting ■ Swallowing difficulties – aspiration (children) ■ Contractions of sternocleidomastoid muscle ■ Paresthesia ■ Gagging ■ Drooling ■ Sleep apnea	■ Lead breakage ■ Infection ■ Psychiatric side effects ■ Seizure worsening ■ Gastroesophageal reflux disease

BOX 18.2. Reported adverse effects of vagus nerve stimulation in dogs.

Acute, surgery related	Chronic, often stimulation related	Chronic, not related to stimulation
■ Seroma formation ■ Horner syndrome ■ Transient bradycardia, asystole and apnea during device test ■ Hoarse bark/dysphonia	■ Coughing ■ Hoarse bark/dysphonia ■ Trembling left thoracic limb ■ Lethargy ■ Neurobehavioral changes	■ Twisting of the lead ■ Detachment of the anchor tether ■ Traumatic lead damage ■ Subcutaneous migration of the pulse generator ■ Increase in seizure frequency

Of all the neurostimulation modalities available at present, VNS appears as one of the most effective in humans. Few patients achieve seizure freedom, but a sustained response, defined as a ≥50% reduction in epileptic seizure frequency, is seen in approximately half of the patients.[51,52] Zabara provided early evidence for the concept of VNS in healthy dogs by

demonstrating that chemically-induced seizures could be aborted by stimulating the vagus nerve.[53] In dogs, only one randomized, placebo-controlled, double-blinded crossover study evaluated the safety and efficacy of VNS in 10 dogs with drug-resistant IE.[20] Dogs were assigned randomly to two 13-week test periods, one with nerve stimulation and one without nerve stimulation. No significant difference in seizure frequency, duration, or severity was detected between the overall 13-week treatment and control periods. During the final 4 weeks of the treatment period, a significant decrease in mean seizure frequency (34.4%) was detected, compared with the control period. Recently, an open-label study investigated the safety and efficacy of a noninvasive VNS (nVNS) system as an add-on treatment for drug-resistant canine IE.[34] Dog owners were provided with a handheld VNS device and instructed on its use. The hair was clipped on the left side of the neck of each dog, and owners were instructed to provide VNS three times daily by applying conductive gel to the shaved area, holding up the device, and stimulating for 1.5–2 minutes. Following baseline assessment during 8 weeks, dogs were randomly assigned to two groups. Group 1 included 9 dogs that received nVNS treatments for the first 8-week period followed by a second 8-week period of continued treatment. Group 2 included 7 dogs that received no change in their current treatment for the first 8-week period, followed by an 8-week period of nVNS treatment. Dogs were examined at 8, 16, and 24 weeks after randomization. Two dogs in Group 1 dropped out before study completion, one due to behavioral AEs and the other due to increase in seizure frequency. No significant difference in overall seizure frequency or frequency of types of seizure was identified between time periods with and without nVNS treatment. Of the 14 dogs that completed the study, 9 had a reduction in seizure frequency and of those, 2 dogs had no seizures following implementation of therapy and 2 were considered responders with a ≥50% reduction in seizure frequency from baseline to the final treatment period. One dog out of 14 had no change, and 4/14 experienced an increase in seizure frequency.

It is likely that VNS exhibits both acute and more chronic effects by recruiting different neuronal pathways and networks. The more chronic effects are thought to be a reflection of modulatory changes in subcortical site-specific synapses with the potential to influence larger cortical areas. In the complex brain, these neuromodulatory processes require time to build up.

Once established, certain antiepileptic neural networks may be more easily recruited, e.g., by changing stimulation parameters that may then be titrated to the individual need of the patient. This raises hope for potential antiepileptogenic properties of VNS using long-term optimized stimulation parameters that may affect and potentially reverse pathological processes that have been installed over a long period of time. However, from a clinical point of view, so far VNS cannot be considered a curative treatment.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a noninvasive and painless neurostimulation technique that was first utilized in humans in 1985.[54] In general, single-pulse TMS (including paired-pulse TMS) is used to explore brain functioning, whereas repetitive TMS (rTMS) is used to induce changes in brain activity that can last beyond the stimulation period. The principle behind rTMS is Faraday's law of electromagnetic induction.[55] More precisely, short alternating electrical currents pass through a stimulation coil, which generates a secondary alternating magnetic field parallel and in the opposite direction to the primary electrical current. This field, when perpendicularly oriented to the head, can bypass the scalp and reach the cerebrospinal fluid and brain, unhindered by the skull and soft tissues. The magnetic field induces a secondary electrical current, which modulates the cortical neurons and therefore creates the desirable neurobiological effects[56,57] (Fig. 18.6).

While the precise mechanism of action is still unclear and under investigation, rTMS might affect the cerebral blood flow, activity of certain enzymes, neurotransmitters, excitatory synaptic transmission and inhibitory interneurons, dendritic growth and neurotrophic factors, interactions between cortical and subcortical structures and gene expression. It might therefore affect the plasticity of the brain and formation of new neuronal networks.[58,59]

In rTMS, pulses are applied with specific repetitive protocols. There are two main rTMS treatment protocols: low-frequency rTMS, defined by stimulations at frequencies ≤1 Hz, and high-frequency rTMS, defined by stimulation at frequencies >5 Hz. High-frequency rTMS seems to have

facilitatory effects, whereas low-frequency rTMS seems to have inhibitory effects on cortical excitability. Since epilepsy is characterized by a state of cortical hyperexcitability, the use of low-frequency rTMS for drug-resistant epilepsy has gained increasing interest.[60,61] A series of case reports, open-label studies and randomized clinical trials have been performed to investigate the effects of rTMS on drug-resistant epilepsy in humans, reporting conflicting results. These studies have marked methodological differences, which might explain why the role of rTMS in the management of drug-resistant epilepsy is still a matter of debate. Currently, there is insufficient clinical evidence to strongly support the efficacy of rTMS in humans, although the limited published studies have shown encouraging and promising results.[6,18,62]

Adverse effects may occur during or after rTMS and in humans these are most commonly mild and transient, including headache, dizziness, tinnitus, jerking arm movement during stimulation, vomiting, and a transient visual defect in 12–18.3% of the study participants.[63,64] Skin irritation, jerking arm movement, and transient visual defects were only reported with high-frequency stimulation, whereas headache seems more prevalent in association with low-frequency stimulation.[65] Seizure induction is the most common AE immediately following rTMS procedure and the risk may be higher in patients with a high seizure frequency.[65] In a recent systematic review in human epileptic patients, it was found that the risk of having an epileptic seizure following rTMS is 2.9%.[64]

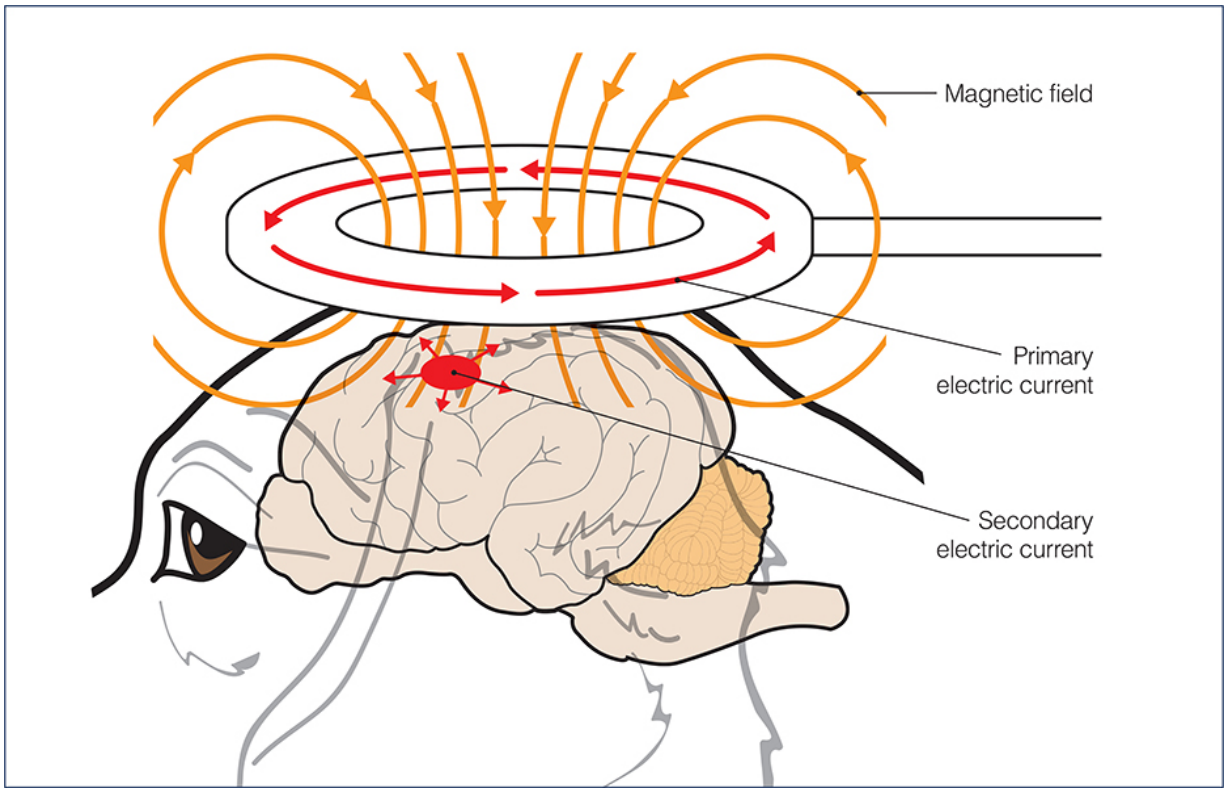


FIGURE 18.6. Illustration of a canine brain during active rTMS. A round coil is applied parallel to and in contact with the dog's skull. A short lasting alternating electrical current is sent through a stimulation coil to induce a rapidly changing magnetic field. This field is oriented perpendicular to the plane of the current and passes the canine scalp unimpeded by tissue (e.g., bone) or cerebrospinal fluid. In turn, the time-varying magnetic field induces a secondary electrical current affecting the function of the cerebral neurons.

One conference abstract is available that describes the application of rTMS in 3 dogs with epilepsy. The results showed an increased epileptic seizure–free interval after stimulation compared to the baseline, but no further details on the outcome were reported.[66] In 2020, the first single-blinded, randomized, placebo-controlled clinical trial on the efficacy and safety of rTMS in dogs with drug-resistant IE was performed[57] (Figs. 18.7 and 18.8 and Video 18.1). The study consisted of two trials: (I) a single-blinded, randomized, sham-controlled clinical trial (active rTMS [n = 7] or sham [n = 5]) and (II) an open-label uncontrolled clinical trial (dogs previously treated by sham stimulation [n = 5] received active rTMS treatment). The dogs received rTMS (active or sham) for 1 hour daily during 5 consecutive days. Monthly seizure frequency (MSF), monthly seizure day frequency (MSDF), and number of cluster seizures (CS) were evaluated for a 3-month pre-TMS and post-rTMS period and safety were

assessed. Overall, the stimulation parameters and study environment were the same in both groups, the only difference being that the sham group received inactive stimulation by placing the operating (round) coil perpendicular to the skull and 20 cm above the head in order to circumvent brain stimulation. In dogs receiving active rTMS treatment, the round coil was applied in parallel and in contact with the dog's skull with its center located at the vertex. Dogs in both groups were sedated (dexmedetomidine and butorphanol). In trial I, MSF and MSDF compared to baseline decreased significantly in the active group (n = 7). In the sham group (n = 5), no significant changes were found in MSF or MSDF. The frequency of CS did not change significantly in either group. In trial II, previously sham-treated dogs (n = 5) received active rTMS and significant decreases in MSF and MSDF were noted. The overall effect of rTMS lasted for 4 months. No AEs were reported during or after rTMS treatment.

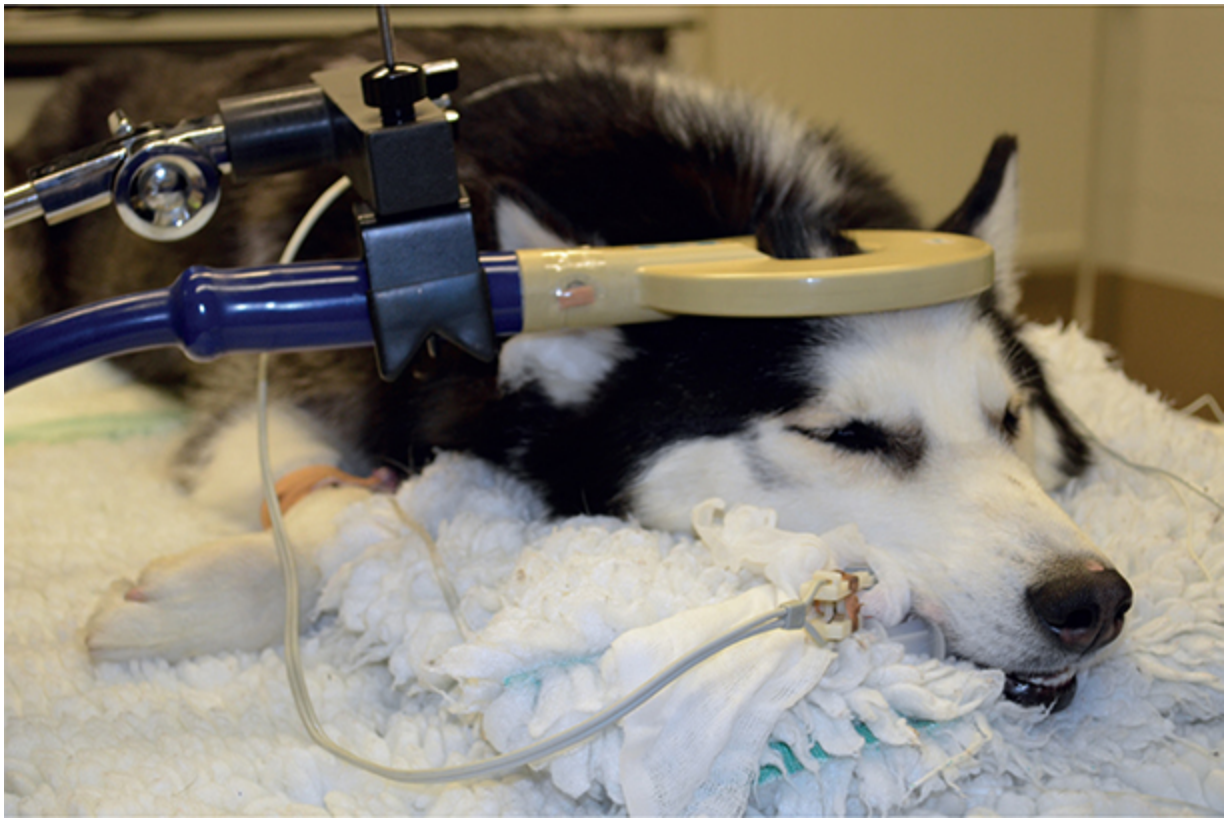


FIGURE 18.7. A dog with drug-resistant idiopathic epilepsy under sedation during rTMS procedure. A round coil is applied in parallel and in contact with the dog's skull with its center located at the vertex.

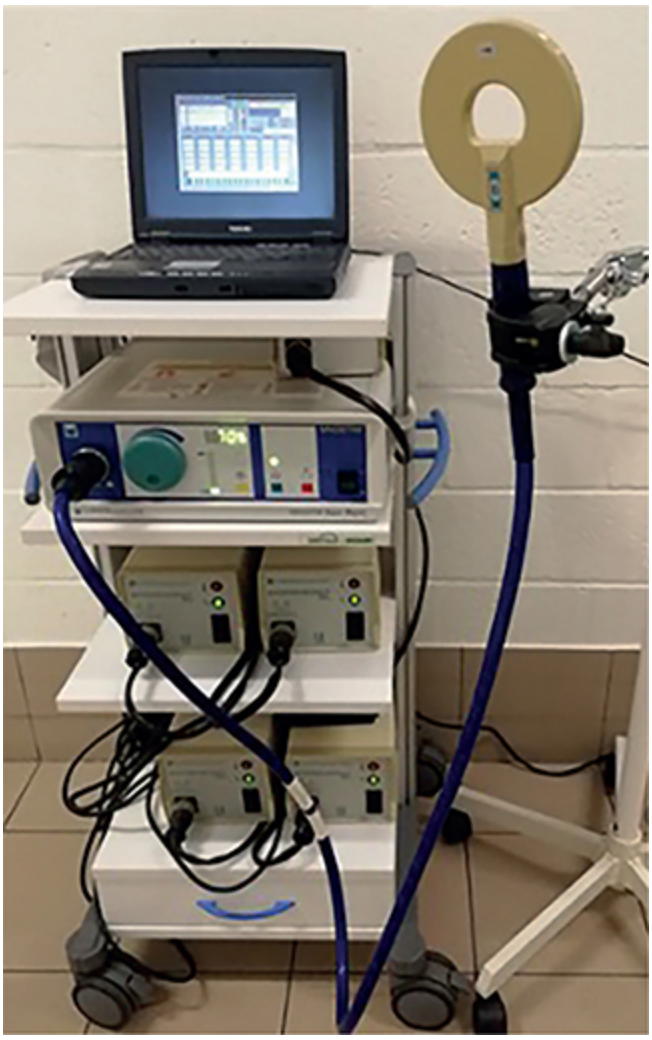


FIGURE 18.8. Equipment needed for rTMS.

