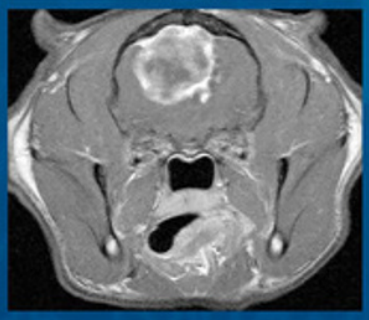










Second Edition

Seizures in Dogs and Cats

Sean Sanders

with website

WILEY

Seizures in Dogs and Cats

SECOND EDITION

Sean Sanders, DVM, PhD, DACVIM-Neurology

WILEY

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For Dogs and Cats
and the People who take care of them.

For Nicole, Jonathan Huska, Luath, Stevie and Zenda.
Thanks for your patience.

Contents

	Preface	vii
	Acknowledgments	xi
	About the Companion Website	xiii
1	Historical Perspectives	1
2	The Biology of Seizures	17
3	Epileptic Seizure Classification and Syndromes	61
4	Client Communication	119
5	Diagnosis	135
6	Medical Management of Seizures	197
7	Antiseizure Medications	255
8	Emergency Management of Seizures	351
9	Alternative, Integrative, and Complementary Therapy	383
10	Advanced Invasive Therapy for Seizures	431

Appendix 1 Glossary of Descriptive Terminology for Veterinary Ictal Semiology 467

Appendix 2 The Neurological Exam and Clinical Exam Forms 475

Appendix 3 Antiseizure Medication Formulary and Common Formulas 501

Index 531

Preface

I approached the second edition of *Seizures in Dogs and Cats* with the notion of updating many of the topics, fixing typos, and adding a few more figures. A year later, I was again reinvigorated by the subject. I knew it had not been "stale" in the decade since the last edition came out but I honestly had no idea it was so alive and vibrant. I hope the reader can take away some inspiration, as well.

I love teaching. Even more, I love teaching those who want to be taught. Students, veterinarians, *and* worried pet owners (Figure P1). There is no greater joy for a teacher than to see a student "get it." I hope this text is useful for students, nurses, interns, residents, primary care veterinarians, specialists and to some degree, pet owners. Basically, anyone with an interest in this side of veterinary neurology.

No one has the capacity to learn everything but everyone has the ability to learn something. A great teacher is the catalyst. I hope anyone reading these pages will try. Solve the problem. Keep trying. I added a bit of an outline to the beginning of each chapter to hopefully make it a little easier to jump to where you want to go. I also added a few ideas to "takeaway" from the chapter and some fun facts - myelominutia!

This book begins with observation. Understanding our surroundings and where we came from. Realizing at any given time in history "that time" was the peak of understanding our physical world. Through observation, we think, we compare, we ask questions, and we apply.

The second chapter attempts to summarize a hugely complex subject giving the reader a basic knowledge of neuroscience and epileptology. When I think of all that has to go right to keep from going wrong—I am amazed a few chemicals got together—formed a little glob of goo and a few billion years later ...well, here we are.

In the third chapter, we have to create a "story." We need structure to tell the story. Classification schemes are continually evolving. Like science, our ideas change as we gather more evidence. Classification provides us with a foundation for communication. Hopefully, I made it a little more interesting than it sounds.

Once we have a story, it helps to be able to convey the story to others. Our ability to influence is predicated by our ability to effectively communicate. From uttering a cohesive sentence to explaining a complex subject, ensuring your audience walks away with an understanding—even if rudimentary, continues the chain of education. Chapter 4 creates a foundation with real-life examples, which at the very least may have your clients saying, "can you be my doctor" at the end of the appointment.

In Chapter 5 we start doing something about the problem. One of my mentors would say "you are only as good as your differential list." Having a differential list gives structure to know where to look. You cannot know everything but knowing where to look for the answer, whether a book, website, diagnostic test, or colleague (the one with the eidetic memory would be a good start) is the beginning of the journey. We find the problem or at least what we think it is, in order to manage and influence it (hopefully, make it go away).

The second half of the book is devoted to treating the problem. While we often hear the more tools in the toolbox the easier it is to fix something; a core concept I hope the reader will take away

is to use the appropriate tool at the appropriate time and before you reach for the next tool, make sure the first is no longer able to do the job. I encourage all clinicians to embrace the EEG. It's a game changer.

Medical management of epilepsy is the core of our ability to affect the lives of our patients and their families. A solid grasp of the tools you have will allow you to make tactical and strategic decisions regarding treatment. And the core of medical management is pharmacology. This section is up-to-date with the literature as of right ... now. But by the time the book comes out, it will be out-of-date. What I really hope the reader takes away and I may have mentioned it like 3000 times ... is to make sure you use one drug at a time. Avoid polypharmacy until, and only if you need it (I'm talking to you *pseudoresistance*).

The emergency treatment of epilepsy is the culmination of the toolbox metaphor. Have a plan and stick to it. Treat status like cardiac arrest. Use the chart. Use the strategies. Then use what works for you. In the end, it doesn't matter what map you use as long as you arrive at the destination.

The clinician should at least be aware of non-conventional treatment options. Your clients will ask and if you do not give them sound advice, they will probably do the wrong thing. They trust you. You owe it to them to at least be able to scratch the surface. Keeping cannabidiol in this section was questionable. Now that there is an FDA-approved anti-epileptic of purified cannabidiol, it could be argued it belongs in Chapter 7 with the conventional medications.

The last chapter is to me the most exciting. Ten years ago, with the first edition, I predicted surgical treatment for epilepsy in veterinary patients may not be a treatment that ever broke the "research" barrier. Wow, was I wrong. This subspecialty brings my two favorite things under the same roof—epilepsy and neurosurgery. Talk about giving a patient a chance. The researchers paving the way in this field, along with the neurodiagnostics (and those experts who can wield the tools) necessary to define the problem are what inspire me. I hope the next generation of curious cutters grabs the torch and continues the race.



FIGURE P1 A captive audience.

The appendices are updated and a few expanded. In the last 10 years, I have had the opportunity and pleasure to teach neurology and neurosurgery to veterinarians around the globe. I see a massive desire to learn but often the trepidation to ask the question until that elemental trust is developed. Once you leave the institution, you are just getting started on a learning journey. I hope this book can be a breadcrumb to help you on your way. I have added more places to look for the answer.

One last thought—in an attempt to keep it "readable" I left out many, many references. I find the end of a sentence followed by 12 references to be ... disruptive. So, in an attempt to make the sentences more readable, I have focused on the references which will lead you along the way to further investigation (and more references). One last word of caution—with all things medical, where a patient's life may be at stake—do your diligence and double-check doses and recommendations. And then check them again.

Sean Sanders

Seattle
April, 2025

Veterinarians tend to associate conditions with a particular patient—one that sticks with us. For me, epilepsy means Mikey—a nine-year-old pit bull with a gentle face and a family I've grown to know well. For six years, I was there. The calls always came at the worst times. Friday evening. Rushing out the door for date night that's been delayed for too long. I'm stopped by our technician, "Wait, Mikey had another seizure." I'd run through the checklist—meds, dosages, drug levels. "Phenobarbital, levetiracetam, topiramate." "What's his phenobarbital level?" "34." "Levetiracetam?" "60 mg/kg TID." We're running out of room to escalate. "Let's go with nasal midazolam, an extra levetiracetam. If there are three more, send him in." Then I'd head home, pushing Mikey to the back of my mind, hoping I'm not too late for our reservation.