Video 18.1.

A dog with drug-resistant idiopathic epilepsy under sedation during an rTMS procedure.

Based on the results of this trial, low-frequency rTMS might be considered a safe, noninvasive and effective treatment for reducing epileptic seizure frequency in dogs. Repetitive TMS might be a good adjunctive

treatment to ASDs in canine drug-resistant idiopathic generalized epilepsy, with potential neuromodulatory effects. The effect of rTMS is temporary; its duration varies for each dog and is likely related to the short-term brain network neuromodulation. Because the effects of rTMS are transient, repeated rTMS sessions—determined on an individual basis—would be advisable to achieve adequate epileptic seizure control and better quality of life and potentially allow this technique to be used as a long-term treatment in dogs with drug-resistant epilepsy. Since the stimulation parameters used are vital for the degree and duration of the rTMS antiseizure effect, altering and optimizing the stimulation protocols on an individual basis can lead to longer-lasting effects. Therefore, a better understanding of the precise mechanism of action of rTMS in epilepsy would allow clinicians and researchers to choose the ideal stimulation parameters for better epileptic seizure control and to develop canine-based trials with a larger number of subjects in order to optimize the protocols used for both human and veterinary patients with epilepsy.

CONCLUSIONS

Despite potentially promising results of multiple neurostimulatory techniques in canine IE, these modalities remain uncommon in canine patients, likely due to the cost, use of sophisticated equipment, lack of expertise and lack of data to support its efficacy. However, exploring the antiseizure properties of noninvasive neurostimulatory procedures in drug-resistant canine IE remains important.

Neurostimulation also carries the advantages that stimulation parameters can be customized and adapted individually to each patient and treatment is reversible.[67,68] Although a substantial reduction in seizure frequency and improved quality of life can be achieved in a considerable number of patients, neurostimulation treatments are considered palliative because seizure freedom is rarely achieved.[67,69] The effectiveness of neurostimulation often improves over time, which could indicate a long-lasting neuromodulatory effect, either at a molecular level or by reorganization of certain brain circuits,[70] but the precise mechanism of action remains unknown. In a chronic disease such as epilepsy, such long-

term effects are of critical importance for ranking treatment options and for patient counseling on the chances and risks of selected treatments. The biggest challenge is to determine which patients are most sensitive to specific types of neurostimulation.[71] Since canine and human epilepsy share many clinical, pathophysiological and therapeutic mechanism similarities,[72] future translational studies might offer a new insight in the management of drug-resistant epilepsy both in dogs and in humans.

TAKE-HOME MESSAGES

- ✔ In canine drug-resistant IE, nonpharmacological management strategies are essential to adequately control epileptic seizure frequency, duration and severity.
- ✔ Currently, neurostimulation in canine drug-resistant IE remains uncommon due to multiple reasons such as cost, availability, lack of expertise and lack of data to support its efficacy.
- ✔ Preliminary evidence on the potential antiseizure effect and safety profile of certain neurostimulatory techniques (i.e., VNS and rTMS) in dogs with drug-resistant IE has been shown.
- ✔ Large-scale trials in dogs with epilepsy evaluating noninvasive neurostimulation (such as rTMS, TNS, and tVNS) and optimizing the stimulation parameters should be performed to provide definitive conclusions with respect to the efficacy of these techniques in dogs with drug-resistant IE.

REFERENCES

1. LÖSCHER W, SCHMIDT D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia*. 2011; 52:657–678.
2. POTSCHKA H, FISCHER A, LÖSCHER W et al. International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy. *BMC Vet Res*. 2015; 11:177.
3. PACKER RM, VOLK HA. Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs. *Vet Rec*. 2015; 177:306–315

4. KEEZER MR, SISODIYA SM, SANDER JW. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol*. 2016; 15:106–115.
5. ENGEL J Jr, MCDERMOTT MP, WIEBE S et al. Early Randomized Surgical Epilepsy Trial (ERSET) Study Group. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA*. 2012; 307:922–930.
6. BOON P, DE COCK E, MERTENS A, TRINKA E. Neurostimulation for drug-resistant epilepsy: a systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. *Curr Opin Neurol*. 2018; 31:198–210.
7. ZANGIABADI N, LADINO LD, SINA F et al. Deep brain stimulation and drug-resistant epilepsy: A review of the literature. *Front Neurol*. 2019; 6:601.
8. MATIAS CM, SHARAN A, Wu C. Responsive neurostimulation for the treatment of epilepsy. *Neurosurg Clin N Am*. 2019; 30:231–242.
9. SUN FT, MORRELL MJ. Closed-loop neurostimulation: the clinical experience. *Neurotherapeutics*. 2014; 11:553–563.
10. WU K, WANG Z, ZHANG Y et al. Transcutaneous vagus nerve stimulation for the treatment of drug-resistant epilepsy: a meta-analysis and systematic review. *ANZ J Surg*. 2020; 90:467–471.
11. SLAGHT SJ, NASHEF L. An audit of external trigeminal nerve stimulation (eTNS) in epilepsy. *Seizure*. 2017; 52:60–62.
12. GSCHWIND M, SEECK M. Transcranial direct-current stimulation as treatment in epilepsy. *Expert Rev Neurother*. 2016; 16: 427–1441.
13. HOLDER LK, WERNICKE JF, TARVER WB. Treatment of refractory partial seizures: preliminary results of a controlled study. *Pacing Clin Electrophysiol*. 1992; 15:1557–1571.
14. GEORGE R, SALINSKY M, KUZNIECKY R et al. Vagus nerve stimulation for treatment of partial seizures: 3. long-term follow-up on first 67 patients exiting a controlled study. First International Vagus Nerve Stimulation Study Group. *Epilepsia*. 1994; 35:637–643.
15. SALINSKY MC, UTHMAN BM, RISTANOVIC RK et al. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. *Arch Neurol*. 1996; 53:1176–1180.
16. MORRIS GL 3rd, MUELLER WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Vagus Nerve Stimulation Study Group E01-E05. *Neurology*. 1999; 53:1731–1735.
17. DEGIORGIO CM, SCHACHTER SC, Handforth A et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia*. 2000; 41:1195–2000.
18. SCHULZE-BONHAGE A. Long-term outcome in neurostimulation of epilepsy. *Epilepsy Behav*. 2019; 91:25–29.
19. MONTEIRO R, ADAMS V, KEYS D, PLATT SR. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. *J Small Anim Pract*. 2012; 53:526–530.
20. MUÑANA KR, VITEK SM, TARVER WB et al. Use of vagal nerve stimulation as a treatment for refractory epilepsy in dogs. *J Am Vet Med Assoc*. 2002; 22:977–983.
21. MARTLÉ V, VAN HAM LM, BOON P et al. Vagus nerve stimulator placement in dogs: surgical implantation technique, complications, long-term follow-up, and practical considerations. *Vet Surg*. 2016; 45:71–78.
22. LANDY HJ, RAMSAY RE, SLATER J et al. Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy. *J Neurosurg*. 1993; 78:26–31.

23. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol*. 2002;1: 477–482.
24. Vonck K, Thadani V, Gilbert K et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol*. 2004; 21:283–289.
25. Foley J, DuBois FS. Quantitative studies of the vagus nerve in the cat. The ratio of sensory and motor fibres. *J Comp Neurol*. 1937; 67:49–67.
26. Agostoni E, Chinnock JE, De Daly MB, Murray JG. Functional and histological studies of the vagus nerve and its branches to the heart, lungs and abdominal viscera in the cat. *J Physiol*. 1957; 135:182–205.
27. Paintal AS. Vagal sensory receptors and their reflex effects. *Physiol Rev*. 1972; 53:159–227.
28. Banzett RB, Guz A, Paydarfar D et al. Cardiorespiratory variables and sensation during stimulation of the left vagus in patients with epilepsy. *Epilepsy Res*. 1999; 35:1–11.
29. Asconapé JJ, Moore DD, Zipes DP et al. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. *Epilepsia*. 1999; 40:1452–1454.
30. Kamath MV, Upton AR, Talalla A, Fallen EL. Neurocardiac responses to vagoafferent electrostimulation in humans. *Pacing Clin Electrophysiol*. 1992; 15:1581–1587.
31. Spuck S, Nowak G, Renneberg A et al. Right-sided vagus nerve stimulation in humans: An effective therapy? *Epilepsy Res*. 2008; 82:232–234.
32. Kahlow H, Olivecrona M. Complications of vagal nerve stimulation for drug-resistant epilepsy: A single center longitudinal study of 143 patients. *Seizure*. 2013; 22:827–833.
33. Martlé V, Bavegems V, Van Ham L et al. Evaluation of heart rate variability in dogs during standard and microburst vagus nerve stimulation: a pilot study. *Vet J*. 2014; 202:651–653.
34. Robinson K, Platt S, Stewart G, Reno L et al. Feasibility of non-invasive vagus nerve stimulation (gammaCore VET™) for the treatment of refractory seizure activity in dogs. *Front Vet Sci*. 2020; 7:569739.
35. Zagon A, Kemeny AA. Slow hyperpolarization in cortical neurons: a possible mechanism behind vagus nerve simulation therapy for refractory epilepsy? *Epilepsia*. 2000; 41:1382–1389.
36. Evans MS, Verma-Ahuja S, Naritoku DK, Espinosa JA. Intraoperative human vagus nerve compound action potentials. *Acta Neurol Scand*. 2004; 110:232–238.
37. Henry TR, Bakay RA, Votaw JR et al. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. *Epilepsia*. 1998; 39:983–990.
38. Van Laere K, Vonck K, Boon P et al. Perfusion SPECT changes after acute and chronic vagus nerve stimulation in relation to prestimulus condition and long-term clinical efficacy. *J Nucl Med*. 2002; 43:733–744.
39. Naritoku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Res*. 1995; 22:53–62.
40. Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia*. 1998; 39:709–714.
41. Osharina V, Bagaev V, Wallois F, Larnicol N. Autonomic response and Fos expression in the NTS following intermittent vagal stimulation: importance of pulse frequency. *Auton Neurosci*. 2006; 126–127:72–80.
42. Cunningham JT, Mifflin SW, Gould GG, Frazer A. Induction of c-Fos and DeltaFosB immunoreactivity in rat brain by vagal nerve stimulation. *Neuropsychopharmacology*. 2008;

33:1884–1895.

43. Proctor M, Gale K. Basal ganglia and brain stem anatomy of the afferent vagal system, In: Engel J, Pedley TA (eds.). *Epilepsy, the Comprehensive CD-rom*. Philadelphia: Lippincott Williams and Wilkins; 1999.
44. Hammond EJ, Uthman BM, Wilder BJ et al. Neurochemical effects of vagus nerve stimulation in humans. *Brain Res*. 1992; 583:300–303.
45. Ben-Menachem E, Hamberger A, Hedner T et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Res*. 1995; 20:221–227.
46. Follesa P, Biggio F, Gorini G et al. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Res*. 2007; 1179:28–34.
47. Roosevelt RW, Smith DC, Clough RW et al. Increased extracellular concentrations of norepinephrine in cortex and hippocampus following vagus nerve stimulation in the rat. *Brain Res*. 2006; 1119:124–132.
48. Hassert DL, Miyashita T, Williams CL. The effects of peripheral vagal nerve stimulation at a memorymodulating intensity on norepinephrine output in the basolateral amygdala. *Behav Neurosci*. 2004; 118:79–88.
49. Martlé V, Peremans K, Raedt R et al. Regional brain perfusion changes during standard and microburst vagus nerve stimulation in dogs. *Epilepsy Res*. 2014; 108:616–622.
50. Martlé V, Raedt R, Waelbers T et al. The effect of vagus nerve stimulation on CSF monoamines and the PTZ seizure threshold in dogs. *Brain Stimul*. 2015; 8:1–6.
51. Cascino GD. When drugs and surgery don't work. *Epilepsia*. 2008; 49:79–84.
52. Pati S, Alexopoulos AV. Pharmacoresistant epilepsy: From pathogenesis to current and emerging therapies. *Cleve Clin J Med*. 2010; 77:457–467.
53. Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. *Epilepsia*. 1992; 33:1005–1012.
54. Groppa S, Oliviero A, Eisen A et al. A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. *Clin Neurophysiol*. 2012; 123:858–882.
55. Barker AT. An introduction to the basic principles of magnetic nerve stimulation. J *Clin Neurophysiol*. 1991; 8:26–37.
56. Peng Z, Zhou C, Xue S, et al. Mechanism of repetitive transcranial magnetic stimulation for depression. *Shanghai Arch Psychiatry*. 2018; 30:84–92.
57. Charalambous M, Van Ham L, Broeckx BJG et al. Repetitive transcranial magnetic stimulation in drug-resistant idiopathic epilepsy of dogs: A noninvasive neurostimulation technique. *J Vet Intern Med*. 2020; 34(6):2555–2561.
58. Chervyakov AV, Chernyavsky AY, Sinitsyn DO, Piradov MA. Possible mechanisms underlying the therapeutic effects of transcranial magnetic stimulation. *Front Hum Neurosci*. 2015; 9:303.
59. Gangitano M, Valero-Cabré A, Tormos JM et al. Modulation of input-output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex. *Clin Neurophysiol*. 2002; 113:1249–1257.
60. Anschel DJ, Pascual-Leone A, Holmes GL. Anti-kindling effect of slow repetitive transcranial magnetic stimulation in rats. *Neurosci Lett*. 2003; 351:9–12.

61. Lefaucheur JP, André-Obadia N, Antal A et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014; 125:2150–2206.
62. Larkin M, Meyer RM, Szuflita NS et al. Post-traumatic, drug-resistant epilepsy and review of seizure control outcomes from blinded, randomized controlled trials of brain stimulation treatments for drug-resistant epilepsy. *Cureus*. 2016; 8:e744.
63. Pereira LS, Müller VT, da Mota Gomes M et al. Safety of repetitive transcranial magnetic stimulation in patients with epilepsy: A systematic review. *Epilepsy Behav*. 2016; 57:167–176.
64. Carrette S, Boon P, Dekeyser C et al. Repetitive transcranial magnetic stimulation for the treatment of refractory epilepsy. *Exp Rev Neurother*. 2016; 16:1093–1110.
65. Poma R, Ives JR, Rotenberg A, Pacual-Leona A. Repetitive transcranial magnetic stimulation in 3 epileptic dogs: techniques of stimulation and results. In: *AES Proceedings*; 2006, 337.
66. Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurol*. 2004; 3:111–118.
67. Gigante PR, Goodman RR. Responsive neurostimulation for the treatment of epilepsy. *Neurosurg Clin N Am*. 2011; 22:477–480.
68. Fisher RS. Therapeutic devices for epilepsy. *Ann Neurol*. 2012; 171:157–168.
69. Vonck K, de Herdt V, Sprengers M, Ben-Menachem E. Neurostimulation for epilepsy. *Handb Clin Neurol*. 2012; 108:955–970.
70. Ben-Menachem E. Neurostimulation-past, present, and beyond. *Epilepsy Curr*. 2012; 12:188–191.
71. Potschka H, Fischer A, von Rüden EL et al. Canine epilepsy as a translational model? *Epilepsia*. 2013; 54:571–579.

Management of Status Epilepticus and Cluster Seizures in Dogs and Cats

19

Marios Charalambous, Sofie F.M. Bhatti

Status epilepticus

Status epilepticus (SE) is defined clinically as prolonged seizure activity lasting >5 minutes or multiple epileptic seizures with incomplete recovery in between; it remains a common neurological emergency.[1–3] Status epilepticus can occur in dogs and cats with idiopathic epilepsy (IE), structural epilepsy (epilepsy due to brain pathology) and reactive seizures (seizures due to metabolic causes or intoxication) (see chapters 1, 2 and 5).[4–6] Dogs with SE represent approximately 0.5–2.6% of emergency cases,[7,8] and SE is seen in 16.5% of the dogs taken to the clinic due to seizure activity. Status epilepticus has been identified as the first clinical manifestation of a seizure disorder in 58% of dogs.[4,7] Specifically, 27–59%, 32–40%, and 7–23% of dogs with IE, structural epilepsy and reactive seizures, respectively, can present with SE.[4–7] Risk factors for developing SE, in particular for dogs with IE, include being of a large breed (e.g., German Shepherds, Golden Retrievers) and having a greater body weight, while early appropriate seizure treatment does not appear to decrease the risk of SE.[6] Other risk factors include sex (e.g., spayed females have a higher risk than intact females and male dogs have a higher risk than

females),[4,7,9] low antiseizure drug (ASD) serum concentrations and inadequate epileptic seizure control.[4,6] No association between severity and frequency of SE and age or breed was reported in one study.[10] Regarding survival rates, dogs presented with SE due to IE or intoxication have more favorable outcomes and better survival rates than those with SE due to structural epilepsy.[7] The overall mortality rate of dogs with SE is 25.3–38.5%.[4,7]

Status epilepticus can lead to permanent brain damage and severe systemic complications; the occurrence and severity of SE-induced complications are proportionally related to the duration of seizure activity.[11–15] Specifically, brain edema and damage characterized by neuronal necrosis, gliosis and network reorganization can occur.[14,15] In the canine brain, it has been documented that the longer SE lasts, the worse and more widespread neuronal necrosis becomes.[12,16] Systemic complications reported with <30 minutes of continuous seizure activity include hypertension, tachycardia, hyperglycemia, hyperthermia, cardiac arrhythmias, acidosis, rhabdomyolysis, hypotension, shock, noncardiogenic pulmonary edema and acute tubular necrosis.[11,13] Following >30 minutes of continuous seizure activity, systemic hypotension, hypoglycemia, hyperthermia, hypoxia, respiratory impairment, acidosis, hyperkalemia, hyponatremia, uremia and autonomic dysfunction are often present.[11,13] Therefore, effective and quick first-line management at home and in the hospital is by far essential and life-saving.

THERAPY

General considerations

The goals of SE therapy include cessation of seizure activity, prevention of additional seizures, and management of seizure complications and underlying etiological conditions. It has been shown that the earlier seizure cessation is achieved, the better the overall outcome is (i.e., successful treatment of complications and response to ASDs).[11,13,14,17–21]

Status epilepticus progresses to more refractory (drug-resistant) stages over time due to dysfunctional mechanisms on a molecular basis. Precisely, there is loss of γ-aminobutyric acid (GABA)-induced inhibition, combined

with an upregulation of glutamate receptor excitation induced by N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA).[22] GABAergic drugs (e.g., benzodiazepines [BDZs]) are commonly used in the management of SE, but their effectiveness may gradually decrease with prolonged SE due to reduced synaptic targets (i.e., internalization of GABA receptors).[23] Also, a significant upregulation by 87–166% of endothelial P-glycoprotein (a membrane protein that actively exports drugs out of the cells) was demonstrated in the canine brain following SE, which leads to enhanced blood–brain barrier (BBB) efflux of ASDs from the brain, thereby limiting the drug's concentration in the tissue.[24]

A methodological therapeutic approach is essential for effective and rapid management of in- and outpatients. Administration of ASDs with different mechanisms of action and through different routes is fundamental for the management of SE. Although monotherapy is preferable to avoid drug interactions and minimize the incidence of drug-related adverse effects (AEs), polytherapy is usually necessary to reach the therapeutic aims. Ideally, ASDs should penetrate the brain well and provide a rapid onset and lasting duration of action, have a favorable safety profile with minimal AEs on cardiorespiratory function and level of consciousness, and be easy to administer. However, no medication is ideal. Factors that increase a drug's rate of entry into the brain include lack of protein-binding, high serum concentrations, and lipid solubility of the drug, as well as sufficient cerebral blood flow.

Management of seizure activity

Status epilepticus can be subdivided into four stages (Fig. 19.1), which differ in terms of sensitivity to the ASDs used, treatment options as well as morbidity and mortality rates.[11,13,14,17–21] These stages are, in order of increasing severity:

- Impending SE:
  - Less than 5 minutes of continuous epileptic seizure activity.
  - Seizures are likely responsive solely to first-line ASD therapy.
- Established SE:
  - Less than 30 minutes of continuous seizure activity.
  - Seizures are still, but likely less, responsive to first-line ASD therapy.

    - Adjunctive nonanesthetic (e.g., phenobarbital [PB], levetiracetam [LEV], fosphenytoin) or general anesthetic (e.g., propofol, ketamine, pentobarbital, etomidate, inhalation anesthetics) ASD therapy might be needed.
- Refractory SE:
    - Greater than 30–60 minutes of continuous seizure activity.
    - Seizures are resistant to first-line and nonanesthetic ASD therapy.
    - Adjunctive general anesthetic ASD therapy is needed.
- Super-refractory SE:
    - Greater than 24 hours of continuous seizure activity or seizure recurrence after initiation of treatment with general anesthetic ASD therapy.
    - Seizures are likely resistant to any ASD therapy.

A summary of all the commonly used ASDs for SE in dogs and cats including their dosages is provided in Box 19.1. An algorithm for the in-hospital management of SE and cluster seizures in dogs and cats is also provided (Fig. 19.2).

First-line treatment – benzodiazepines

First-line effective treatment is of paramount importance and should be potent enough to terminate seizures quickly to avoid progression of SE to more drug-resistant stages, complications, and adjunction of further anesthetic and nonanesthetic ASDs that can lead to AEs. Benzodiazepines, in particular midazolam (MDZ) and diazepam (DZP), have been used for decades as first-line ASDs due to their high potency and rapid onset of action. They act on the pre- and postsynaptic $GABA_A$-ergic transmission leading to a neuronal influx of chloride; the latter increases the depolarization threshold and, therefore, causes inhibition of nerve impulse transmission.[20,25,26] The AEs of BZPs include respiratory and central nervous system (CNS) depression and hypotension.[11]

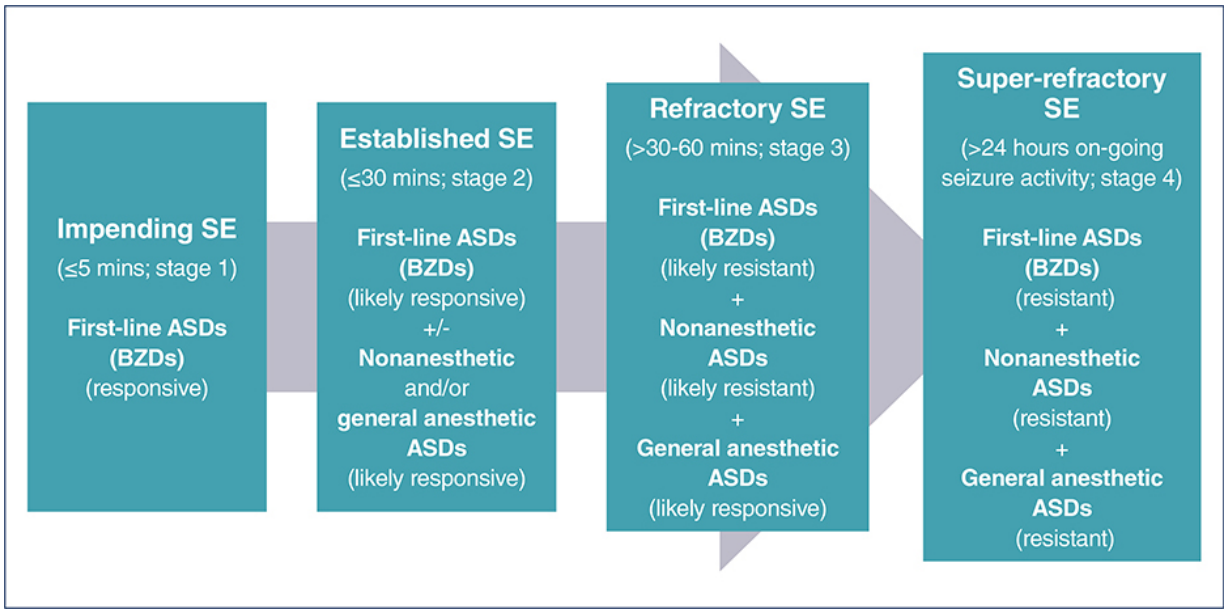


FIGURE 19.1. Stages of status epilepticus (SE) and responsiveness to antiseizure drugs (ASDs) per stage. As the stage of SE become more advanced, the responsiveness to ASDs, in particular first-line drugs (benzodiazepines [BZDs]), lessens. In more advanced stages of SE, further ASDs might be gradually added on to control the seizures.

BOX 19.1. Recommended dosages of antiseizure drugs used in dogs and cats with status epilepticus.

Antiseizure drug	Recommended dosages
Midazolam	**Dogs:** 0.2–0.5 mg/kg IV, IN, IM bolus 0.2–0.5 mg/kg/hour IV CRI **Cats:** Same as in dogs IN administration route has not been evaluated in cats
Diazepam	**Dogs:** 0.5–2.0 mg/kg IV, IN, rectal bolus; can be repeated 2–3 times in 24 hours, not more frequently than every 5 minutes Dose at lower range when coadministered with levetiracetam Dose at higher range when coadministered with phenobarbital 0.1–0.5 mg/kg/hour IV CRI **Cats:** 0.5–2.0 mg/kg IV, rectal bolus; can be repeated 2–3 times in 24 hours, not more frequently than every 5 minutes IV CRI is not recommended in cats
Phenobarbital	**Dogs:** Loading dose: 3.0–5.0 mg/kg IV, IM, PO in multiple administrations, with a total dose of 15–24 mg/kg in 24–48 hours Maintenance dose: 2.5–3 mg/kg every 12 hours **Cats:**

	Loading dose scheme has not been precisely defined, but is likely to be similar to that for dogs Maintenance dose: 1.5–2.5 mg/kg every 12 hours
Levetiracetam	**Dogs:** 60 mg/kg IV (administered over 5 min), rectal, or PO once; followed by 20 mg/kg every 8 hours IV, rectal or PO **Cats:** Same as for dogs
Fosphenytoin	**Dogs:** 15 mg/kg IV bolus **Cats:** Fosphenytoin/phenytoin has not been thoroughly evaluated in cats with SE
Propofol	**Dogs:** 1.0–6.0 mg/kg IV bolus followed by 0.1–0.6 mg/kg/minute IV CRI IV CRI is advised to be administered for at least 6 hours; thereafter, administration can be continued if seizures relapse **Cats:** 1.0–6.0 mg/kg IV bolus IV CRI is not recommended in cats
Ketamine	**Dogs:** 3.0–5.0 mg/kg IV bolus followed by 0.1–0.5 mg/kg/hour IV CRI **Cats:** Same as in dogs, although ketamine has not been thoroughly evaluated in cats with SE
Dexmedetomidine	**Dogs:** 0.5–3.0 µg/kg IV bolus followed by 0.5–7.0 µg/kg/hour IV CRI **Cats:** Same as in dogs
Pentobarbital	**Dogs:** 3.0–15 mg/kg IV bolus (slow; administered with caution) followed by 0.2–1.0 mg/kg/hour IV CRI **Cats:** Same as in dogs

IV, intravenous; IN, intranasal; IM, intramuscular; CRI, constant rate infusion; PO, per os; SE, status epilepticus.

In dogs, both DZP and MDZ can be effective in ceasing seizure activity, but MDZ might be more potent than DZP. In one study in dogs, MDZ showed a higher suppressive effect on lidocaine-induced seizures compared to DZP.[27] In addition, MDZ has gained greater popularity in the management of SE due to its more favorable safety profile (i.e., MDZ-

induced brain and respiratory depression are less severe compared to DZP).[20] Midazolam is a hydrophilic drug, but it becomes more lipophilic at a physiological pH (i.e., tissues), leading to rapid diffusion into the brain.[20] Midazolam has a short elimination half-life ($t_{1/2}$) (approximately 1 hour in dogs), so frequent dosing or intravenous (IV) constant rate infusion (CRI) is required for effectiveness. Midazolam is administered at a dose of 0.2–0.5 mg/kg. An IV CRI (0.2–0.5 mg/kg/hour) might be needed to sustain good seizure control after an initial MDZ bolus dose. Findings from a recent retrospective study suggest that MDZ CRI is safe and effective in controlling seizures in 67% (18/27) of dogs with SE.[28] An hourly dose of MDZ should be calculated for the CRI, and the CRI is delivered with an infusion pump and is usually diluted in 0.9% saline or 5% dextrose, with the volume administered being equal to the hourly maintenance fluid requirement. The infusion rate should be reduced by 50% every 6 hours for at least two reductions before discontinuing the drug. In humans, it has been shown that MDZ's $t_{1/2}$ increases after CRI;[29] although this has not been demonstrated in animals, it is likely to occur.

Diazepam is a lipophilic drug that quickly diffuses into the brain. Because of its lipophilicity, parenteral DZP is diluted in a propylene glycol vehicle that can cause phlebitis and hypotension when administered rapidly. Central IV access is therefore recommended to help prevent phlebitis. Diazepam also adsorbs to plastic[30] and should not be stored in plastic syringes or infusion lines for any length of time (if a CRI is needed, it is useful to precoat the infusion lines with DZP before administration). Diazepam is light sensitive[31] so the infusion line should be wrapped in foil or another dense material to protect the drug from light when administered as a CRI. Diazepam is administered at the dose of 0.5–2.0 mg/kg. Repeat DZP boluses lead to accumulation and high concentrations of the drug in the CNS, cerebrospinal fluid (CSF) and serum. Although this can result in prolonged antiseizure activity, it can also cause severe CNS depression and cardiorespiratory collapse.[32] Therefore, only 2–3 DZP doses should be administered, not more frequently than every 5 minutes and, if unsuccessful, an IV CRI (0.1–0.5 mg/kg/hour) or another ASD should be considered. Coadministration of LEV enhances DZP's antiseizure effect and a decreased dose might be adequate for effective seizure management.[33] Conversely, chronic administration of PB causes increased hepatic clearance of DZP, which results in reduced serum drug concentration; a

higher dose might thus be needed.[34] Propylene glycol toxicity (e.g., neurological abnormalities, metabolic acidosis, hyperosmolality, and organ dysfunction) is of vital concern especially in cats and DZP CRI is not recommended in this species.[35]

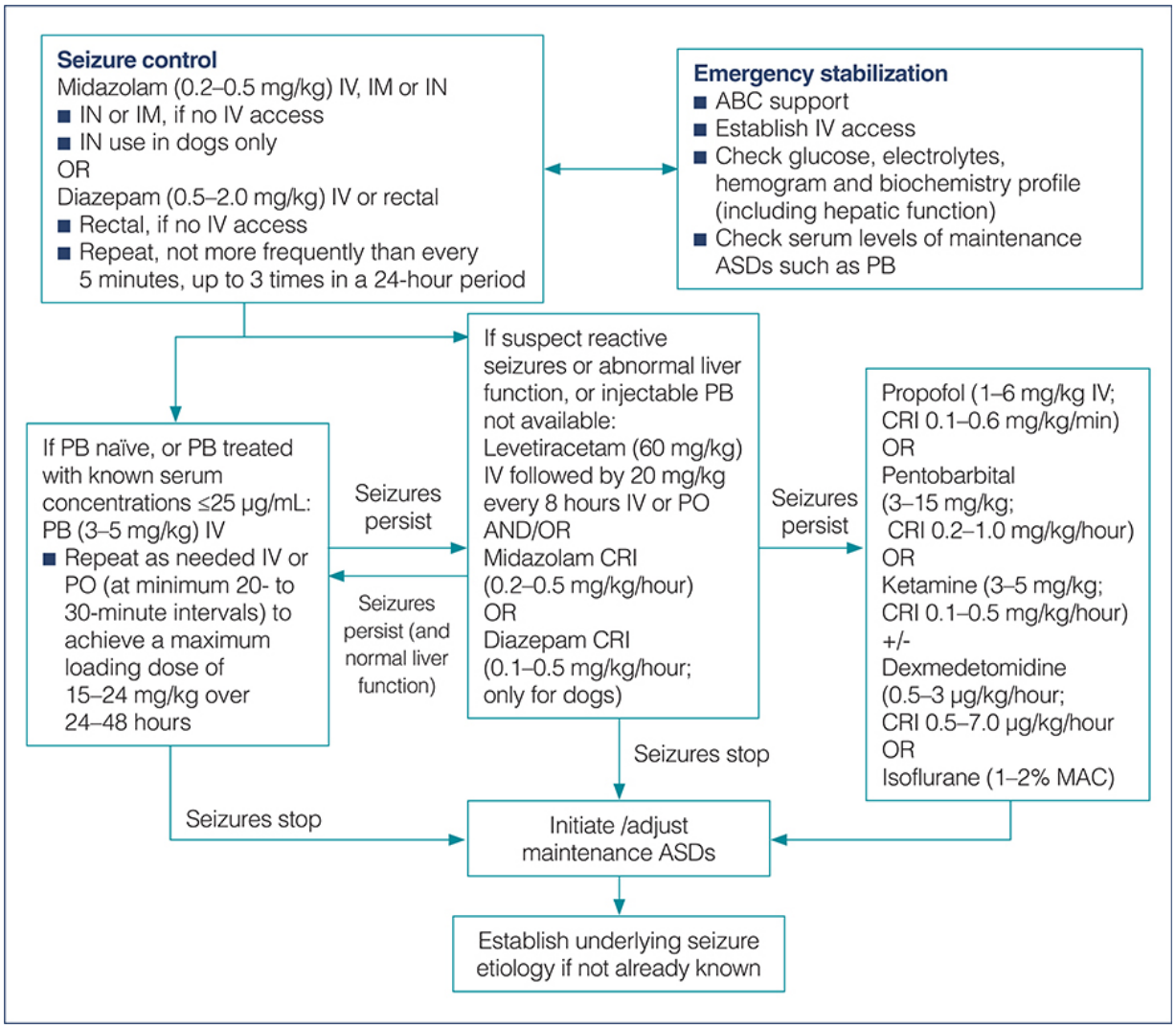


FIGURE 19.2. Algorithm for the in-hospital management of status epilepticus and cluster seizures in dogs and cats.
IV, intravenous; IM, intramuscular; IN, intranasal; ABC, airway/breathing/circulatory; ASD, antiseizure drugs; PB, phenobarbital; CRI, constant rate infusion; MAC, minimal alveolar concentration.

Various BDZ administration routes[36] have been evaluated for the management of SE in animals and people:

- Intravenous
- Rectal (R)

- Intranasal (IN)
- Intramuscular (IM)
- Buccal
- Sublingual

Intravenous route of administration

Intravenous administration of BDZs has been considered the "gold-standard" for providing effective and quick seizure cessation; however, one of the main challenges encountered in veterinary practice is the fact that ASDs often need to be given by non-IV routes either in out-of-hospital settings by the owner or upon admission to a veterinary clinic before IV access has been established. In addition, IV administration requires hospitalization or skilled medical staff[37,38] and establishing IV access might be difficult during SE.[39] Therefore, because SE management should be commenced as early as possible, there is a need for an effective treatment that can be administered by owners in the out-of-hospital environment as well as by clinicians in the hospital setting.[40] Recommendations for the initial management of SE in the home setting are included in Box 19.2.