But for Mikey's family, the night was just beginning.

Dad crouched on the floor beside Mikey's postictal body, while Mom hung up the phone and stared down another sleepless night. They comply with our plan, but they know better. The second seizure always comes. Panic sets in—dosing confusion, fear of mistakes, accusations in the chaos. Their other dog gets too close mid-seizure and is nearly bitten. Mikey's dad ends up scratched and bleeding. The house is filled with dread, fear, and regret. They haven't vacationed in six years. They don't have date nights anymore. What began as joy in adopting a COVID-19 puppy has transformed into constant vigilance and emotional exhaustion.

They are not alone. Packer et al. showed what many of us intuitively knew—seizure caregivers suffer measurable physiologic stress. Their cortisol levels rise. Their neuroses deepen. And yet, our tools remain limited.

Seizure management in veterinary medicine is still, by many accounts, primitive. We meet these families, strangers to us, and alter their lives for the foreseeable future: "Twice daily pills—not to stop the seizures, but to make them less bad." And if you miss a dose? Horrific events and that's on you. Also, don't forget the liver risks, behavioral changes, and drug interactions. We make no promises. It's a hard sell. Compare this to human medicine, where epilepsy is parsed by phenotype (>50 syndromes), gene (over 900 associations), and electroclinical pattern—in veterinary neurology, the diagnostic specificity is worlds behind. We know some breeds respond better than others (Why Australian Shepherds, why?). Idiopathic epilepsy is not one disease, but many, unified by a single event but in so many other respects completely different.

That's why this book matters.

The first edition of *Seizures in Dogs and Cats* changed the way I think about this disease. It challenged my assumptions, offered new dosing strategies, and proposed alternative approaches that actually made more clinical sense. "Bridge therapy"—a term I hadn't truly appreciated—suddenly felt obvious. So did targeted, conditional drug use during high-risk periods. Introducing new drugs, revisiting old ones, and considering non-pharmaceutical interventions aren't fringe ideas—they're compassion in action. This wasn't just for refractory epilepsy. It was for all of us managing cases, where "adequate control" still didn't feel adequate.

This second edition takes that foundation even further. It is a source of information synthesis regarding treatment recommendations, expands on advanced treatment options and detection, and acknowledges the role of the client not just as caregiver, but as data partner.

With these tools, seizure mimics are easier to rule out, true events are easier to confirm, and—one day—forecasting may become reality.

For Mikey and every family like his, I am grateful for this book and for Sean's unwavering dedication. We don't yet have a cure for epilepsy. But we have an obligation to stay current, creative, and committed—to stand with our patients and their people, not behind them. I believe this text will arm you with the tools and confidence to do just that.

Dr. Fred Wininger
Owner/Neurologist/Neurosurgeon
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Acknowledgments

I may be the only name on the cover but there are few original thoughts in this book. My mind has been shaped over the years by those researchers, veterinarians, and teachers who not only came before me but continue to be active in their fields. And even if something seems like an original thought—it was influenced by many others. This book is a summation of their work (and certainly not a complete one). It is a miniscule *abstract* of decades of research, clinical observation, and practical application by others. Some of the names you will recognize over and over again as they tend to show up in the literature. What drives them to produce original work is inspiring. Their names are at the ends of the sentence bracketed by parentheses. They may be the first author but they also begin and end with "et al." To all of the middle authors and et al.'s, past, present, and future—thank you so much for your time and dedication to your work.

Thanks to Sreemol, Praveen, Susan, and Erica for all of your efforts in making this happen and for giving me the chance to write this—again. Wiley has given me an amazing platform for this dissertation. I truly appreciate it.

I have *occasionally* been called a "windbag" (I *think* [hope] somewhat in jest ...). There was a good reason my staff would schedule new seizure patients for the last appointment of the day. I can talk for hours about this fascinating subject. I have keen interest in solving neurological puzzles and helping pet owners to understand the puzzles we struggle with. Put a whiteboard in the room and it's game over.

I'll again acknowledge my gratitude to my mentors and teachers and their mentors and teachers. This unbroken chain continues today largely by the desire to learn and the gift of being able to teach. I am reminded daily in the way I practice, through the mentorship of Dr. Rod Bagley, who taught me a clinician can have all of the answers but those answers are meaningless if you don't ask the questions and get to the patient through its guardian. He taught me to practice medicine with empathy and compassion for the patient *and* their caretakers, fostered by a healthy dose of tactical precision and skepticism of convention. He taught me to take chances and solve problems. Above all, he taught me to "treat the patient, not the disease." Dr. Joe Harding fueled my desire to learn and inspired me to study the "myelominutia," the micro-details and awe-inspiring wonder of science. By the way, it was Dr. Bagley who coined that term when I would come out of the lab and enter the "real world" (Myelominutia: Def. The precise details of the nervous system often looked upon as "trivial."). Dr. Val Limburg, Dr. Neal Robison, and Dr. Glenn Johnson of the Edward R. Murrow College of Communication taught me a *craft* that to this day goes far beyond reporting the news. It was an invaluable experience. My official career as a journalist may have been brief, but I like to think of this book as "reporting" of a sort (if you will allow some poetic license).

I am a sucker for a captive audience. To the residents, interns, and students who are involuntarily exposed to my "lessons," you may not have an interest in the subject but the message is not about doses and diagnostics—it's about problem-solving and gaining confidence to take a chance and I'll say it again and again ... giving people Hope. You may not be ready to dive into the deep end but I encourage you to consider dipping your toe. Some advice—find a mentor and grab on like a baby monkey.

I am continually amazed and inspired by the people who care for pets with epilepsy. The devotion to their animal companions inspires me every day. Giving them *any* degree of hope is an incredible sense of accomplishment. These people, our "clients," are some of the best teachers. They are unencumbered by an institutional "snow globe." Ask lots and lots of questions but mostly—listen to Them. They often come to you, as the last book on the shelf. If there is one take-away from all these pages—it's "always assume the best."

Mom and Dad, thanks again for teaching me humility and hard work. It's not lost on me how incredibly lucky I was to be raised by two wonderful people and I hope you look back at raising the other four kids as a massive accomplishment itself. I am blessed to continue to have two very supportive parents, who unknowingly continue to teach and guide me every day.

The billions (yes with a "B") of research animals who involuntarily gave their lives for the advancement of medicine should not go without the greatest measure of gratitude. Our success as a species is paved by their unwilling sacrifice.

My own pets and my patients (yes, even the cats who make me sneeze) are the ultimate teachers, therapists, and inspiration. They continuously give and give, and ask for very little in return.

Finally, Nicole. Not a day goes by where I do not look back and smile at the laughter you bring to us. Sharing a life with another neuroscientist is pretty cool. Thanks again for all of the support while I was squirreled away in the office. My fact-checker. My best friend.