Rectal route of administration

Rectal administration is one of the most common routes used by owners at home or by clinicians when there is no IV access. Rectal DZP (R-DZP) has been utilized in both humans[41–44] and dogs[45–48] as a management option for SE. An empty rectum provides a stable environment with low activity of degrading enzymes that favors absorption of drugs into the systemic circulation, although the presence of fecal material may impair drug absorption.[49] However, leakage of drugs together with other organic fluids can be problematic, and rectal administration can be difficult to perform correctly during SE.[50] In addition, rectally administered drugs can be partially subject to first-pass hepatic metabolism, which reduces their bioavailability and increases their onset of action.[49,50]

Intranasal route of administration

The IN route provides a noninvasive method of drug administration, aiming for local, systemic as well as CNS action. Compared to other routes, IN administration avoids first-pass hepatic metabolism and provides a more direct access for drugs to the brain,[36,51–53] as illustrated in Figure 19.3.

Intranasal MDZ can enter the brain via two main pathways, i.e., the bloodstream (indirect pathway) and nerves (direct or nose-brain pathway) (Fig. 19.4). It therefore provides efficient drug delivery pathways to the brain and is a good alternative to the IV and other non-IV routes of administration as supported by studies conducted in several species.[36,50,54–69] Two clinical trials assessed the use of IN-MDZ in dogs with SE and showed that IN-MDZ was safe for both animals and caregivers administering the drug, and was significantly more effective and quicker than R-DZP in terminating the seizures. Additionally, when the time to place an IV catheter in a seizuring dog was considered, IN-MDZ also stopped seizures significantly more rapidly than IV-MDZ.[50, 69]

BOX 19.2. Recommendations for the management of status epilepticus in the home setting.

- Status epilepticus is an emergency situation, and treatment should be commenced as soon as possible.
- The owner should be educated on the need to provide their pet emergency care if:
  - A seizure lasts >5 minutes.
  - Mulitple epileptic seizures occur with incomplete recovery in between.
- Prescribed at-home treatment can be administered to attempt to control seizure activity:
  - Midazolam (0.2–0.5 mg/kg), intranasal route (only in dogs).

  OR
  - Diazepam (0.5–2.0 mg/kg), rectal route.
- Dosing can be repeated, not more frequently than every 5 minutes, up to 3 times in a 24-hour period.
- If seizure activity persists for >5 minutes, or seizures recur within 24 hours, the animal should be taken to a veterinary clinic for emergency care.

In these two studies evaluating treatment of SE in dogs,[50,69] establishing venous access by placing an IV catheter[69] or using a syringe for drug rectal administration was perceived more difficult[50] than administering IN-MDZ via a mucosal atomization device (MAD). The MAD is a specific nasal spray device that consists of a syringe with a conical soft plug attached to it, which turns the solution into an atomized mist. This administration method may be more efficient than using a solution because it allows better distribution within the nasal cavity and faster absorption by the mucosa.[50,69] If such a device is not available, a plain syringe (with no needle attached) can be used for immediate IN drug delivery; however, the drug's efficacy might be affected due to potential slower absorption or outflow of the liquid drug from the nasal cavity. Although approaching a dog's head and mouth during seizures for administering IN medication might be considered

challenging (i.e., risk of accidental bites to the caregiver due to dog's jaw chomping), this potential risk was assessed in the clinical trials and no such events were reported.[50,69] The appropriate method to approach and administer IN medication to a dog is shown in Figure 19.5. Several attempts and practice might be necessary before clinicians or owners become familiar and competent with the IN drug delivery procedure. Lastly, despite the reported superiority of IN-MDZ over other treatment options, such as R-DZP, rectal administration might be preferable under specific conditions, for example, in cats with SE (IN route was not evaluated in these species) or in case of severe jaw chomping or postictal aggressive behavior (potential risk of accidental bites to caregivers). The use of this route will also depend on the owner's or clinician's preference, skills or confidence.

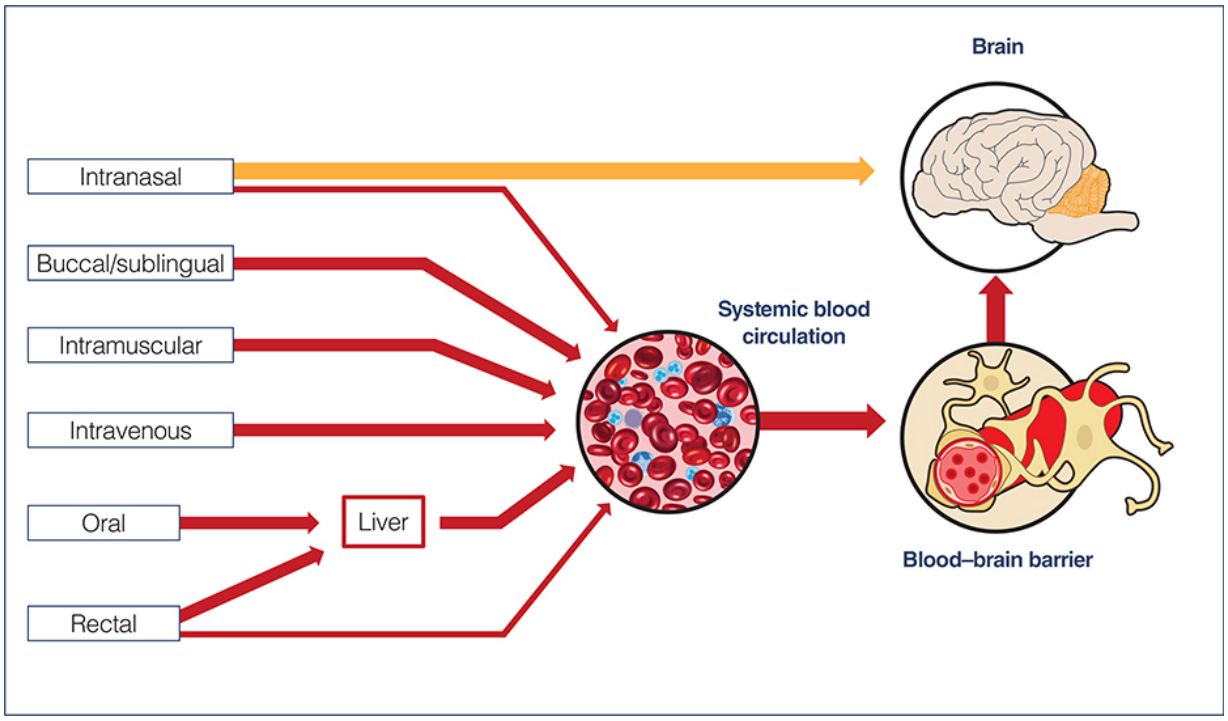


FIGURE 19.3. Schematic illustration of the pathways to the brain for different routes of antiseizure drug administration. The intranasal route is the only route that provides a direct pathway to the brain that avoids the blood–brain barrier (BBB) (orange arrow), along with an indirect pathway (red arrow). The remaining routes reach the brain indirectly (red arrows) via the systemic circulation and passage through the BBB. The oral and rectal routes can undergo first-pass hepatic metabolism, although rectally administered drugs could potentially avoid the first-pass metabolism if they do not reach the more cranial parts of the colon.

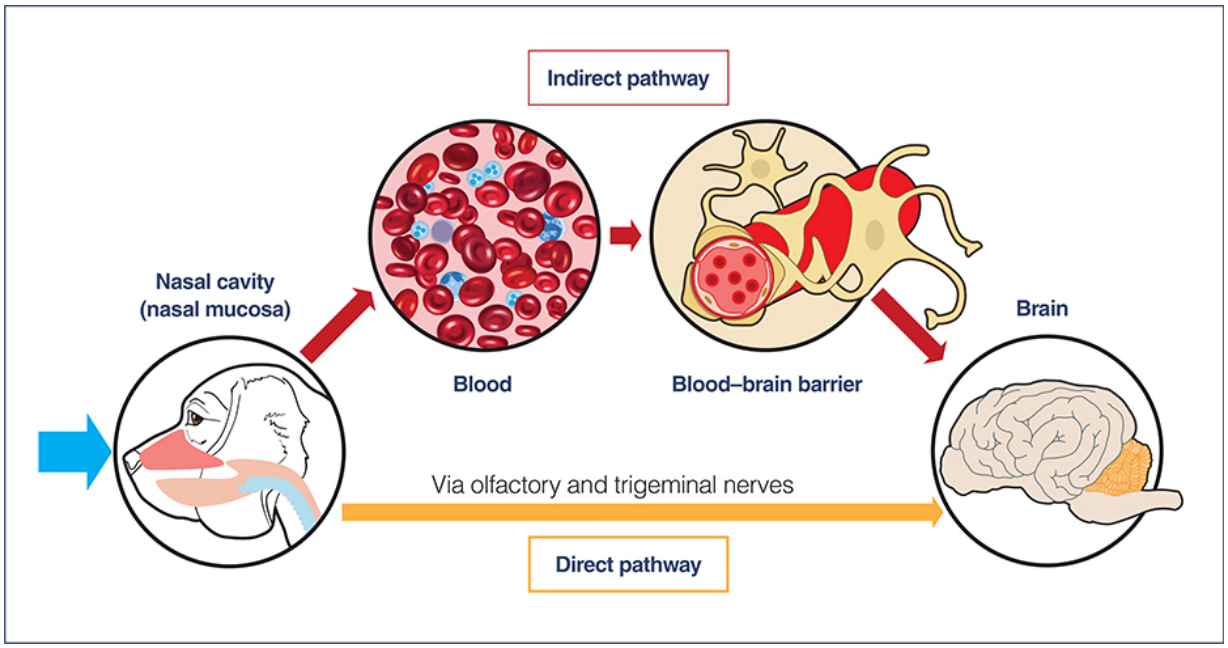


FIGURE 19.4. Schematic illustration of the indirect and direct nose-to-brain drug delivery pathways. Drugs administered intranasally can penetrate directly into the brain through the olfactory and/or trigeminal nerve pathways or indirectly following absorption into the systemic circulation.

Intramuscular route of administration

Intramuscular BZD administration is another non-IV delivery method that has been evaluated for the management of SE in human clinical trials.[70,71] Such trials have not been conducted in dogs, apart from pharmacokinetic (PK) studies that have demonstrated good absorption and bioavailability of MDZ after IM injection.[72,73] However, IM drug delivery can be problematic or pose risks of injury when administered by nonexperienced, non-medically-trained individuals.[53]

Buccal route of administration

Buccal MDZ provides an alternative administration option in humans due to its ease of use and the fact that it is socially acceptable.[74] However, in cases of hypersalivation during SE, administering the correct dose via the buccal route poses limitations (e.g., risk of incomplete absorption and aspiration and need for patient's cooperation),[75] which might be higher in dogs. Another concern regarding this route is the risk of accidental bites to the caregiver during drug administration. Additionally, some amount of the buccally administered drug can be swallowed, which can lead to decreased bioavailability and delayed time to peak concentration due to first-pass

hepatic metabolism and the gastrointestinal tract absorption time, respectively.[51,76] In dogs, only PK studies have been performed; one study showed that buccal MDZ as a gel formulation has a favorable PK profile in healthy dogs[34] and another one showed pH-dependent absorption.[77]

Sublingual route of administration

The sublingual route is another administration method within the oral cavity and shares similar advantages and limitations with buccal administration. However, the sublingual route provides a thinner and more permeable layer of absorption compared to buccal mucosa and is characterized by a more rapid onset of action.[78] In dogs, no studies evaluating sublingual BZD administration have been performed.



FIGURE 19.5. Correct method for administering intranasal medication to a dog. The seizuring dog should be approached from above, with one hand holding the base of the head near the neck and the other hand administering the medication into the nose.

Oral route of administration

Oral administration is considered a practical and easy route but, as occurs with buccal administration, it can be dangerous during SE. Certain oral

drugs including BZDs, and in particular MDZ, display low bioavailability, reduced efficacy and prolonged onset of action due to their slow absorption and enzyme-induced degradation in the gastrointestinal system (mainly small intestine and stomach) as well as extensive first-pass hepatic metabolism.[79] In addition, oral BZDs cannot be administered to people with difficulty swallowing or severe CNS depression[80] as occurs in SE cases, as this may lead to aspiration pneumonia, especially after administering oily solutions such as DZP. Similar limitations exist in dogs, which impair the effect of oral BDZs in SE.

Nonanesthetic antiseizure drugs

Phenobarbital

Although PB can also be considered an anesthetic drug, it is mainly used as an ASD in epileptic seizure disorders for both long-term treatment (see Chapter 10) and emergency seizure management. This section will cover the use of PB for emergency treatment of SE. Phenobarbital is an effective and relatively safe ASD, based on systematic reviews/meta-analyses in dogs[81,82] and cats[83]. Phenobarbital acts on postsynaptic $GABA_A$ receptors, leading to an increased influx of chloride ions into neurons and hyperpolarization of the postsynaptic membrane. This results in an increase of the epileptic seizure threshold and decrease of the spread of epileptic seizure activity.[11,84] The $GABA_A$ receptor binding site for PB is different from the BZD binding site and, therefore, these two drugs can be coadministered. Phenobarbital also causes inhibition of glutamate and calcium influx into the neurons,[85] has neuroprotective effects, and decreases body temperature, which can be beneficial in SE.[14]

Phenobarbital is a lipophilic drug, but less so than DZP; it can therefore distribute into the CNS, but this may require up to 30 minutes. Phenobarbital can be administered IV, IM or orally (PO). The maintenance dose is 2.5–3 mg/kg every 12 hours in dogs and 1.5–2.5 mg/kg every 12 hours in cats (see Chapter 10). When the desired therapeutic concentrations need to be achieved more rapidly than 2–3 weeks after maintenance treatment initiation, a dose of 3.0–5.0 mg/kg can be administered multiple times (at least 20–30 minutes apart), up to a total dose of 15–24 mg/kg in 24–48 hours (loading dose).

The loading dose can be also calculated according to the following formula (also see Chapter 10):

Loading dose (mg/kg) = desired serum concentration (μg/mL) x 0.77

Details on serum PB concentration monitoring is presented in Chapter 10, Box 10.2. A loading dose has not been defined in cats, but it is likely similar to that used in dogs. Respiratory depression, ataxia and sedation are common AEs and it is recommended that PB loading be performed in the hospital setting, particularly when the maximum total loading dose is administered. In dogs and cats with pre-existing hepatic disease, the use of PB is not recommended and LEV could be used instead. In animals with a history of severe lethargy and respiratory and cardiovascular depression after PB and/or DZP administration, LEV is preferable. Lastly, it is important to remember that if an animal is on maintenance PB therapy, blood should be collected to assess serum concentrations before any adjustments in PB dosage are performed.

Levetiracetam

Levetiracetam has gained popularity as an ASD in emergency seizure management due to its rapid onset of action and favorable safety profile. Based on systematic reviews/meta-analyses on ASDs, LEV is considered one of the safest ASDs in both dogs[82] and cats[83]. Levetiracetam binds to synaptic vesicle protein 2A in neurons and modifies the calcium-dependent exocytosis of neurotransmitters, causes a presynaptic decrease in glutamate-mediated excitatory transmission and may also have neuroprotective effects.[86–89]

Levetiracetam can be given at a dose of 20–60 mg/kg IV, rectally or PO. In dogs, IV administration at a dose of 60 mg/kg can achieve desired serum concentrations for up to 8 hours.[90] Intravenous LEV can be administered undiluted as a slow bolus over 5 minutes.[91] There is an isolated case report of cardiorespiratory collapse in a dog administered LEV at a dose of 60 mg/kg as a rapid IV injection.[92] Rectal LEV administration (40 mg/kg) can also achieve desired serum concentrations.[93,94] Intramuscular and, to a lesser extent, subcutaneous (SC) administration have also been reported as safe alternative routes.[95] The authors recommend a LEV loading dose of 60 mg/kg IV followed by 20 mg/kg IV or PO every 8 hours until the dog or cat

is seizure-free for 48 hours, at which time LEV can be discontinued if not recommended as part of the maintenance ASD regimen. In dogs administered PB for 4 or more weeks, a higher LEV dose (within the reference range) might be needed as PB increases LEV clearance.[96] In a double-blinded, placebo-controlled randomized study, 19 dogs with SE or cluster seizures that initially received DZP were administered either LEV (30–60 mg/kg) or placebo IV. Seizure activity cessation with no relapse occurred in 56% of dogs in the LEV group compared to 10% of dogs in the placebo group, but this difference was not statistically significant.[91] In human SE, LEV has been shown to be equally effective to BZD administration, although individuals administered LEV were less likely to experience respiratory or cardiovascular depression.[97] Such a comparison has not been performed in veterinary medicine and no further studies have compared LEV to other ASDs in the emergency management of seizures.

The adverse effects of LEV are mild to moderate and dose-dependent (mainly sedation and ataxia),[82] which is ideal for animals suffering from severe CNS and/or respiratory and cardiovascular depression. Also, LEV is not metabolized in the liver, making this ASD preferable to PB or DZP in individuals with impaired hepatic function. Levetiracetam is excreted by the kidneys, which limits PK interactions with other ASDs, but its use can be problematic in animals with impaired kidney function and a dose decrease should be considered in these patients.