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/sanders/seizures2e 

This website includes:

- Videos
- Seizure Log (blank)
- Neurology Exam forms (blank)
- Seizure Questionnaire for pet owners

Historical Perspectives CHAPTER 1

KEY TAKEAWAYS

Seizures were likely one of the first recognized ailments observed by early humans to affect themselves and animals.

Throughout the ancient world, the care of domesticated animals developed at roughly the same time.

The development of human medicine and veterinary medicine started off on parallel tracts, diverged, and once again are closely tried together.

Prehistoric and Ancient Observation	1	The Enlightenment	7
Early Civilization	4	The Modern Era	10
The Middle Ages	6	The 20th Century	11
The Renaissance	7	Six Thousand Years Later	14

Myelominutia: All domesticated cats today can trace their genealogical origin to *Felis silvestris lybica*, the African wildcat, originally native to the Middle East—still roaming around today—pretty much everywhere and looking like house cats.

PREHISTORIC AND ANCIENT OBSERVATION

The first ancient humans who witnessed an animal having a seizure were probably as "wide eyed," surprised, and scared as people are today. That first observed seizure likely corresponds to the beginning of the human/animal relationship. The very first human/animal relationship originated at a point in our history, where we as a species started to feed off the leftover scraps of organized packs of wild dogs. Thus began a relationship with canines, most likely around the time, we decided to supplement our diet with more than what Mother Nature would provide. We became hunter-gatherers rather than just gatherers. At some point in human history, we started to spend more time observing animals in their natural environment, learning *from* them (e.g., how they hunted, social interactions, etc.) as opposed to just killing them for food (Figure 1.1). Considering the fact dogs were the earliest purposeful cohabitants of humans, early domesticated dogs were perhaps the first animals (other than our own species) humans witnessed to have a seizure. Ancient humans were well on their way toward higher cognitive abilities, which allowed them to associate the characteristics of a convulsing wolf/dog as comparable to those of a human exhibiting similar signs. Considering the genetic predisposition to have seizures in both species, epileptic seizures secondary to brain injury may have been observed as commonly as spontaneous seizures.

Seizures in Dogs and Cats, Second Edition. Sean Sanders.
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Companion website: www.wiley.com/go/sanders/seizures2e



FIGURE 1.1 Some of the first observations by humans of canines having seizures may have occurred while watching wild dogs hunt. While the incidence of epileptic seizures in dogs is similar to humans, seizures secondary to head trauma were most likely witnessed during these early observations. Heinrich Harder (1858–1935) / Wikimedia Commons / Public Domain.

Traumatic brain injury to either a human or a dog would probably account for some of the first observed occurrences of seizures. Seizures and epilepsy have undoubtedly been part of our species from the very bottom of the evolutionary tree. Historically, epileptic seizures are one of the oldest described afflictions of humans. As early man would recognize a cut on their finger as similar to a cut on an animal's digit, so too would they recognize the similarities in symptoms associated with a convulsion, fit, or seizure among humans, dogs, and cats.

It is estimated the natural occurrence of seizures in dogs is similar to that of humans (about 0.5 to ~1% of the population), whereas in cats, seizures may be less common or more common in the population compared to dogs depending on which reference you read (Berendt *et al.*, 2004; Schriefl *et al.*, 2008; Heske *et al.*, 2014; O'Neill *et al.*, 2020). Regardless of the percentage in the population, epileptic seizures are the most common neurological condition a veterinarian will encounter. Observation of the first cat having a seizure would most likely to have occurred following head trauma inflicted on a wild cat by another animal or man or with the domestication of cats, as opposed to natural observation, since they tend to have more reclusive lives. The earliest *recorded* history of animal observation dates to approximately 51,200 years ago, when the Neanderthals painted images of animals on cave walls in what is now modern-day Indonesia (Figure 1.2). The earliest recorded history of animal/human *cohabitation* dates back to Cro-Magnon humans (early *Homo sapiens*) at around 20,000–15,000 BP, when humans started to dabble in agriculture and the domestication of animals, which naturally came with it. It is suspected, however, that humans and animals coexisted together thousands of years prior to 15,000–20,000 BP. The discovery of a child's footprint along with that of a large dog in the Chauvet Cave of southern France suggests humans and dogs (wolf/dogs) coexisted as early as 26,000 BP (Garcia, 2005). Humans and dogs began hunting together around 12,000 BP. This time also coincides with the development of early civilizations, further strengthened by the domestication of livestock, namely, sheep and goats (Wilkinson, 1992).

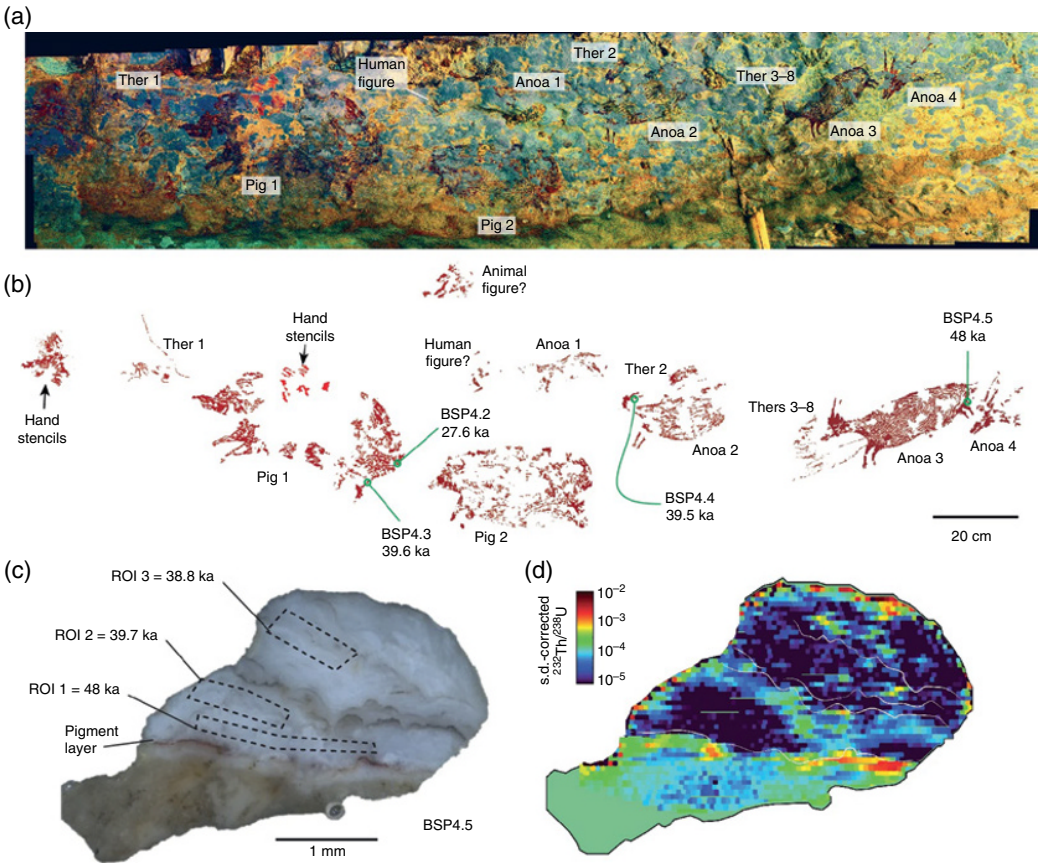


FIGURE 1.2 Cave painting at Leang Karampuang, Indonesia, is the current oldest known cave painting of animals. In the painting, three humans are shown interacting with a wild pig. Dated to 51,200 years ago. (a) Photo-stitched panorama of the rock art. (b) Tracing of the dated rock art panel showing the results of LA-U-series dating. (c) Transect view of the rock art sample BSP4.5 after removal from the artwork, highlighting the paint layer and the three integration zones (ROIs) and associated age calculations. (d) LA-MC-ICP-MS imaging of the BSP4.5 $^{232}Th/^{238}U$ isotopic activity ratio. From: Oktaviana, A.A., Joannes-Boyau, R., Hakim, B. et al. Narrative cave art in Indonesia by 51,200 years ago/Springer Nature/ CC BY 4.0 Adhi Agus Oktaviana et al., (2024) / Springer Nature / CC BY 4.0