Phenytoin/fosphenytoin

Phenytoin is used in human SE[98] and acts by inhibiting voltage-gated sodium channels and calcium flux across neuronal membranes.[99] In dogs, the use of phenytoin is not advised due to AEs (severe hypotension and local soft tissue reaction after IV and IM administration, respectively) or PK limitations (variable $t_{1/2}$ and absorption after IV and IM administration, respectively).[100–102] In cats, phenytoin's effects can last up to 108 hours due to the drug's limited ability to conjugate with glucuronic acid.[103]

Fosphenytoin sodium is a phosphate ester prodrug of phenytoin. Fosphenytoin is hydrophilic, which allows parenteral solutions to be prepared without the need for a propylene glycol vehicle, and results in safe and rapid absorption after IM administration.[99,104] After administration, fosphenytoin is converted to phenytoin, which is responsible for the drug's antiseizure action.[99] Fosphenytoin has improved tolerability and is less

likely to cause pain and phlebitis in humans than phenytoin when administered IV, but hypotension and arrhythmias may still occur.[105] Although fosphenytoin can be infused more rapidly than phenytoin, the time needed to achieve desired serum concentrations for the two drugs is similar due to the time needed for the conversion of fosphenytoin to phenytoin.[99,104] In dogs, approximately 80% of fosphenytoin is converted to phenytoin within 30 minutes after IV administration.[106] In a PK study in healthy dogs, fosphenytoin administered at the dose of 15 mg/kg IV resulted in unbound phenytoin plasma concentrations within the reference range (1.0–2.0 μg/mL) used to treat SE in humans within 30–60 minutes of administration and without any significant AEs.[107] In a double-blinded, placebo-controlled randomized study comparing fosphenytoin to a placebo in canine SE, it was demonstrated that seizure cessation was achieved in 63% of dogs administered 15 mg/kg phenytoin equivalent of fosphenytoin compared to 22% of dogs in the placebo group. Vomiting was the most significant drug-related AE.[108]

Anesthetic antiseizure drugs

Propofol

Propofol is a common anesthetic drug with a very short $t_{1/2}$ allowing for quick control of anesthetic depth and recovery.[14,109] Propofol is cleared more rapidly and induces less severe hypotension than barbiturates. Propofol acts on GABA receptors (in sites different from those of BZDs and PB) and NMDA receptors, and regulates slow calcium ion channels.[109,110] In people, propofol is an effective treatment for established and refractory SE.[109,111,112] In veterinary medicine, propofol has been used to manage seizure activity after surgery for portosystemic shunts and SE unresponsive to BZDs and PB.[113–116] The use of a CRI rather than repeat boluses is advised due to propofol's short duration of action. A bolus of 1.0–6.0 mg/kg IV can be administered, followed by a CRI of 0.1–0.6 mg/kg/minute. The IV CRI should be administered for a minimum of 6 hours; thereafter, the IV CRI can be continued (i.e., for 24 hours) if seizure activity relapses.

Adverse effects include cardiovascular and respiratory depression, pain at the injection site and loss of gag reflex (predisposing animals to aspiration pneumonia).[117] Therefore, cardiovascular and respiratory function should be closely monitored, and endotracheal intubation should be

anticipated. Propofol is usually formulated with 2% benzyl alcohol to prolong the drug's shelf life. This formulation is not labelled for CRI use, as it may cause neurological or cardiovascular AEs, although, in a study in cats, no significant differences were detected between animals receiving several propofol boluses at a dose of up to 24 mg/kg with and without 2% benzyl alcohol.[118] Propofol CRI is not advised in cats as it may cause Heinz body anemia and prolonged recovery time.[119] In people, a propofol-infusion syndrome (cardiac dysfunction, hyperkalemia, rhabdomyolysis, and acidosis) with high morbidity and mortality has been reported after prolonged anesthesia.[14] However, such an event has not been reported in veterinary medicine to date. Lastly, seizure-like phenomena have been reported with propofol administration in humans and animals, likely related to glycine antagonism at the level of the spinal cord.[115,120] This usually occurs after anesthetic induction, due to changes in propofol serum concentrations.[121] Epileptic seizure activity has been detected on electroencephalogram (EEG) monitoring during these seizure-like phenomena in some studies, although no epileptic activity has been shown in others.[122–124] Therefore, EEG monitoring would be beneficial during propofol infusion to distinguish true epileptic seizure activity from seizure-like phenomena.

Ketamine +/- dexmedetomidine

Ketamine is an anesthetic and analgesic drug that acts as an NMDA glutamate receptor antagonist, thereby decreasing the excitatory activity of glutamate that is overexpressed in refractory SE stages.[125] Ketamine also has neuroprotective effects by inhibiting NMDA receptor–mediated glutamate excitotoxicity and neuronal cell necrosis.[125] Ketamine can be used in refractory SE, where it might be effective in controlling seizure activity based on human[33,126–129] and canine studies[130,131]. Although ketamine administration is considered beneficial for (super)refractory SE, there are reports that ketamine might potentially reduce the seizure threshold.[126,132,133] This could be problematic in individuals with increased intracranial pressure or a pre-existing epileptic disorder. Ketamine can be administered as a bolus at a dose of 3.0–5.0 mg/kg IV, followed by a CRI of 0.1–0.5 mg/kg/hour. A recent retrospective study of 15 dogs suggested that ketamine boluses (5.0 mg/kg IV) might be useful in the treatment of refractory SE.[134] Regarding the safety profile, experimental studies in rats

showed that ketamine administration can lead to cholinergic excitotoxicity via NMDA receptor antagonism, which can cause degenerative alterations in neurons.[135] These changes have not been reported in dogs administered ketamine for SE,[130] although the potential risk cannot be excluded. Other AEs that occur primarily with high dosages include cardiorespiratory depression, seizures, muscle tremors and vomiting.

Dexmedetomidine is an α_2-adrenoreceptor agonist that acts by decreasing excitatory neurotransmitters via suppression of sympathetic nervous system stimulation and noradrenaline release, mainly in the regions of the amygdala, hippocampus and cerebral cortex.[136,137] In addition, dexmedetomidine has neuroprotective properties,[138] decreases cerebral metabolic and oxygen demands (which are significantly increased during SE), induces vasoconstriction (which can decrease brain edema resulting from seizure activity) and helps maintain a normal mean arterial pressure.[116] In a study in cats, microinfusion of an α_2-adrenoreceptor agonist into the amygdala led to protection against seizure induction.[139] In rats, dexmedetomidine administration led to the termination of refractory SE.[137,140] Dexmedetomidine can also be beneficial in reducing agitation during recovery. It can be administered as a bolus at the dose of 0.5–3.0 µg/kg IV, followed by a CRI of 0.5–7.0 µg/kg/hour.[131] Adverse effects include shallow respiration, bradycardia, cardiac arrhythmias and hypothermia.

According to a case report of 3 dogs with IE that presented with super-refractory SE, the use of a ketamine-dexmedetomidine combination and induction of mild hypothermia (36.7–37.7 °C) resulted in their complete recovery.[131] Dogs were administered an IV bolus of ketamine (1 mg/kg) followed by dexmedetomidine (3 µg/kg), and then a CRI of ketamine (1 mg/kg/hour) and dexmedetomidine (3–7 µg/kg/hour) for 12 hours. Continuous rate infusion of ketamine-dexmedetomidine likely preserves respiratory function and swallowing reflex (thus, endotracheal intubation is not needed), and replacement of propofol CRI after 24 hours with ketamine-dexmedetomidine CRI may limit propofol's adverse effects.[116, 131]

Pentobarbital

Pentobarbital and sodium thiopental (thiopentone) are barbiturates used to induce general anesthesia and terminate seizures in cases of refractory

SE.[141,142] They may also scavenge oxygen free radicals and reduce cerebral oxygen consumption.[143] Pentobarbital is most commonly used in the treatment of SE and can be given at the dose of 3.0–15 mg/kg IV to effect, but it should be closely monitored as overdose can be fatal. Barbiturates can cause significant cardiovascular and respiratory depression, hypotension, and hypothermia. Sodium thiopental administration in animals carries a higher risk of cardiac toxicity compared to pentobarbital. During recovery from both pentobarbital and sodium thiopental administration, animals may display seizure-like movements and vocalize, and this can pose a clinical challenge as these phenomena might be misinterpreted as epileptic seizures.[141,143] Electroencephalography might be useful to differentiate epileptic seizures from these phenomena.

Inhalation anesthetics

Inhalation anesthetics are usually reserved for refractory SE and act by enhancing the inhibitory effect of GABA receptors, by decreasing thalamic neuronal membrane excitability, and by increasing cerebral blood flow while minimizing oxygen cerebral consumption.[144,145] Isoflurane and desflurane, two inhalation anesthetics, result in dose-dependent suppression of spontaneous epileptiform discharges in humans.[146,147] These two agents are preferred over others because only a small percentage of these drugs is metabolized by the liver, resulting in a reduced risk of liver toxicity.[148] Halothane is another option, but the risk of hepatotoxicity is higher due to its higher degree of hepatic metabolism.[149] Similarly, sevoflurane can also damage the liver and have epileptogenic properties. Veterinary studies are lacking, although the use of isoflurane for refractory SE in animals has been suggested.[141] Inhalation anesthetics require endotracheal intubation and ventilation, and can cause hypotension as they decrease systemic vascular resistance.[141] Lastly, EEG may be useful to evaluate the effects of inhalation agents, titrate their dose, and, therefore, reduce the risk of AEs.

Nonpharmacological interventions

Neurostimulation techniques—including vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and electroconvulsive therapy—have been investigated in humans with refractory and super-refractory SE, demonstrating a favorable safety profile and variable success rates (VNS, 67%; rTMS, 43.5%; DBS, 75%;

electroconvulsive therapy, 59%).[150] In dogs, neurostimulation is at an early stage of evaluation: only two clinical trials have investigated the efficacy and safety of VNS in dogs with IE,[151,152] three preclinical studies have evaluated the VNS procedure and its mechanism of action in healthy dogs,[153–155] and one clinical trial has evaluated the efficacy and safety of rTMS in dogs with drug-resistant IE[156] (see Chapter 18). To date, no clinical trials on SE have been performed. Manual vagal maneuvers such as ocular compression and carotid massage have been reported as noninvasive beneficial adjunctive management options, but evidence is lacking to support their efficacy. In humans, there is some evidence to suggest that the use of magnesium, immunoglobulin IV and ketogenic diets might be beneficial adjunctive options to ASDs, especially for super-refractory SE,[14,157,158] but these options have not been evaluated in veterinary medicine.

Management of status epilepticus complications

Initial assessment

An assessment of a patient's airway and breathing, followed by cardiovascular parameters and neurological status should be performed. The clinician should carefully evaluate the findings from the general physical examination, which should include, but is not limited to, respiratory rate and pattern, heart rate and rhythm, arterial oxygenation, blood pressure, body temperature, and urine production and specific gravity, as well as a neurological examination (Fig. 19.6); these are essential for early and prompt management of SE complications. Alterations in these parameters can also be secondary to the effects of ASDs or the underlying SE etiology.

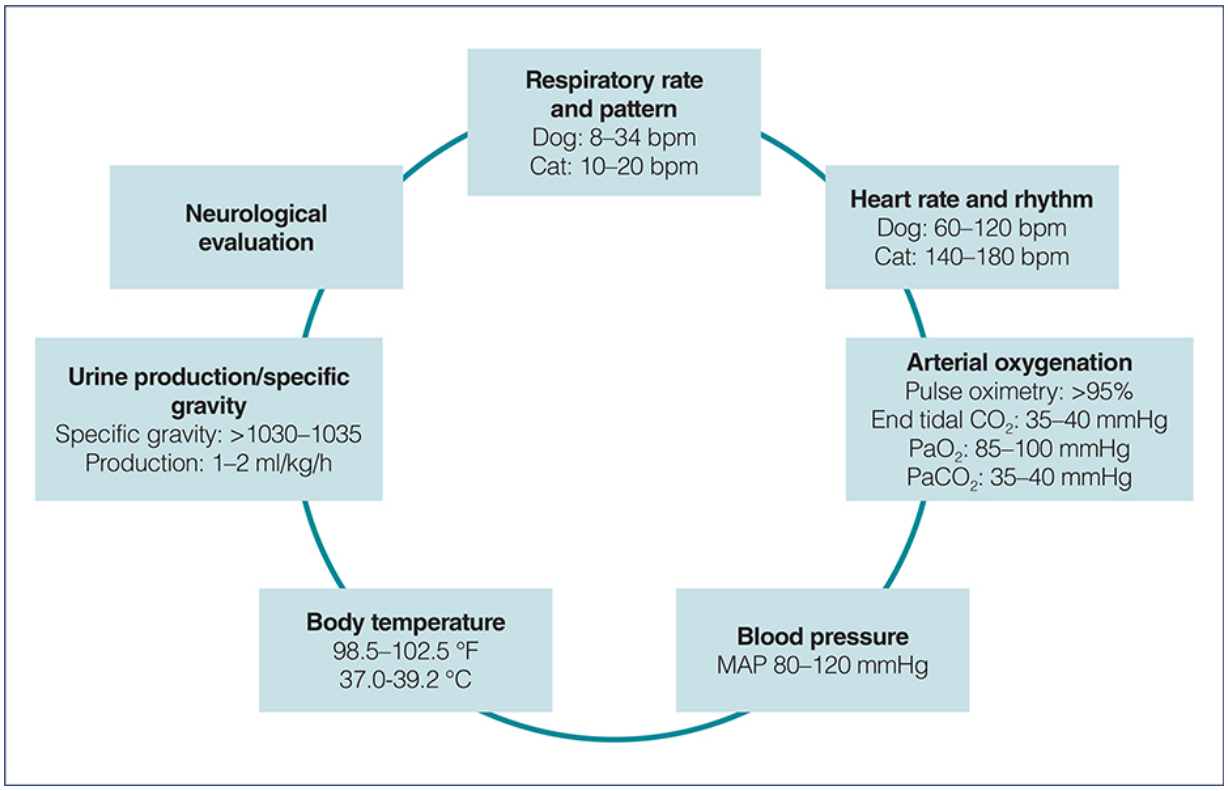


FIGURE 19.6. Monitoring of animals with status epilepticus.
PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; MAP, mean arterial pressure.

Laboratory evaluation

It is vital to perform hematology; serum biochemistry; lactate, acid–base and arterial blood gas analysis; and urinalysis to identify systemic abnormalities. Measuring ASD serum concentrations in animals receiving maintenance therapy is also necessary to identify deficiencies in the chronic drug management of epileptic seizures and adjust drug dosages for better seizure control (see Chapter 9 and ASD-specific chapters). Lactate levels can be a useful marker for defining mortality and seizure severity, but is likely less reliable for tissue hypoxia.[159] Appropriate IV fluid therapy is vital in managing acid–base and electrolyte abnormalities and maintaining normotension and normovolemia. Specific recommendations are included in Box 19.3.

Assessment of blood pressure and intravascular volume status

In case of hypovolemia and hypotension, IV crystalloid fluid administration is essential to restore normotension (mean arterial pressure [MAP] of 80–

120 mmHg) to avoid brain and systemic tissue hypoperfusion and ischemia.

Cerebral perfusion pressure (CPP) is related to MAP and intracranial pressure (ICP) according to the formula:

$$CPP = MAP - ICP$$

Therefore, decreased MAP due to hypotension or hypovolemia or increased ICP can have a negative impact on CPP. Up to a degree, the brain can utilize autoregulatory mechanisms to preserve normal CPP (50–150 mmHg). However, severe systemic hypotension or hypovolemia as well as SE can lead to a failure in autoregulation resulting in a decrease in CPP.[160] Hypoxemia (PaO_2 <50 mmHg) should be managed aggressively, because normal blood oxygenation helps prevent tissue ischemia and ICP increase due to enhanced cerebral blood flow. Performing arterial blood gas analysis, using pulse oximetry and evaluating the end-tidal CO_2 will reveal the degree of hypoxemia and ventilation status.[161]

BOX 19.3. Recommendations for the monitoring and treatment of dogs and cats with status epilepticus.

- In case of hypocalcemia (serum ionized calcium concentration <1.1 mmol/L or 4.5 mg/dL):
  - Administration of 10% calcium gluconate at a dose of 0.5–1.5 ml/kg slowly IV over 10 minutes is advised.
  - Heart rate and rhythm should be monitored, ideally via an electrocardiogram, and calcium gluconate administration should be stopped if bradycardia occurs.
  - Long-term administration of calcium at a dose of 25 mg/kg PO every 8–12 hours and calcitriol at the dose of 2.5–10 ng/kg PO every 24 hours, as well as regular monitoring of calcium serum concentration might be required.
- In case of sodium abnormalities (hyponatremia: serum sodium concentration <140 mmol/L or mEq/L for dogs and <150 mmol/L or mEq/L for cats; hypernatremia: serum sodium concentration >150 mmol/L or mEq/L for dogs and >160 mmol/L or mEq/L for cats):
  - These should be corrected slowly with appropriate IV fluid therapy, especially if the abnormalities are suspected to have been present for >24 hours, since rapid correction can result in further neurological complications and decline.
  - Serum sodium concentration should be monitored regularly, initially every 2–4 hours, to ensure that the rate of correction is acceptable, and to allow for appropriate IV fluid therapy adjustments.
- In case of hypoglycemia (serum glucose concentration <3.3 mmol/L or 60 mg/dL):
  - A bolus of 50% dextrose at the dose of 0.5–1.0 mL/kg IV should be administered.
  - Dilution is advised to decrease the risk of phlebitis related to the hyperosmolar dextrose solution.
  - Alternatively, dextrose can then be added to IV fluids aiming to create a 2.5% or 5% solution.
- In case of hyperthermia (core body temperature >40 °C):

- Cooling measures to reduce body temperature (37.0–39.0 °C) should be applied.
- Effective IV fluid therapy and seizure activity cessation will also lead to normothermia.