The domestication of cats is thought to follow dogs by several thousand years. The contribution of cats to the survival of humans is a little more ... nuanced. They certainly benefit our emotional well-being, and one could argue they help to prevent the spread of infectious disease by annoying the rodents in our lives. The domestication of the cat was purely for companionship and maybe to keep early habitations pest free. Truth be told, cats pretty much *domesticated us*. And to add to that, they really do not need us to survive in the wild. The common house mouse moved in with humans once we figured out *shelter*, to feed off spilled grains and other food, and cats being obligate carnivores followed the mice. All domestic cats originate from a common ancestor, the European wildcat, *F. silvestris lybica*, native to the Middle East (look it up, these cats still look pretty much like house cats). Originally, it was thought the Egyptians were the first to live among cats; then, it was thought to be the ancient people of what is today modern-day China. Current evidence for the cohabitation of humans and cats points to the Middle East at a time of roughly 10,000 years

ago, based on a burial site on the island of Cyprus, where a human and a cat were buried together. Cats are not native to Cyprus, so it is hypothesized, they traveled to the island by boat (with people) from the Middle East (Driscoll *et al.*, 2009).

With the development of a relationship centered on cohabitation, humans were now applying their knowledge of "self" to other species. The earliest development of medicine would have little distinction between that practiced on other humans and that practiced on animals. The origins of comparative medicine likely began with animal sacrifice, as those doing the sacrificing were the earliest vivisectionists and often local healers. Humans would easily be able to make the connection between similar medical conditions, such as a vomiting dog being very comparable to a vomiting human. Unless a medical condition was the result of a known trauma, most afflictions were thought to be due to a combination of mystical or magical sources. Demonic possession by many cultures was the foundation of early medicine, although this was shadowed by the development of religious explanations for "disease." The application of medical knowledge between species was in parallel and often applied to each species by the same "medical" (often religious) practitioner. Our understanding of prehistoric medicine is deduced from the first *recorded* history on the planet.

EARLY CIVILIZATION

While we do not think of epilepsy today as a disease per se, historically, it was regarded as one of the earliest recognized afflictions of humans. It has been described in ancient Mesopotamian, Babylonian, Indian, Egyptian, and Chinese civilizations. The earliest description of epilepsy in humans dates back to about 6000 years ago (4000 BP) in a Babylonian text describing epileptic psychoses. The *magico-mystical* or *magico-religious* notion that seizures (and most diseases in general) occurred through possession of an individual by spirits or punishment of an individual by the gods for evil doing arose in ancient Mesopotamia. The earliest *documented* recorded history of human observation of animals dates roughly to 4500–3750 BP in ancient China. According to myth, Fuxi, the god who created humanity along with his wife, Nuwa, taught humans how to domesticate animals, so they would not have to spend so much time hunting them and then how to take care of them using acupuncture, medicinal herbs, various procedures, and incantations. Similar development of the care of animals would follow in Mesopotamia (modern-day Iraq) and the Asian subcontinent (modern-day India).

Further descriptions of seizures were made around 1000 BP within a Babylonian text on diagnostic medicine known as the *Sakikku* (meaning "all diseases") (Reynolds and Kinnier Wilson, 2008). The Mesopotamian word *antašubbû* is commonly referred to as "the falling disease" or "the hand of sin," which was brought about by the god of the moon and the notion that it was a manifestation of the possession by evil spirits (i.e., "lunatic" from *lūnāris*, Latin for "cresent-shaped") (Labat, 1951). The Ayurvedic medical texts describe the oldest known medical system, developed in ancient India between 4500 and 1500 BP, and within the *Charaka Samhita*, dated at around 450 BP, is a description of a condition labeled as "apasmara" (meaning "loss of consciousness") (Magiorkinis and Diamantis, 2011). In contrast to other civilizations, the ancient people of present-day India did not think of disease from a magico-religious stance; rather, they believed the cause of seizures was due to physiological and physiochemical disorders of the body. Rather than praying to the gods or visiting temples, they took a more practical and proto-scientific approach to treat the condition through altering etiological factors, diet changes, and lifestyle changes, which allowed those afflicted with the condition to have better management of their seizures (Manyam, 1992).

References to rabies in animals can be found as early as 2000 BP in the *Codex of Eshnunna*. These collections of laws inscribed on two cuneiform tablets are similar to the *Laws of Hammurabi*, which are also of the early Mesopotamian origin. The laws specifically refer to the penalties

one might face if a rabid dog they owned was to bite a person. Certainly, we can infer if rabies was being observed in dogs, then seizures were being observed in dogs.

With specific reference to animal disease, the earliest written description may come from the veterinary papyrus of Kahun. By this time, domestication of the dog, including selective breeding for various traits, was well underway (Figure 1.3). This document produced in ancient Egypt at around 1900 BP contains the oldest known veterinary writings outside the Ayurvedic texts. Within the Kahun papyrus is a specific passage, which *could be* (note: extreme emphasis on "could be") interpreted as the description of a dog having a seizure or collapse:



FIGURE 1.3 (a) Egyptian depictions of various domesticated dogs painted by Guiseppe Angelelli, Gaetano Rosellini, Salvador Cherubini, and Ippolito Rosellini and engraved by Carlo Lasinio; Pisa, Italy. From: The New York Public Library / https://digitalcollections.nypl.org/items/510d47d9-47cb-a3d9-e040-e00a18064a99 / Last accesed on May 26, 2025 . (b) The Veterinary Papyrus of Kahun was produced during the Middle Kingdom of Egypt ca. 1825 BP. Flinders Petrie discovered the fragments in 1889. With thanks to the Petrie Museum of Egyptian Archaeology, UCL. University College London UC32037/Wikipedia/CC BY SA 4.0.

. . . if when it courses (?) scenting (?) the ground, it falls down, it should be said "mysterious prostration as to it." When the incantations have been said, I should thrust my hand within its hemu, a henu of water at my side. When the hand of a man reaches to wash the bone of its back, the man should wash his hand in this henu of water each time that the hand becomes gummed (?) until thou hast drawn forth the heat-dried blood, or anything else or the hesa (?). Thou wilt know that he is cured on the coming of the hesa.

Of course, much can be said about the *interpretation* of the passage (focusing on the phrase "it falls down"); however, similar behaviors observed in humans would have been applied to those observed in animals, especially, the domesticated animals, for which humans interacted with the most. There is no ancient Egyptian word for "veterinarian"; therefore, it is presumed ancient Egyptian physicians treated both humans and animals (Gordon and Schwabe, 2004).

Shalihotra (ca. 2350 BP), one of the earliest Ayurvedic *veterinary* practitioners, focused on the anatomy, physiology, surgery, and diseases of horses and elephants in the *Shalihotra Samhita* text (Singh and Chauhan, 2001). He is considered the "Father of Veterinary Medicine." An important distinction should be made. Even at this time in ancient India, similar to ancient Egypt, those who provided medical service to animals and humans were the same individuals. The division between the practice of veterinary medicine and human medicine is fairly vague, and its definition was dependent on where one lived and to which specific culture they belonged. For the most part up to the *Renaissance*, there was no division between the medical treatment of humans and animals. Because many afflictions were thought to be due to possession of the body by evil spirits or the punishment from angry gods, mystics, or members of the religious orders often performed the "treatments." Medicines (loosely speaking) used to treat humans and animals were often identical or very similar.

In the late 6th century BP, a switch started to occur from the traditional mythological and theological explanations of the world to one more grounded on pure reason. The birthplace of natural science and philosophy (in a Western sense) was the city of Miletus, which was a Greek city at the time and is now on the Aegean coast of modern-day Turkey. Here, what came to be known as the *Milesian philosophy* started as an attempt to explain the physical universe through observation, reason, and the beginning of the ancient scientific method. *Hippocrates* (ca. 400 BP) was the first to link epilepsy to the brain and the potential for a hereditary basis of the disease. He also noted that the prognosis associated with epileptic seizures was worse the earlier it was seen in life and that it could often be brought on by head injuries. Additionally, we can attribute the term *grand mal* to Hippocrates, who called epilepsy "the great sickness." *Dioscorides* (AD 40–90) was one of the first individuals documented to prescribe medications based on observed properties of certain herbal remedies to help with epileptic seizures. He used *mugwort* (*Artemisia vulgaris*) or ragweed to treat epileptic seizures (Chapter 9). The first classification scheme of the epilepsies is attributed to *Galen* (AD 131–201), who derived the system of idiopathic (primary disorder of the brain), secondary epilepsy due to abnormalities of cardiac flow to the brain, and a third type due to a disorder of another part of the body that is secondarily transmitted to the brain.

THE MIDDLE AGES

Just when it looked like that humans were starting to get a head start on science, the *Dark Ages* came with the fall of the Roman Empire, and the figurative *pause button* was pressed on science. In Medieval times (ca. AD 6th century to 13th century), mysticism, religious fanaticism, and dogmatism were the common themes in all aspects of life, including science. Humans went from treating epilepsy with empirical results derived from herbs to exorcism and trephination to *rid the body of demonic possession*. How animals who experienced seizures in these times were treated remains unknown; however, because it was thought animals could be possessed by demons, we

would assume the same "sorcerer, magician, priest, or alchemist" would be called upon to cure the animal of seizures (if the animal was considered valuable enough). Diseases such as rabies and the plague were present in many civilizations, and to a significant degree, the *value* of animals was more related to their ability to provide food, fiber, and work as opposed to companionship. People were having a hard time taking care of themselves, let alone their animals. Farriers, around the time of the beginning of the Middle Ages, were the first professionals to focus their attention on the health of animals. Toward the end of the Middle Ages and the beginning of the Renaissance, farriers in London were organized with the goal of providing better care to horses. This organization is thought to be the beginning of modern veterinary medicine.

THE RENAISSANCE

The Renaissance marked the beginning of the end of the notion that epileptic seizures were brought on by demonic possession, evil spirits, or bad luck. Advances in anatomy, physiology, and pathophysiology led to the connection between symptomology correlated with pathophysiology and anatomy. Additionally, a distinction began to arise between the medical treatment of humans and animals. *Gaston de Foix* wrote about the sickness and care of dogs in *Livre de la Chasse* (translated to *Book of the Hunt*) between AD 1387 and AD 1390. He described many common maladies of dogs and how to treat them, including mange, broken bones, neovascularization of the cornea, and the various forms of rabies (Figure 1.4). His description of disease and its treatment in dogs is rational and based chiefly on observation utilizing common remedies at the time, such as valerian and other herbs (Chapter 9). Of special note is the lack of superstition or any reference to a magico-religious cause for disease. It is also apparent ole' Gaston cared deeply for the dogs he wrote about. The original book was copied many times over by other authors claiming the work to be their own or referring to it heavily. *Edward of Norwich*, the second Duke of York, translated the book and added some of his own comments in *The Master of Game* between 1406 and 1413 (Baillie-Grohman and Baillie-Grohman, 2005). In his descriptions of the various forms of rabies, he refers to a form that does not result in the death of the dog nor does the dog run about biting "man and other beast." In this form of *madness*, referred to as "running madness," the dog will show many of the same signs as a dog with rabies with the exception of biting other animals or humans and eventual death. The dog will run about howling and crying in a form of madness, ". . . go up or down without any form of abiding." This phrase means there are no lasting or enduring features of the condition as one would *expect* with transient epileptic seizures.

Charles Drélincourt (1633–1694) was the first recorded experimenter to induce seizures in a dog by placing a needle into the dog's fourth ventricle (Temkin, 1971). Experimentation on animals was extremely common during the transition from the Renaissance to the Enlightenment and was one of the driving forces toward the age of reason and the beginning of the modern biological sciences.