Monitoring for signs of increased intracranial pressure

Special consideration should be given when systemic hypertension combined with severe CNS depression and reflex bradycardia (Cushing's reflex) are present, as this can indicate increased ICP. In Cushing's reflex, increased ICP causes a rise in MAP as the brain tries to maintain normal CPP (CPP = MAP – ICP). Reflex bradycardia can occur due to increased MAP, but in animals with hypovolemia, it might not be present. Immediate measurements should be taken to decrease ICP via the use of hyperosmolar therapy (e.g., mannitol, hypertonic saline). Hyperosmolar therapy decreases the water content in the CNS, but it requires an intact BBB.[162] Mannitol is an osmotic agent that increases plasma osmolality and creates an osmotic gradient between the brain's intravascular space and the extracellular space. This gradient causes free water, but not electrolytes, to move from the parenchyma into the plasma, and therefore cerebral edema and ICP are decreased. Another property of mannitol is that it acts as a free radical scavenger and minimizes oxidative injury to the brain. Mannitol can be administered at the dose of 0.5–2.0 g/kg IV slowly (over 20–30 minutes) through a filter. A decrease in ICP is expected within 30 minutes of administration, and the duration of action may last up to 6–8 hours.[163] Additional boluses can be administered as needed every 6–8 hours; CRI is not advised because the osmotic gradient responsible for removing water from the brain is lost with constant administration of mannitol. Adverse effects include electrolyte imbalance, hypovolemia, and cardiovascular collapse due to free water diuresis and, thus, it should not be administered in hypovolemic animals and should always be combined with appropriate IV fluid therapy to correct any dehydration. Acute kidney injury can occur with high doses of mannitol due to intrarenal vasoconstriction and hypovolemia.[162] Hypertonic saline (7%) is another hyperosmolar agent that also decreases ICP through osmotic effects when administered at the dose of 2–4 mL/kg IV slowly (over 15–20 minutes). Adverse effects include hypervolemia due to intravascular volume expansion and hypernatremia. The choice of hypertonic saline or mannitol for the management of increased ICP is not yet clear in veterinary medicine, although a systematic

review/meta-analysis in humans showed that mannitol is more effective than hypertonic saline.[164]

Monitoring neurological status

It is important to perform a baseline neurological examination upon presentation to compare to follow-up neurological examinations; such examinations are advised to be frequent, as alterations in neurological status in animals presented with SE can be sudden. Particular attention should be given to the level of consciousness, posture, menace response, cranial nerve and spinal reflexes as well as size, symmetry and responsiveness of the pupils to light. Using a good light source such as a Finoff transilluminator or slit lamp can help to accurately assess the pupillary light reflex. The assessment of some parameters (e.g., level of consciousness) can be affected by the anesthetic and nonanesthetic ASDs used. Bilateral miosis can be associated with a diencephalic lesion or diffuse CNS disease, while mydriatic pupils unresponsive to light can indicate a severe or irreversible midbrain lesion or caudal transtentorial herniation. Increased sympathetic tone can also be a cause of mydriasis, but the pupils would still be expected to respond to light. Progression from miotic to mydriatic pupils can indicate rising ICP and rapid intervention should be initiated.[165] With respect to postural abnormalities, decerebellate rigidity (extension of the thoracic limbs, hip flexion and opisthotonos with unaffected consciousness) is related to a cerebellar lesion or cerebellar herniation and decerebrate rigidity (extension of all limbs, opisthotonos and severely depressed level of consciousness) indicates brainstem compression secondary to severe intracranial lesion, increased ICP or herniation.[166]

Additional measurements and procedures

Adequate pain relief medication should be provided if the animal shows signs of pain, as uncontrolled pain can lead to increased ICP.[167] Stress and procedures such as performing jugular compression or placing a cervical bandage or nasal tubes (e.g., nasogastric tubes and oxygen delivery tubes) should be limited as they can also lead to increased ICP.[166] Urinary catheterization is advised for monitoring urine production and for hygiene purposes. Soft bedding should be provided, and recumbent position should be changed every 4 hours to prevent decubital ulcers and lung atelectasis.

Lubricating the eyes in anesthetized animals or animals unable to blink is important to prevent ophthalmological complications.[166,168]

Electroencephalography is routinely performed in humans with SE, not only because it differentiates epileptic seizures from other paroxysmal events or disorders causing impaired consciousness, but also because it provides vital information regarding the location of the epileptogenic foci as well as a prognosis and guidance for ASD continuation or treatment endpoints.[169,170] In addition, EEG can provide early data about brain function in case of increased ICP and cerebral ischemia, which can be useful in comatose patients where clinical examination is impractical, and in the diagnosis of nonconvulsive SE.[171–174] Although EEG may provide similar information in dogs with SE (see Chapter 7), it is not routinely performed in veterinary medicine.[175–177] In one study in dogs, EEG was used to diagnose nonconvulsive SE that persisted after the termination of convulsive seizures by anesthetic drugs, and helped guide the ASD treatment plan.[178] In a case report involving a cat, EEG was used to diagnose nonconvulsive SE and set the PB-related therapeutic endpoint.[179] In the absence of EEG, nonconvulsive SE should be suspected in any case with a prolonged period of impaired consciousness following successful management of convulsive seizures, especially after the withdrawal of any general anesthetic or sedative drugs.[180]

Following stabilization of the animal and appropriate management of seizures and SE complications, further diagnostic investigation should be performed to identify the underlying cause of SE (see Chapter 1).

Cluster seizures

Cluster seizures (CS) are defined as the occurrence of ≥2 epileptic seizures over a 24-hour period with complete recovery between epileptic seizure events.[3] Except for SE, most epileptic seizures are self-limiting and do not require immediate or urgent intervention. In the case of CS, there is a defect in the termination mechanisms or increased excitation leading to repetitive epileptic seizure events.[181] In addition, it has been reported that epileptic seizures occurring within 8 hours from the first seizure are likely to

originate from the same epileptogenic foci in humans.[182] This suggests that the initial epileptogenic foci might progress to more excitable (or less inhibited) stages following the first seizure, resulting in CS. These mechanisms, although still unproven, are likely to also occur in dogs. Cluster seizures can occur with either IE or structural epilepsy. Approximately 38–77% of dogs with IE experience CS at least once in their lifetime.[10,183] Up to 94% of Border collies with IE experience CS,[184,185] while 20% and 48% of Australian shepherds with IE manifest CS or both CS and SE, respectively.[186] In cats, CS occurred in 53% and 59% of animals with IE and SE, respectively.[187] Risk factors associated with CS in dogs include gender and neutering status, as well as breed. Specifically, intact dogs have 1.4 times the odds of developing CS compared to neutered dogs, and intact males have twice the odds compared to neutered males. Female dogs have more CS episodes than males, and these episodes are more frequent in intact females than in neutered females.[10] This might be related to hormonal differences, since estrogen has been shown to increase neuronal excitability (proconvulsive effect), while progesterone decreases neuronal excitability (protective effect against epileptic seizures).[188] Testosterone appears to have a less consistent effect.[189] With respect to breed predispositions, Boxers, Rottweilers and German Shepherd dogs were found to be significantly more likely to develop CS.[10,183] In another study, English Foxhounds, Lakeland Terriers, Boston Terriers, toy Poodles and Pugs presented with a higher incidence of CS; 35.1% of these dogs had structural epilepsy.[4] In humans an association between SE and CS is likely present,[190] although no association has been found in dogs.[6,10]

THERAPY

Predicting the occurrence of epileptic seizures would allow treatment to be initiated prior to such events and to prevent CS. However, apart from clinical features (e.g., recognition of prodromal stage, see Chapter 1), which are not always identified, particularly by owners, there is currently no specific method of prediction.

In general, the authors recommend a three-step system for CS management in dogs and cats. An algorithm providing details and

clarifications for the at home management of CS is provided in Figure 19.7. Treatment in the hospital setting is similar to that for SE (see Fig. 19.2). First, to minimize the risk of CS occurrence, it is important to optimize maintenance ASD dosage (see chapters 9, and 10–15). Second, when CS occurs, short-acting treatment can be administered during or immediately after the first epileptic seizure (if the animal is known to always exhibit CS when epileptic seizures occur) or, more commonly, during or after the second seizure within a time frame of 24 hours, with the aim of stopping and preventing further events. Benzodiazepines are an ideal and potent short-acting treatment option in dogs and, as discussed for SE, these can be given IV, IN, IM or rectally either at home or in the hospital. Based on a study in 11 dogs with CS, R-DZP administered at a dose of 0.5 mg/kg provided a significant decrease in the number of CS in a 24-hour period compared to baseline, although its effect was not compared to a control treatment group.[191] In the hospital setting, in particular, IN-MDZ or IV boluses of MDZ or DZP (repeated up to 3 times in a 24-hour period, but not more frequently than every 5 minutes) can be administered. Midazolam IV CRI can be initiated if there is inadequate seizure control or no response to boluses. Based on a recent retrospective study, MDZ CRI was safe and successful in controlling seizures in 81% (64/79) of dogs with CS.[28] In cats, options are limited (particularly at home), but IV MDZ can be administered in the hospital setting. Lastly, long-acting medication should be given with the aim of preventing further epileptic seizures in the near future. Specifically, for animals that already receive maintenance ASD therapy (e.g., PB), an additional dose can be administered after every epileptic seizure; these can be repeated at a minimum of 1-hour intervals and up to a maximum of three times in a 24-hour period. In animals that do not receive any ASDs, treatment initiation with a loading dose of PB (see SE section) can be considered.

Another option of long-acting medication is administration of LEV as a pulse therapy in both dogs and cats. Levetiracetam's PK parameters are favorable for CS, even with oral administration.[95] Levetiracetam is most commonly administered orally to control CS in out-of-hospital settings. Levetiracetam pulse therapy includes an initial dose of 60 mg/kg after the first or second seizure, followed by 20 mg/kg every 8 hours until no epileptic seizures occur for 48 hours.[192] Pulse therapy has been recommended instead of long-term continuous therapy, because it might

reduce the development of tolerance with the drug's chronic use.[192] In dogs that are on chronic PB therapy, a higher dose of LEV may be needed.[192] Animals can have depressed consciousness and a reduced swallowing reflex during the postictal phase, and the oral route should not be used if the animal is not able to prehend and swallow food to minimize the risk of aspiration. Postictal aggression may also occur, and this can pose further risks to the owner when administering oral drugs (in such cases the medication can be disguised in a small amount of food and be given to the animal to eat independently). Rectal administration of LEV at a dose of 40 mg/kg has been also suggested as a successful alternative to oral dosing in dogs.[93,94,193] Within hospital settings, IV administration of LEV is recommended in both dogs and cats. Levetiracetam is a safe drug, with sedation and ataxia as the main AEs that occur more often with high doses (approximately 40% of dogs receiving 60 mg/kg PO may manifest ataxia and/or sedation).[192]

Pulse therapy with longer acting BZDs, such as clonazepam or clorazepate, have also been used for home treatment of CS in dogs, although no studies evaluating their use have been published. Clonazepam is administered orally at a dose of 0.5–2.0 mg/kg after the first seizure as soon as the dog can safely take oral medication, and then every 8–12 hours until the seizure cycle is broken. Clorazepate can be used in a similar manner, at an oral dose of 0.5 mg/kg PO every 8–12 hours. These drugs can be administered in conjunction with rectal or intranasal BZDs and other prescribed ASDs, but should not be used for more than a few days in dogs to prevent the development of tolerance. Neither clonazepam nor clorazepate are recommended for use in cats due to the potential for hepatotoxicity. Further information on these drugs can be found in Chapter 15.

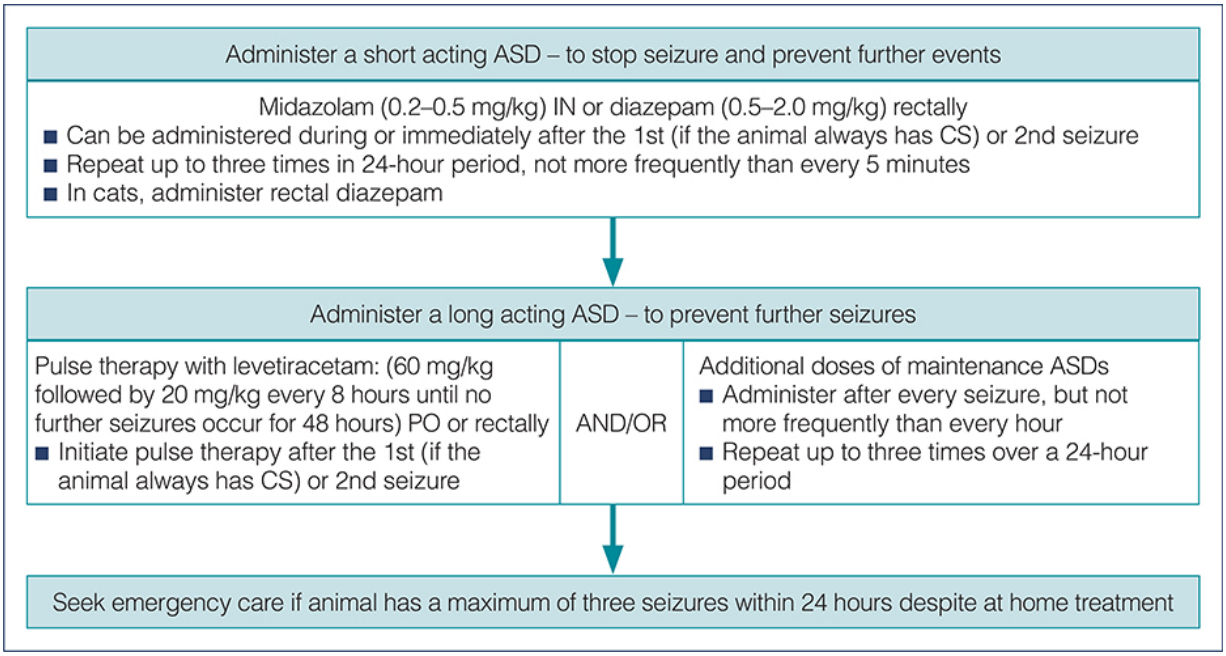


FIGURE 19.7. Algorithm for at-home treatment for dogs and cats with cluster seizures. ASD, antizeisure drug; IN, intranasal; PO, per os; CS, cluster seizures.

TAKE-HOME MESSAGES

- ✔ Status epilepticus and CS are frequent neurological emergencies in dogs and cats associated with high morbidity and mortality, if left untreated.
- ✔ Immediate treatment is vital because SE can cause severe brain and systemic complications, and progress to more drug-resistant stages over time.
- ✔ Successful at-home management of seizures is important because it can:
  - ✔ Prevent seizure progression to SE.
  - ✔ Reduce the risk of SE progression to more drug-resistant stages.
  - ✔ Prevent complications related to continuous seizure activity, hospitalization and adverse effects from multi-drug therapy.
- ✔ Benzodiazepines are first-line potent and fast-acting drugs against SE in dogs and cats and carry an essential role in successful SE management.

- ✔ Intranasal MDZ is likely effective and safe for terminating SE in dogs and provides potential advantages over other routes of administration.
- ✔ At home, IN-MDZ or R-DZP can be used to control SE in dogs. Rectal DZP can be used in cats (IN-MDZ has not been established in this species).
- ✔ In hospital, both IV- and IN-MDZ as well as IV-DZP can be successful first choices for controlling SE in dogs, while IV-MDZ is preferable in cats; IN-MDZ and, to a lesser extent, IM-MDZ are preferable choices for quick BZD administration in dogs before IV access is established.
- ✔ Necessary combined steps for successful outcomes in SE include:
  - ✔ Multi-drug therapy. Benzodiazepines combined with nonanesthetic and anesthetic ASDs.
  - ✔ Thorough laboratory investigations: blood tests to determine maintenance ASD serum concentrations.
  - ✔ Close monitoring of animal's vital signs.
  - ✔ Treatment of underlying conditions or complications.
- ✔ A combined approach is needed for successful cessation and prevention of CS in dogs and cats including:
  - ✔ Administration of short-acting ASDs.
    - ■ Benzodiazepines:
      - ■ Intranasal midazolam or IV-MDZ or R-DZP in dogs.
      - ■ Intravenous midazolam or R-DZP in cats.
  - ✔ Administration of long-acting ASDs.
    - ■ Additional doses of maintenance ASDs, e.g., PB (for animals already on ASDs).
    - ■ Loading doses of long-term ASDs, e.g., PB (for drug-naïve animals).
    - ■ Levetiracetam pulse therapy.
  - ✔ Monitoring of serum concentrations and dose adjustments of maintenance ASDs (for animals already on ASDs).