THE ENLIGHTENMENT

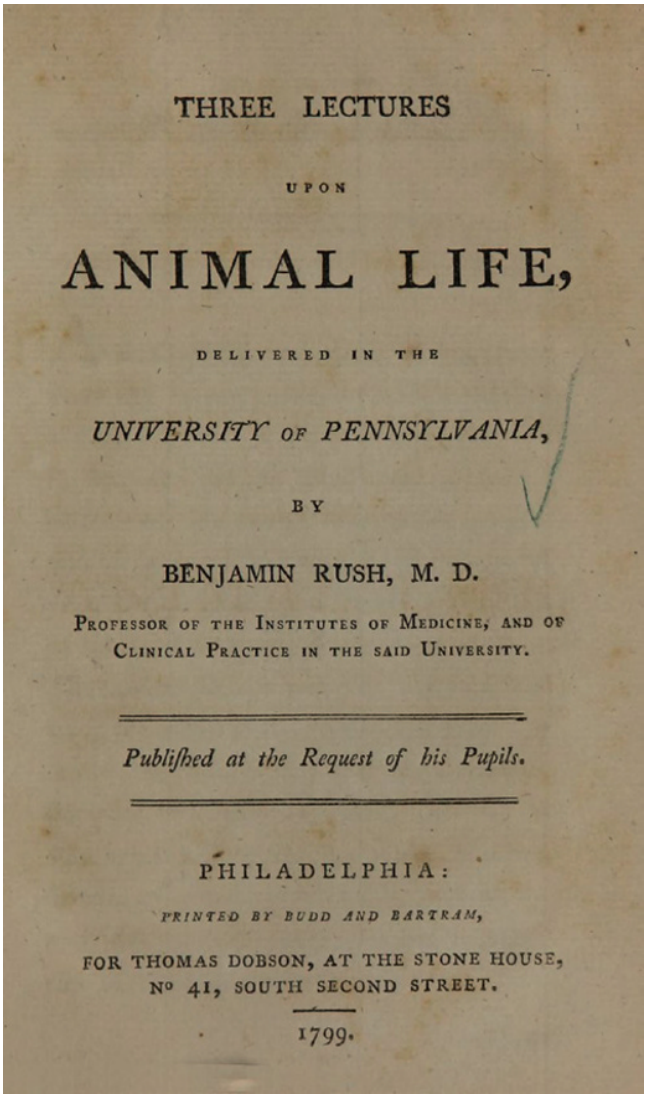
Claude Bourgelat (1712–1779) founded the first veterinary college in 1761 at Lyon, France, in response to a rinderpest outbreak in cattle. Undoubtedly, convulsions in animals, still referred to as *falling sickness*, were addressed similar to the means of his predecessors. However, scientists such as *Felice Fontana* (1730–1803) were beginning to conduct electrical experiments on tissues such as nerves, muscles, and the brains of animals. Fontana demonstrated convulsions could be generated through direct pressure and electrical stimulation on the brain of frogs in 1757 (Marchand and Hoff, 1955). The Veterinary College of London was founded in 1791 as a way for farriers to gain better knowledge regarding the care of horses. For the most part, the science revolving around convulsions was attempting to distinguish epilepsy as a true medical condition as opposed to that which afflicted the insane and in many instances was still considered contagious.



FIGURE 1.4 Veterinary medicine in the Renaissance. An illumination from *Livre de la Chasse* (*Book of the Hunt*) ca. 1390 by Gaston III Phoebus, Count de Foix. with permission of he Pierpont Morgan Library, New York.

Dr. Benjamin Rush (1746–1836), a Philadelphia physician and one of the signers of the Declaration of Independence, addressed a class of medical students at the University of Pennsylvania in 1799. In his speech entitled "On the Duty and Advantages of Studying the Diseases of Domestic Animals," Rush encouraged the young soon-to-be physicians to "embrace his studies and labors the means of lessening the miseries of domestic animals" (Figure 1.5). Rush was inspired by a study abroad at Edinburgh University on the advances of veterinary medicine in Europe, especially when compared to the abysmal practice he witnessed in the fledgling democracy. Rush was instrumental in creating one of the first veterinary colleges in the USA.

The vast majority of investigations looking for a physiological cause for seizures continued to be propagated through animal experimentation, primarily in dogs and cats. Numerous investigators observed convulsions induced through *bloodletting*, although even at the time of Hippocrates, it was



THREE LECTURES

UPON

ANIMAL LIFE,

DELIVERED IN THE

UNIVERSITY OF PENNSYLVANIA,

BY

BENJAMIN RUSH, M. D.

PROFESSOR OF THE INSTITUTES OF MEDICINE, AND OF CLINICAL PRACTICE IN THE SAID UNIVERSITY.

Published at the Request of his Pupils.

PHILADELPHIA:

PRINTED BY BUDD AND BARTRAM,

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1799.

FIGURE 1.5 In 1799, physician Benjamin Rush addressed a group of young medical students, imploring them to use their talents to "lessen the miseries of domestic animals." Rush was instrumental in developing one of the first Veterinary Teaching Colleges in the USA. *Source:* Budd and Bartram, 1799 / Public Domains.

noticed animals would *convulse* when slaughtered (Eadie, 2009). Much like the ancient Egyptians, who noted convulsions with head trauma and paralysis with spinal trauma in animals, early observers of symptomology had no physiological basis to connect the clinical signs to a pathophysiological mechanism for the behavior. The experimentation, which fostered the connection between symptomology and pathophysiological mechanisms, is a hallmark of the Enlightenment. *Charles-Édouard Brown-Séquard* (1817–1894) observed convulsive-like behavior when the spinal cord was transected in animals (Brown-Séquard, 1857). While he was the first to describe the anatomy and function of the spinal cord, he advocated trephination and cauterization of the *larynx* with silver nitrate for the treatment of epilepsy (that sounds ... horrific). Much of his work focused on the *reflex* epilepsies, which could be induced in animals following hemi-transection of the spinal cord. He noted that if the face or neck were scratched, the nonparalyzed side of the animal would involuntarily convulse. He suspected there was a degree of dyscognition; however, it was later speculated that he was inducing an exaggerated scratch reflex. His contemporaries were of the general agreement that a lack of unconsciousness during the convulsions did not fit with standard epilepsy experiments, and therefore, it was

not a good model for the study of convulsions in animals. To this day, there is no good explanation for Brown-Séquard's observation of "spinal epilepsy" (Eadie, 2009).

In 1857, *Edward Sieveking* introduced the use of potassium bromide for the treatment of epileptic seizures, which was further supported by *Charles Locock* (Locock, 1857). However, it was not until 1861 when *Samuel Wilks* provided solid evidence as to the efficacy of potassium bromide, catapulting it into popularity for the treatment of epileptic seizures (Wilks, 1861). This instance was the beginning of modern pharmacology for the treatment of epilepsy. Potassium bromide is still, to this day, widely used to treat epileptic seizures in dogs. *Pietro Albertoni* (1848–1933) performed some of the earliest experiments in the late 1800s, investigating the effects of various drugs and medications on their ability to prevent experimentally induced seizures in animals (Albertoni, 1882). Albertoni demonstrated that single doses or continued high doses of potassium bromide reduced the excitability of the cerebral cortex and prevented convulsions with electrical stimulation of the cortex in dogs. Expanding on this finding, he showed that ethyl ether or chloral hydrate, when administered in doses that left dogs awake, effectively prevented electrically induced seizures. Up to this point, epileptic seizure remedies may have been classified as spiritual (e.g., amulets, prayer, and exorcism), botanical-based (e.g., skullcap, valerian, and mistletoe), chemical (i.e., sulfur, silver nitrate, and mercury), alterations to the physical form (e.g., bleeding, trephination, cauterization, castration, and induced vomiting), and therapies derived from fauna (e.g., seal genitals, tortoise blood, and crocodile feces). Undoubtedly, a lack of perceived benefits led to an early philosophy of therapeutic *nihilism*, in which the intrinsic lack of benefit of anything led to the practice of "doing no harm," as many concoctions had undesirable side effects. Interestingly, we still use this common philosophical practice today.