REFERENCES

1. Trinka E, Brigo F, Shorvon S. Recent advances in status epilepticus. *Curr Opin Neurol*. 2016; 29(2):189–198.
2. Walker M. Status epilepticus: an evidence based guide. *BMJ*. 2005; 331(7518):673–637.
3. Berendt M, Farquhar RG, Mandigers PJ et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11:182.
4. Bateman SW, Parent JM. Clinical findings, treatment, and outcome of dogs with status epilepticus or cluster seizures: 156 cases (1990-1995). *J Am Vet Med Assoc*. 1999; 215(10):1463–1468.
5. Platt SR, Haag M. Canine status epilepticus: a retrospective study of 50 cases. *J Small Anim Pract*. 2002; 43(4):151–153.
6. Saito M, Muñana KR, Sharp NJ, Olby NJ. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects of status epilepticus on outcome and survival time: 32 cases (1990-1996). *J Am Vet Med Assoc*. 2001; 219(5):618–623.
7. Zimmermann R, Hulsmeyer V, Sauter-Louis C, Fischer A. Status epilepticus and epileptic seizures in dogs. *J Vet Intern Med*. 2009; 23(5):970–976.
8. Knowles K. Idiopathic epilepsy. *Clin Tech Small Anim Pract*. 1998; 13(3):144–151.
9. Packer RM, Shihab NK, Torres BB, Volk HA. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. *PLoS One*. 2014; 9(8):e106026.
10. Monteiro R, Adams V, Keys D, Platt SR. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. *Journal of Small Animal Practice*. 2012; 53(9):526–530.
11. Costello DJ, Cole AJ. Treatment of acute seizures and status epilepticus. *J Intensive Care Med*. 2007; 22(6):319–347.
12. Koestner A. Neuropathology of canine epilepsy. *Probl Vet Med.* 1989; 1(4):516–534.
13. Lothman E. The biochemical basis and pathophysiology of status epilepticus. *Neurology*. 1990; 40(5 Suppl 2):13–23.
14. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain.* 2011; 134(Pt 10):2802–2818.
15. Watson C. Status epilepticus. Clinical features, pathophysiology, and treatment. *West J Med*. 1991; 155(6):626–631.
16. Huff JS, Fountain NB. Pathophysiology and definitions of seizures and status epilepticus. *Emerg Med Clin North Am*. 2011; 29(1):1–13.
17. Falco-Walter JJ, Bleck T. Treatment of established status epilepticus. *J Clin Med*. 2016; 5(5):49.
18. Gollwitzer S, Hamer HM. The treatment and prognosis of refractory and super-refractory status epilepticus. *Aktuel Neurol*. 2017; 44(9):662–688.
19. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. *J Am Vet Med Assoc*. 1995; 206(11):1721–1728.
20. Tesoro EP, Brophy GM. Pharmacological management of seizures and status epilepticus in critically ill patients. *J Pharm Pract*. 2010; 23(5):441–454.

21. Zaccara G, Giannasi G, Oggioni R et al. Challenges in the treatment of convulsive status epilepticus. *Seizure*. 2017; 47:17–24.
22. Naylor DE, Liu H, Wasterlain CG. Trafficking of GABA(A) receptors, loss of inhibition, and a mechanism for pharmacoresistance in status epilepticus. *J Neurosci*. 2005; 25(34):7724–7733.
23. Niquet J, Baldwin R, Suchomelova L et al. Benzodiazepine-refractory status epilepticus: pathophysiology and principles of treatment. *Ann N Y Acad Sci*. 2016; 1378(1):166–173.
24. Pekcec A, Unkruer B, Stein V et al. Over-expression of P-glycoprotein in the canine brain following spontaneous status epilepticus. *Epilepsy Res*. 2009; 83(2-3):144–151.
25. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998; 338(14):970–976.
26. Platt SR, Randell SC, Scott KC et al. Comparison of plasma benzodiazepine concentrations following intranasal and intravenous administration of diazepam to dogs. *Am J Vet Res*. 2000; 61(6):651–654.
27. Horikawa H, Tada T, Sakai M et al. Effects of midazolam on the threshold of lidocaine-induced seizures in the dog--comparison with diazepam. *J Anesth*. 1990; 4(3):265–269.
28. Bray KY, Mariani CL, Early PJ et al. Continuous rate infusion of midazolam as emergent treatment for seizures in dogs. *J Vet Intern Med*. 2020; 35(1):388–396.
29. Rossetti AO. Treatment options in the management of status epilepticus. *Curr Treat Options Neurol*. 2010; 12(2):100–12.
30. Winsnes M, Jeppsson R, Sjoberg B. Diazepam adsorption to infusion sets and plastic syringes. *Acta Anaesthesiol Scand*. 1981; 25(2):93–96.
31. Calisto V, Domingues MR, Esteves VI. Photodegradation of psychiatric pharmaceuticals in aquatic environments--kinetics and photodegradation products. *Water Res*. 2011; 45(18):6097–6106.
32. Walker MC, Tong X, Brown S et al. Comparison of single- and repeated-dose pharmacokinetics of diazepam. *Epilepsia*. 1998; 39(3):283–289.
33. Mazarati AM, Baldwin R, Klitgaard H et al. Anticonvulsant effects of levetiracetam and levetiracetam-diazepam combinations in experimental status epilepticus. *Epilepsy Res*. 2004; 58(2-3):167–174.
34. Aldawsari MF, Lau VW, Babu RJ at al. Pharmacokinetic evaluation of novel midazolam gel formulations following buccal administration to healthy dogs. *Am J Vet Res*. 2018; 79(1):73–82.
35. Hansen BD. Analgesia and sedation in the critically ill. *J Vet Emerg Crit Car*. 2005; 15:285.
36. Charalambous M, Volk HA, Van Ham L, Bhatti SF. First-line management of canine status epilepticus at home and in hospital – opportunities and limitations of the various administration routes of benzodiazepines. *BMC Vet Res*. 2021; 17(1):103.
37. Pang T, Hirsch LJ. Treatment of convulsive and nonconvulsive status epilepticus. *Curr Treat Options Neurol*. 2005; 7(4):247–259.
38. Sirven JI, Waterhouse E. Management of status epilepticus. *Am Fam Physician*. 2003; 68(3):469–476.
39. Alldredge BK, Gelb AM, Isaacs SM et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med*. 2001; 345(9):631–637.
40. Lowenstein DH, Cloyd J. Out-of-hospital treatment of status epilepticus and prolonged seizures. *Epilepsia*. 2007; 48 Suppl 8:96–98.

41. Dieckmann RA. Rectal diazepam for prehospital pediatric status epilepticus. *Ann Emerg Med*. 1994; 23(2):216–224.
42. Alldredge BK, Wall DB, Ferriero DM. Effect of prehospital treatment on the outcome of status epilepticus in children. *Pediatr Neurol*. 1995; 12(3):213–216.
43. Dreifuss FE, Rosman NP, Cloyd JC et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med*. 1998; 338(26):1869–1875.
44. Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet*. 1999; 353(9153):623–626.
45. Mealey KL, Boothe DM. Bioavailability of benzodiazepines following rectal administration of diazepam in dogs. *J Vet Pharmacol Ther*. 1995; 18(1):72–74.
46. Papich MG, Alcorn J. Absorption of diazepam after its rectal administration in dogs. *Am J Vet Res*. 1995; 56(12):1629–1636.
47. Probst CW, Thomas WB, Moyers TD et al. Evaluation of plasma diazepam and nordiazepam concentrations following administration of diazepam intravenously or via suppository per rectum in dogs. *Am J Vet Res*. 2013; 74(4):611–615.
48. Wagner SO, Sams RA, Podell M. Chronic phenobarbital therapy reduces plasma benzodiazepine concentrations after intravenous and rectal administration of diazepam in the dog. *J Vet Pharmacol Ther*. 1998; 21(5):335–341.
49. Jannin V, Lemagnen G, Gueroult P et al. Rectal route in the 21st Century to treat children. *Adv Drug Deliv Rev*. 2014; 73:34–49.
50. Charalambous M, Bhatti SFM, Van Ham L et al. Intranasal midazolam versus rectal diazepam for the management of canine status epilepticus: a multicenter randomized parallel-group clinical trial. *J Vet Intern Med*. 2017; 31(4):1149–1158.
51. Anderson GD, Saneto RP. Current oral and non-oral routes of antiepileptic drug delivery. *Adv Drug Deliv Rev*. 2012; 64(10):911–918.
52. Hong SS, Oh KT, Choi HG, Lim SJ. Liposomal Formulations for nose-to-brain delivery: recent advances and future perspectives. *Pharmaceutics*. 2019; 11(10):540.
53. Kapoor M, Cloyd JC, Siegel RA. A review of intranasal formulations for the treatment of seizure emergencies. *J Control Release*. 2016; 237:147–159.
54. Lahat E, Goldman M, Barr J et al. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ*. 2000; 321(7253):83–86.
55. Mahmoudian T, Zadeh MM. Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav*. 2004; 5(2):253–255.
56. Javadzadeh M, Sheibani K, Hashemieh M, Saneifard H. Intranasal midazolam compared with intravenous diazepam in patients suffering from acute seizure: a randomized clinical trial. *Iran J Pediatr*. 2012; 22(1):1–8.
57. Ugwoke MI, Exaud S, Van Den Mooter G et al. Bioavailability of apomorphine following intranasal administration of mucoadhesive drug delivery systems in rabbits. *Eur J Pharm Sci*. 1999; 9(2):213–219.
58. Varshosaz J, Sadrai H, Alinagari R. Nasal delivery of insulin using chitosan microspheres. *J Microencapsul*. 2004; 21(7):761–774.
59. Varshosaz J, Sadrai H, Heidari A. Nasal delivery of insulin using bioadhesive chitosan gels. *Drug Deliv*. 2006; 13(1):31–38.

60. Furubayashi T, Kamaguchi A, Kawaharada K et al. Evaluation of the contribution of the nasal cavity and gastrointestinal tract to drug absorption following nasal application to rats. *Biol Pharm Bull*. 2007; 30(3):608–611.
61. Leonard AK, Sileno AP, Brandt GC et al. In vitro formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response in vivo. *Int J Pharm*. 2007; 335(1-2):138–146.
62. Cattet MR, Caulkett NA, Wilson C et al. Intranasal administration of xylazine to reduce stress in elk captured by net gun. *J Wildl Dis*. 2004; 40(3):562–565.
63. Duque JC, Oleskovicz N, Guirro EC et al. Relative potency of ketamine and S(+)-ketamine in dogs. *J Vet Pharmacol Ther*. 2008; 31(4):344–348.
64. Gerritsmann H, Stalder GL, Seilern-Moy K et al. Comparison of S(+)-ketamine and ketamine, with medetomidine, for field anaesthesia in the European brown hare (Lepus europaeus). *Vet Anaesth Analg*. 2012; 39(5):511–519.
65. Micieli F, Santangelo B, Napoleone G, Di Dona F, Mennonna G, Vesce G. Intranasal fentanyl for acute severe pain episodes control in a dog. *Vet Anaesth Analg*. 2017; 44(6):1400–1401.
66. Shury TK, Caulkett NA, Woodbury MR. Intranasal naltrexone and atipamezole for reversal of white-tailed deer immobilized with carfentanil and medetomidine. *Can Vet J*. 2010; 51(5):501–5.
67. Weiland LC, Kluge K, Kutter APN, Kronen PW. Clinical evaluation of intranasal medetomidine-ketamine and medetomidine-S(+)-ketamine for induction of anaesthesia in rabbits in two centres with two different administration techniques. *Vet Anaesth Analg*. 2017; 44(1):98–105.
68. Vlerick L, Devreese M, Peremans K et al. Pharmacokinetics, absolute bioavailability and tolerability of ketamine after intranasal administration to dexmedetomidine sedated dogs. *PLOS ONE*. 2020; 15(1):e0227762.
69. Charalambous M, Volk HA, Tipold A et al. Comparison of intranasal versus intravenous midazolam for management of status epilepticus in dogs: A multi-center randomized parallel group clinical study. *J Vet Intern Med*. 2019; 33(6):2709–2117.
70. Abou-Khalil B, Wheless J, Rogin J et al. A double-blind, randomized, placebo-controlled trial of a diazepam auto-injector administered by caregivers to patients with epilepsy who require intermittent intervention for acute repetitive seizures. *Epilepsia*. 2013; 54(11):1968–76.
71. Silbergleit R, Durkalski V, Lowenstein D et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012; 366(7):591–600.
72. Court MH, Greenblatt DJ. Pharmacokinetics and preliminary observations of behavioral changes following administration of midazolam to dogs. *J Vet Pharmacol Ther*. 1992; 15(4):343–350.
73. Schwartz M, Muñana KR, Nettifee-Osborne JA et al. The pharmacokinetics of midazolam after intravenous, intramuscular, and rectal administration in healthy dogs. *J Vet Pharmacol Ther*. 2013; 36(5):471–477.
74. McIntyre J, Robertson S, Norris E et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet*. 2005; 366(9481):205–210.
75. Spencer D. Hope for new treatments for acute repetitive seizures. *Epilepsy Curr*. 2014; 14(3):147–149.

76. Musumeci T, Bonaccorso A, Puglisi G. Epilepsy disease and nose-to-brain delivery of polymeric nanoparticles: an overview. *Pharmaceutics*. 2019; 11(3):118.
77. Zhang J, Niu S, Zhang H, Streisand JB. Oral mucosal absorption of midazolam in dogs is strongly pH dependent. *J Pharm Sci*. 2002; 91(4):980–982.
78. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. *J Pharm Sci*. 1992; 81(1):1–10.
79. Gavhane YN, Yadav AV. Loss of orally administered drugs in GI tract. *Saudi Pharm J*. 2012; 20(4):331–344.
80. Costa C, Moreira JN, Amaral MH et al. Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. *J Control Release*. 2019; 295:187–200.
81. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy--a systematic review. *BMC Vet Res*. 2014;10:257.
82. Charalambous M, Shivapour SK, Brodbelt DC, Volk HA. Antiepileptic drugs' tolerability and safety--a systematic review and meta-analysis of adverse effects in dogs. *BMC Vet Res*. 2016; 12:79.
83. Charalambous M, Pakozdy A, Bhatti SFM, Volk HA. Systematic review of antiepileptic drugs' safety and effectiveness in feline epilepsy. *BMC Vet Res*. 2018; 14(1):64.
84. Thomas WB. Idiopathic epilepsy in dogs and cats. *Vet Clin North Am Small Anim Pract*. 2010; 40(1):161–179.
85. Loscher W, Rogawski MA. How theories evolved concerning the mechanism of action of barbiturates. *Epilepsia*. 2012; 53 Suppl 8:12–25.
86. Custer KL, Austin NS, Sullivan JM, Bajjalieh SM. Synaptic vesicle protein 2 enhances release probability at quiescent synapses. *J Neurosci*. 2006; 26(4):1303–1313.
87. Meehan AL, Yang X, McAdams BD et al. A new mechanism for antiepileptic drug action: vesicular entry may mediate the effects of levetiracetam. *J Neurophysiol*. 2011; 106(3):1227–1239.
88. Xu T, Bajjalieh SM. SV2 modulates the size of the readily releasable pool of secretory vesicles. *Nat Cell Biol*. 2001; 3(8):691–698.
89. Wakita M, Kotani N, Kogure K, Akaike N. Inhibition of excitatory synaptic transmission in hippocampal neurons by levetiracetam involves Zn(2)(+)-dependent GABA type A receptor-mediated presynaptic modulation. *J Pharmacol Exp Ther*. 2014; 348(2):246–259.
90. Dewey CW, Bailey KS, Boothe DM et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emerg Crit Car*. 2008; 18(2):153–157.
91. Biddick AA, Bacek LM, Taylor AR. A serious adverse event secondary to rapid intravenous levetiracetam injection in a dog. *J Vet Emerg Crit Car*. 2018; 28(2):157–162.
92. Peters RK, Schubert T, Clemmons R, Vickroy T. Levetiracetam rectal administration in healthy dogs. *J Vet Intern Med*. 2014; 28(2):504–509.
93. Cagnotti G, Odore R, Gardini G et al. Pharmacokinetics of rectal levetiracetam as add-on treatment in dogs affected by cluster seizures or status epilepticus. *BMC Vet Res*. 2018; 14(1):189.
94. Patterson EE, Goel V, Cloyd JC et al. Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics. *J Vet Pharmacol Ther*. 2008; 31(3):253–258.
95. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther*. 2011; 34(1):31–34.