THE MODERN ERA

The modern era in the history of epilepsy begins in the late 19th century with the discovery of potassium bromide, more refined animal experimentation, and a distinct correlation between seizure semiology and pathology. One of the most influential neurologists ever was *John Hughlings Jackson* (1835–1911). The discovery that organic disease (brain tumors, pus, or head trauma) was often present in humans and animals on necropsy further solidified the notion that seizures were not a disease but rather a *sign of brain dysfunction*. Granted, even the ancients were able to make the association between head trauma and seizures. While their ability to recognize symptomology was impressive, they did not have the underlying knowledge of pathophysiology needed to link the two. Jackson, through observation, was able to draw many conclusions, including the notion that epileptic seizures originated from the cerebral cortex gray matter (Jackson, 1873). *Eduard Hitzig* (1838–1907) and *Gustav Fritsch* (1838–1927) performed some of the earliest experiments in dogs when they applied electrical current to portions of the dog's cerebral cortex in order to elicit muscular contractions. Following the cessation of cerebral stimulation, Hitzig and Fritsch noted the convulsions spread to affect both sides of the dog's body with extensor rigidity and dilated pupils (Eadie, 2009). John Hughlings Jackson was able to bring together both symptomology and physiology in a more complete *pathophysiological* model of epilepsy (Jackson, 1869, 1873). Jackson came to the conclusion that epilepsy was not one disease but many different etiologies, which brought about epileptic convulsions based on the area of gray matter which was discharged (Engel, 2013). Jackson was aided greatly by the experiments of his friend and colleague *Sir David Ferrier* (1843–1928), who used electricity to stimulate areas of the brain of dogs, cats, and rabbits to provide an early understanding of the somatotopic organization of the brain (Ferrier, 1873) (Figure 1.6). His experiments on animals validated the semiology of what Jackson observed in humans with epileptic seizures and, in Jackson's words, were the "starting point for a comparative physiology of the convulsions" (Jackson, 1873). *Luigi Luciani* (1842–1991) performed cerebral resections in dogs and demonstrated that removing portions of the cerebrum could result in

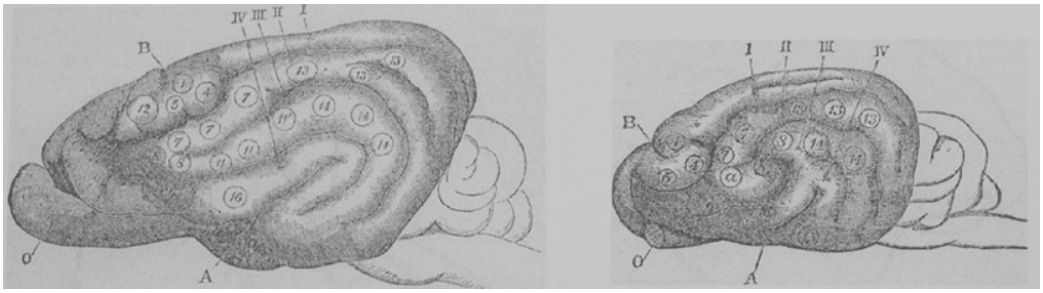


FIGURE 1.6 Experimental electrical stimulation points and associated movements in the dog and cat brain as described by Sir David Farrier in 1890. From Ferrier, D. 1890. The Croonian Lectures on Cerebral Localisation. *The British Medical Journal*. 1(1537). 1349–1355. *Source:* Public Domain.

convulsions. Surprisingly, some dogs *survived* his surgeries and would go on to continue to have convulsions. Luciani's work further validated the cortical origin of epileptic seizures (Manni and Petrosini, 1997). *Charles Horsley*, a neurosurgeon—guided by the observations of Jackson, a neurologist, and Ferrier, an electrophysiologist—applied his colleagues' observations in an attempt to cure epilepsy by removing brain tissue suspected to be epileptogenic in a man who suffered from focal motor seizures secondary to a depressed skull fracture. The surgery performed in 1886 was successful, resulting in a seizure-free patient (Horsley, 1886).

At about the same time, Jackson and Ferrier were formulating the beginning of our modern understanding of the functional brain (thank you, by the way, dogs, cats, frogs, and rabbits), veterinary medicine in the USA was getting its formal start. *Dr. James Law* (1838–1921), of Cornell University, published *The Farmer's Veterinary Adviser* in 1876. In this document, epilepsy was also referred to as "falling sickness." It was associated with distemper, teething in the young animal, and parasitic infection (two out of three isn't bad). A reference was made to *reflex* seizures elicited in guinea pigs by Brown-Séquard by tickling the neck and how a similar condition may be observed in humans. A description of the symptoms was followed by treatment recommendations consisting of removal of possible inciting causes, such as verminous infestations, restriction of diet, and more exercise for "excitable animals" (at least Dr. Law was consistent) (Law, 1876). Epileptic seizures were treated with injections of chloral hydrate or inhalation of chloroform or ether. "Convulsions and fits" of young dogs and cats were considered separately from epilepsy but still under the category and chapter concerning disease of the nervous system. Interestingly, treatment did not include potassium bromide but rather the removal of the offending cause (worms or "other irritating matters"), good feeding, air, exercise, lodging, and tonics made of bitters and iron. In the ninth edition (1889), salts of bromide were advised as treatments for excitability of the nervous system, along with the aforementioned tonics of bitters, chloral hydrate, chloroform, and ether.

THE 20TH CENTURY

Advances in the anatomy, physiology, and pathophysiology of the nervous system continued into the early 20th century. Thousands of years of experimental research on dogs, cats, and other animals built a foundation for our understanding of the brain and epilepsy. The development of the electroencephalograph (EEG) in the same year as phenobarbital (1912) provided a noninvasive way both to continue to study the electrical activity of the brain and to treat seizures with the first effective drug since the introduction of potassium bromide over 50 years prior. The first EEG recording of a mammal (a dog) and published photograph of an EEG were made by *Vladimir Pravdich-Neminsky* in 1912, at that time referred to as the "electrocerebrogram" (Niedermeyer *et al.*, 2011). It would be another 12 years before the first human EEG was recorded by *Hans Berger* in 1924, who is credited with inventing the *electroencephalograph* (sorry, Vladimir).

In 1912, a sleep-deprived resident psychiatrist, *Alfred Haupmann*, gave phenobarbital (then marketed as a hypnotic) to the epileptic patients within the ward he presided over so that he might get some high-quality "Z's." Not only did the patients (and Al) sleep throughout the night, but he also discovered they had fewer seizures during the day (I'd call that a *win-win*). Haupmann published his serendipitous finding, and phenobarbital went on to become the most widely used anticonvulsant to this day (Brodie, 2010). A cat model of experimentally induced seizures was used to screen a group of potential anticonvulsant drugs with presumably less sedative effects compared to phenobarbital. *Putnam* and *Merritt* reported a detailed description of the *cat electrocution apparatus* (yikes) in a 1937 *Science* article (Putnam and Merritt, 1937). In the report, the authors stated, "The method appears to involve no undue cruelty and indeed is similar to that used for executing stray animals by some animal protective societies" (Figure 1.7). One year later, Merritt and Putnam (1938) published the results describing the anticonvulsive effects of phenytoin. Prior to the discovery of the anticonvulsive effects of phenytoin, potassium bromide and phenobarbital were the most advanced pharmacological agents used to treat epileptic seizures. The ketogenic diet developed by *Dr. Russell Wilder* of the Mayo Clinic in 1921 was also used to a lesser degree (see Chapter 9) (Wheless, 2008). Cerebral cortical resection was performed in a limited number of cases to treat (and often *cure*) epilepsy. Following the discovery of phenytoin, the ketogenic diet fell out of favor, and a strong push was made to actively pursue other pharmacological-based therapies.