96. HARDY BT, PATTERSON EE, CLOYD JM et al. Double-masked, placebo-controlled study of intravenous levetiracetam for the treatment of status epilepticus and acute repetitive seizures in dogs. *J Vet Intern Med*. 2012; 26(2):334–340.
97. MISRA UK, KALITA J, MAURYA PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. *J Neurol*. 2012; 259(4):645–648.
98. WILDER BJ, RAMSAY RE, WILLMORE LJ et al. Efficacy of intravenous phenytoin in the treatment of status epilepticus: kinetics of central nervous system penetration. *Ann Neurol.* 1977; 1(6):511–518.
99. ERIKSSON K, KERANEN T, KALVIAINEN R. Fosphenytoin. *Expert Opin Drug Metab Toxicol*. 2009; 5(6):695–701.
100. FREY HH, LOSCHER W. Pharmacokinetics of anti-epileptic drugs in the dog: a review. *J Vet Pharmacol Ther*. 1985; 8(3):219–233.
101. OVERDUIN LM, VAN GOGH H, MOL JA, VAN NES JJ. Pharmacokinetics of three formulations of diphenylhydantoin in the dog. *Res Vet Sci*. 1989; 46(2):271–273.
102. SMITH RD, LOMAS TE. Modification of cardiovascular responses to intravenous phenytoin by dopamine in dogs: evidence against an adverse interaction. *Toxicol Appl Pharmacol*. 1978; 45(3):665–673.
103. HASSELL TM, MAGUIRE JH, COOPER CG, JOHNSON PT. Phenytoin metabolism in the cat after long-term oral administration. *Epilepsia*. 1984; 25(5):556–563.
104. FISCHER JH, PATEL TV, FISCHER PA. Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. *Clin Pharmacokinet*. 2003; 42(1):33–58.
105. TRINKA E. What is the relative value of the standard anticonvulsants: Phenytoin and fosphenytoin, phenobarbital, valproate, and levetiracetam? *Epilepsia*. 2009; 50:40–43.
106. LEPPIK IE, PATTERSON EN, COLES LD et al. Canine status epilepticus: a translational platform for human therapeutic trials. *Epilepsia*. 2011; 52 Suppl 8:31–34.
107. COLES LD, LEPPIK IE, PATTERSON EE et al. Use of IV fosphenytoin pharmacokinetics to determine the loading dose for a clinical trial of canine status epilepticus. *Epilepsia*. 2015; 56(6):888–894.
108. PATTERSON EE, LEPPIK IE, COLES LD et al. Canine status epilepticus treated with fosphenytoin: A proof of principle study. *Epilepsia*. 2015; 56(6):882–887.
109. ROSSETTI AO, REICHHART MD, SCHALLER MD et al. Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia*. 2004; 45(7):757–763.
110. SAN-JUAN D, CHIAPPA KH, COLE AJ. Propofol and the electroencephalogram. *Clin Neurophysiol*. 2010; 121(7):998–1006.
111. MACKENZIE SJ, KAPADIA F, GRANT IS. Propofol infusion for control of status epilepticus. *Anaesthesia*. 1990; 45(12):1043–1045.
112. PITT-MILLER PL, ELCOCK BJ, MAHARAJ M. The management of status epilepticus with a continuous propofol infusion. *Anesth Analg*. 1994; 78(6):1193–1194.
113. GOMMEREN K, CLAEYS S, DE ROOSTER H et al. Outcome from status epilepticus after portosystemic shunt attenuation in 3 dogs treated with propofol and phenobarbital. *J Vet Emerg Crit Care (San Antonio)*. 2010; 20(3):346–351.
114. HELDMANN E, HOLT DE, BROCKMAN DJ et al. Use of propofol to manage seizure activity after surgical treatment of portosystemic shunts. *J Small Anim Pract*. 1999; 40(12):590–594.
115. STEFFEN F, GRASMUECK S. Propofol for treatment of refractory seizures in dogs and a cat with intracranial disorders. *J Small Anim Pract*. 2000; 41(11):496–499.

116. Heidenreich DC, Giordano P, Kirby BM. Successful treatment of refractory seizures with phenobarbital, propofol, and medetomidine following congenital portosystemic shunt ligation in a dog. *J Vet Emerg Crit Care (San Antonio)*. 2016; 26(6):8316.

117. Hashim MA, Waterman AE. Effects of thiopentone, propofol, alphaxalone-alphadolone, ketamine and xylazine-ketamine on lower oesophageal sphincter pressure and barrier pressure in cats. *Vet Rec*. 1991; 129(7):137–139.

118. Taylor PM, Chengelis CP, Miller WR et al. Evaluation of propofol containing 2% benzyl alcohol preservative in cats. *J Feline Med Surg*. 2012; 14(8):516–526.

119. Andress JL, Day TK, Day D. The effects of consecutive day propofol anesthesia on feline red blood cells. *Vet Surg*. 1995; 24(3):277–282.

120. Bevan JC. Propofol-related convulsions. *Can J Anaesth*. 1993; 40(9):805–809.

121. Walder B, Tramer MR, Seeck M. Seizure-like phenomena and propofol: a systematic review. *Neurology*. 2002; 58(9):1327–1332.

122. Jaggy A, Bernardini M. Idiopathic epilepsy in 125 dogs: a long-term study. Clinical and electroencephalographic findings. *J Small Anim Pract*. 1998; 39(1):23–29.

123. Samra SK, Sneyd JR, Ross DA, Henry TR. Effects of propofol sedation on seizures and intracranially recorded epileptiform activity in patients with partial epilepsy. *Anesthesiology*. 1995; 82(4):843–851.

124. Sneyd JR, Samra SK, Davidson B et al. Electrophysiologic effects of propofol sedation. *Anesth Analg*. 1994; 79(6):1151–1158.

125. Fujikawa DG. Starting ketamine for neuroprotection earlier than its current use as an anesthetic/antiepileptic drug late in refractory status epilepticus. *Epilepsia*. 2019; 60(3):373–380.

126. Cohen SP, Bhatia A, Buvanendran A et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Region Anesth Pain M*. 2018; 43(5):521–546.

127. Bertram EH, Lothman EW. NMDA receptor antagonists and limbic status epilepticus: a comparison with standard anticonvulsants. *Epilepsy Res*. 1990; 5(3):177–184.

128. Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. *Epilepsy Res*. 2000; 42(2-3):117–122.

129. Williamson JM, Lothman EW. The effect of Mk-801 on kindled seizures: implications for use and limitations as an antiepileptic drug. *Ann Neurol*. 1989; 26(1):85–90.

130. Serrano S, Hughes D, Chandler K. Use of ketamine for the management of refractory status epilepticus in a dog. *J Vet Intern Med*. 2006; 20(1):194–197.

131. Gioeni D, Di Cesare F, D'Urso ES et al. Ketamine-dexmedetomidine combination and controlled mild hypothermia for the treatment of long-lasting and super-refractory status epilepticus in 3 dogs suffering from idiopathic epilepsy. *J Vet Emerg Crit Care (San Antonio)*. 2020; 30(4):455–460.

132. Galvez V, McGuirk L, Loo CK. The use of ketamine in ECT anaesthesia: A systematic review and critical commentary on efficacy, cognitive, safety and seizure outcomes. *World J Biol Psychiatry*. 2017; 18(6):424–444.

133. Hirshman CA, Krieger W, Littlejohn G et al. Ketamine-aminophylline-induced decrease in seizure threshold. *Anesthesiology*. 1982; 56(6):464–467.

134. Roynard P, Bilderback A, Dewey WC. Intravenous Ketamine bolus(es) for the treatment of Status Epilepticus/Cluster seizures in dogs: Ketamine terminates refractory status epilepticus.

Front Vet Sci. 2021; 8:547279.

135. Olney JW. Excitatory transmitter neurotoxicity. *Neurobiol Aging*. 1994; 15(2):259–260.
136. Mantz J, Josserand J, Hamada S. Dexmedetomidine: new insights. *Eur J Anaesthesiol*. 2011; 28(1):3–6.
137. Szot P, Lester M, Laughlin ML et al. The anticonvulsant and proconvulsant effects of alpha2-adrenoreceptor agonists are mediated by distinct populations of alpha2A-adrenoreceptors. *Neuroscience*. 2004; 126(3):795–803.
138. Halonen T, Kotti T, Tuunanen J et al. Alpha 2-adrenoceptor agonist, dexmedetomidine, protects against kainic acid-induced convulsions and neuronal damage. *Brain Res*. 1995; 693(1–2):217–224.
139. Shouse MN, Langer J, Bier M et al. The alpha 2 adrenoreceptor agonist clonidine suppresses seizures, whereas the alpha 2 adrenoreceptor antagonist idazoxan promotes seizures: pontine microinfusion studies of amygdala-kindled kittens. *Brain Res*. 1996; 731(1-2):203–207.
140. McCarren HS, Arbutus JA, Ardinger C et al. Dexmedetomidine stops benzodiazepine-refractory nerve agent-induced status epilepticus. *Epilepsy Res*. 2018; 141:1–12.
141. Platt SR, McDonnell JJ. Status epilepticus: Patient management and pharmacologic therapy. *Comp Cont Educ Pract*. 2000;22(8): 722–729.
142. Raines A, Blake GJ, Richardson B, Gilbert MB. Differential selectivity of several barbiturates on experimental seizures and neurotoxicity in the mouse. *Epilepsia*. 1979; 20(2):105–113.
143. Boothe DM. Anticonvulsant therapy in small animals. *Vet Clin North Am Small Anim Pract*. 1998; 28(2):411–448.
144. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature*. 1994; 367(6464):607–614.
145. Ries CR, Puil E. Mechanism of anesthesia revealed by shunting actions of isoflurane on thalamocortical neurons. *J Neurophysiol*. 1999; 81(4):1795–1801.
146. Langmoen IA, Hegstad E, Berg-Johnsen J. An experimental study of the effect of isoflurane on epileptiform bursts. *Epilepsy Res*. 1992; 11(3):153–157.
147. Sharpe MD, Young GB, Mirsattari S, Harris C. Prolonged desflurane administration for refractory status epilepticus. *Anesthesiology*. 2002;97(1): 261–264.
148. Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. *Arch Neurol*. 2004; 61(8):1254–1259.
149. Kenna JG, Jones RM. The organ toxicity of inhaled anesthetics. *Anesth Analg*. 1995; 81(6 Suppl):S51–66.
150. Trinka E, Brigo F. Neurostimulation in the treatment of refractory and super-refractory status epilepticus. *Epilepsy Behav*. 2019; 101(Pt B):106551.
151. Muñana KR, Vitek SM, Tarver WB et al. Use of vagal nerve stimulation as a treatment for refractory epilepsy in dogs. *J Am Vet Med Assoc*. 2002; 221(7):977–983.
152. Robinson K, Platt S, Stewart G et al. Feasibility of non-invasive vagus nerve stimulation (gammaCore VET™) for the treatment of refractory seizure activity in dogs. *Front Vet Sci*. 2020; 7:569739.
153. Martle V, Peremans K, Raedt R et al. Regional brain perfusion changes during standard and microburst vagus nerve stimulation in dogs. *Epilepsy Res*. 2014; 108(4):616–622.
154. Martle V, Raedt R, Waelbers T et al. The effect of vagus nerve stimulation on CSF monoamines and the PTZ seizure threshold in dogs. *Brain Stimul*. 2015; 8(1):1–6.

155. Martle V, Van Ham LM, Boon P et al. Vagus nerve stimulator placement in dogs: surgical implantation technique, complications, long-term follow-up, and practical considerations. *Vet Surg*. 2016; 45(1):71–78.

156. Charalambous M, Van Ham L, Broeckx BJG et al. Repetitive transcranial magnetic stimulation in drug-resistant idiopathic epilepsy of dogs: A noninvasive neurostimulation technique. *J Vet Intern Med*. 2020; 34(6):2555–2561.

157. Trinka E, Hofler J, Leitinger M, Brigo F. Pharmacotherapy for Status Epilepticus. *Drugs*. 2015; 75(13): 499–1521.

158. Rai S, Drislane FW. Treatment of Refractory and Super-refractory Status Epilepticus. *Neurotherapeutics*. 2018; 15(3):697–712.

159. Kushimoto S, Akaishi S, Sato T et al. Lactate, a useful marker for disease mortality and severity but an unreliable marker of tissue hypoxia/hypoperfusion in critically ill patients. *Acute Med Surg*. 2016; 3(4):293–297.

160. Rangel-Castilla L, Gopinath S, Robertson CS. Management of intracranial hypertension. *Neurol Clin*. 2008; 26(2):521–41, x.

161. Castro D, Keenaghan M. *Arterial Blood Gas*. Treasure Island (FL): StatPearls; 2020.

162. Ropper AH. Hyperosmolar therapy for raised intracranial pressure. *N Engl J Med*. 2012; 367(8):746–752.

163. Syring RS. Assessment and treatment of central nervous system abnormalities in the emergency patient. *Vet Clin North Am Small Anim Pract*. 2005; 35(2):343–358, vi.

164. Kamel H, Navi BB, Nakagawa K et al. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med*. 2011; 39(3):554–559.

165. Platt S. Altered states of consciousness in small animals. *Vet Clin North Am Small Anim Pract*. 2014; 44(6):1039–1058.

166. Kuo KW, Bacek LM, Taylor AR. Head Trauma. *Vet Clin North Am Small Anim Pract*. 2018; 48(1):111–128.

167. Bershad EM, Humphreis WE 3rd, Suarez JI. Intracranial hypertension. *Semin Neurol*. 2008; 28(5):690–702.

168. Cooper SJ. Methods to prevent ventilator-associated lung injury: a summary. *Intensive Crit Care Nurs*. 2004; 20(6):358–365.

169. Beniczky S, Aurlien H, Brogger JC et al. Standardized computer-based organized reporting of EEG: SCORE - Second version. *Clin Neurophysiol*. 2017; 128(11):2334–2346.

170. Smith SJ. EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry*. 2005; 76 Suppl 2:ii2-7.

171. Claassen J, Mayer SA. Continuous electroencephalographic monitoring in neurocritical care. *Curr Neurol Neurosci Rep*. 2002; 2(6):534–540.

172. Gaspard N, Manganas L, Rampal N et al. Similarity of lateralized rhythmic delta activity to periodic lateralized epileptiform discharges in critically ill patients. *JAMA Neurol*. 2013; 70(10):1288–1295.

173. Hirsch LJ, LaRoche SM, Gaspard N et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol*. 2013; 30(1):1–27.

174. Ney JP, van der Goes DN, Nuwer MR et al. Continuous and routine EEG in intensive care: utilization and outcomes, United States 2005-2009. *Neurology*. 2013; 81(23):2002–2008.

175. Berendt M, Hogenhaven H, Flagstad A, Dam M. Electroencephalography in dogs with epilepsy: similarities between human and canine findings. *Acta Neurol Scand*. 1999; 99(5):276–283.

176. Davis KA, Sturges BK, Vite CH et al. A novel implanted device to wirelessly record and analyze continuous intracranial canine EEG. *Epilepsy Res*. 2011; 96(1-2):116–122.

177. Pakozdy A, Gruber A, Kneissl S et al. Complex partial cluster seizures in cats with orofacial involvement. *J Feline Med Surg*. 2011; 13(10):687–693.

178. Raith K, Steinberg T, Fischer A. Continuous electroencephalographic monitoring of status epilepticus in dogs and cats: 10 patients (2004-2005). *J Vet Emerg Crit Care (San Antonio)*. 2010; 20(4):446–455.

179. Cuff DE, Bush WW, Stecker MM, Williams DC. Use of continuous electroencephalography for diagnosis and monitoring of treatment of nonconvulsive status epilepticus in a cat. *J Am Vet Med Assoc*. 2014; 244(6):708–714.

180. Shah AM, Vashi A, Jagoda A. Review article: Convulsive and non-convulsive status epilepticus: an emergency medicine perspective. *Emerg Med Australas*. 2009; 21(5):352–366.

181. Tauboll E, Lundervold A, Gjerstad L. Temporal distribution of seizures in epilepsy. *Epilepsy Res*. 1991; 8(2):153–165.

182. Haut SR, Legatt AD, O'Dell C et al. Seizure lateralization during EEG monitoring in patients with bilateral foci: the cluster effect. *Epilepsia*. 1997; 38(8):937–940.

183. Packer RM, Shihab NK, Torres BB, Volk HA. Risk factors for cluster seizures in canine idiopathic epilepsy. *Res Vet Sci*. 2016; 105:136–138.

184. Hulsmeyer V, Zimmermann R, Brauer C et al. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. *J Vet Intern Med*. 2010; 24(1):171–178.

185. Kwiatkowska M, Tipold A, Huenerfauth E, Pomianowski A. Clinical risk factors for early seizure recurrence in dogs hospitalized for seizure evaluation. *J Vet Intern Med*. 2018; 32(2):757–763.

186. Weissl J, Hulsmeyer V, Brauer C et al. Disease progression and treatment response of idiopathic epilepsy in Australian Shepherd dogs. *J Vet Intern Med*. 2012;26(1): 116–25.

187. Pakozdy A, Leschnik M, Sarchahi AA et al. Clinical comparison of primary versus secondary epilepsy in 125 cats. *J Feline Med Surg*. 2010; 12(12):910–916.

188. Van Meervenne SA, Volk HA, Van Ham LM. Association between estrus and onset of seizures in dogs with idiopathic epilepsy. *J Vet Intern Med*. 2015; 29(1):251–253.

189. Rosciszewska D, Buntner B, Guz I, Zawisza L. Ovarian hormones, anticonvulsant drugs, and seizures during the menstrual cycle in women with epilepsy. *J Neurol Neurosurg Psychiatry*. 1986; 49(1):47–51.

190. Haut SR, Shinnar S, Moshe SL. Seizure clustering: risks and outcomes. *Epilepsia*. 2005; 46(1):146–149.

191. Podell M. The use of diazepam per rectum at home for the acute management of cluster seizures in dogs. *J Vet Intern Med*. 1995; 9(2):68–74.

192. Packer RMA, Nye G, Porter SE, Volk HA. Assessment into the usage of levetiracetam in a canine epilepsy clinic. *BMC Vet Res*. 2015; 11.

193. Cagnotti G, Odore R, Bertone I et al. Open-label clinical trial of rectally administered levetiracetam as supplemental treatment in dogs with cluster seizures. *J Vet Intern Med*. 2019; 33(4):1714–1718.