In the *People's Home Stock Book* by veterinarian W.C. Fair, published in 1919, there is little mention of the contemporary anticonvulsants used by humans to treat animals (Figure 1.8). There is no mention of epilepsy in dogs, other than convulsions associated with distemper. Cats, on the other hand, have a treatment section on "Fits–Convulsions" and "Epilepsy." It was noted that epilepsy in cats differed from fits and convulsions in that there was no *delirium* associated with convulsions (possibly similar to focal motor seizures of cats we identify today). Cats were treated with a cathartic of either buckthorn syrup or castor oil and wrapped in a hot

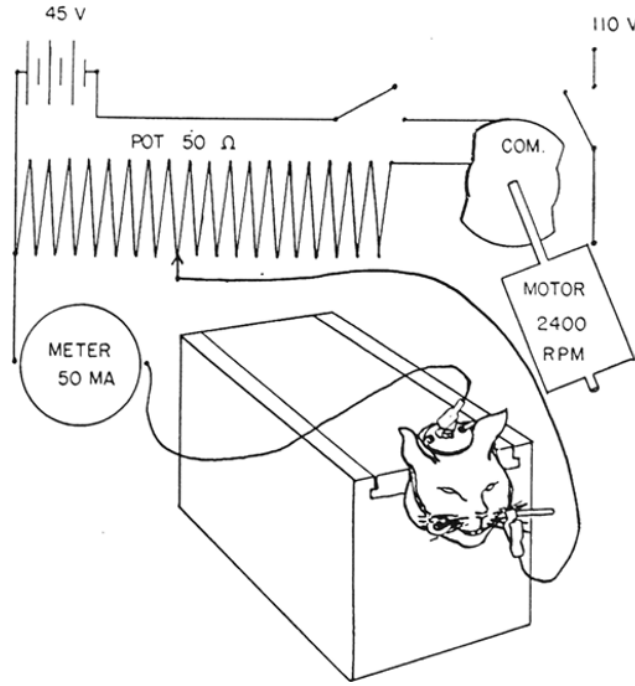


FIGURE 1.7 The *cat electrocution apparatus* utilized by Putnam and Merritt to test potential antiseizure drugs. Thousands of years of experimentation on animals helped greatly to expand human understanding and treatment of epilepsy. Putnam, T.J. and Merritt, H.H. 1937/ with permission of Elsevier.

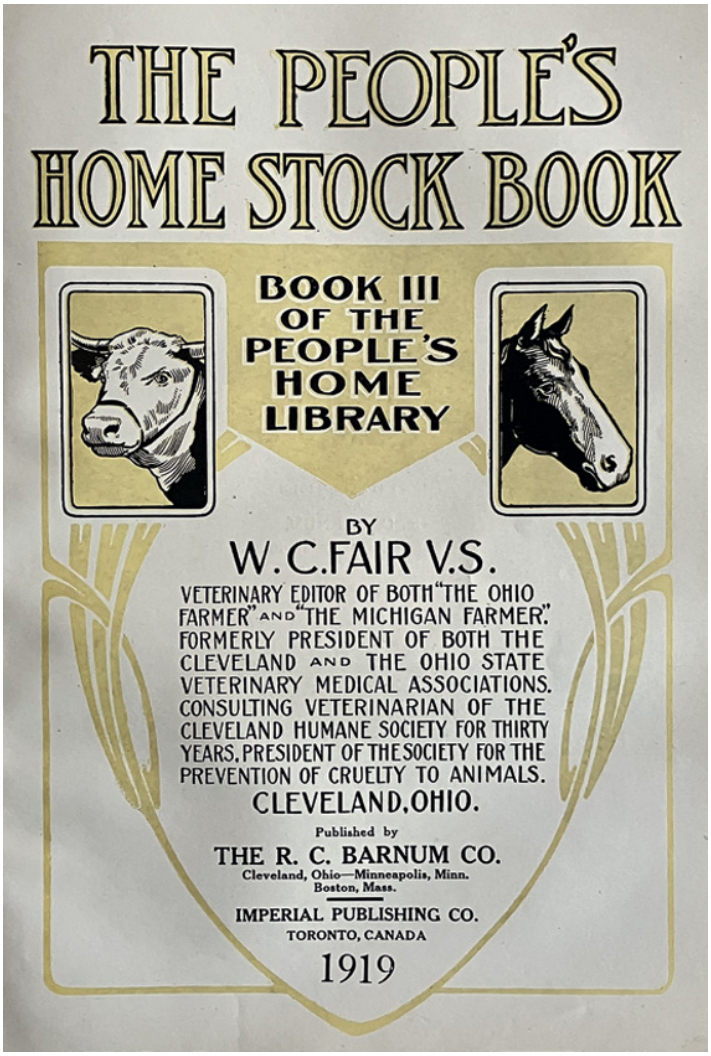


FIGURE 1.8 Even in the early 20th century, contemporary treatment of seizures in dogs and cats did not rely on the most "advanced" drugs at the time, such as potassium bromide and phenobarbital. Rather, emphasis was placed on numerous different treatments, including herbal remedies, good diet, and exercise. The R.C. Barnum Company, 1919 / Public Domain.

blanket or dropped in warm water (all but the head). It was also recommended to give "two grains of bromide of potash four times a day" (Fair, 1919). For epilepsy, cats were given laudanum (tincture of opium) or chloral hydrate, syrup of buckthorn (to move the bowels), and it was recommended to feed a highly digestible diet and exercise the animal (exercise a cat?). In the human medicine section of the same book (*The People's Home Library*, Book One), epilepsy was under the category "Falling Fits" and treated with "bromide of potassium." Oxide of zinc and stramonium ointment (herbal remedy derived from Jimson weed) were also recommended as a treatment for the falling sickness.

Advances in the treatment of epilepsy for dogs and cats primarily, and to this day, rely on pharmacology similar to humans. Although there is a significant difference between the species, there are limitations with regard to the use of various antiseizure medications in dogs and cats. In the 1960s, carbamazepine and the benzodiazepines were introduced. Benzodiazepines found significant use in veterinary medicine, especially for controlling status epilepticus. Several dozen pharmaceutical options have been available in the last seven decades for the treatment of epileptic seizures in humans. Disposition limitations and toxic effects of certain human drugs prevent the

current use of many of these medications in dogs and cats; however, despite this, the pharmacological success in treating seizures of dogs and cats is similar (if not slightly better) to humans. Phenobarbital and potassium bromide continue to be the most commonly prescribed antiseizure medications in dogs, and for cats, phenobarbital is by far the most widely used antiseizure drug.

A more direct focus on the advancement of diagnosis and treatment of disease of the nervous system of dogs and cats was developed following World War II. Veterinarians such as *J.T. McGrath*, *A.C. Palmer*, *B.F. Hoerlein*, *John Lorenz*, and *Alexander de Lahunta* gave special attention to the nervous system of dogs and cats. Their research, textbooks, and education of thousands of veterinarians significantly advanced the field of veterinary neurology and opened the door for many others to follow in their footsteps.

Advances in experimental techniques and a general pejorative view on animal experimentation shifted the bulk of animal research to rodent models in the late 1970s. The discovery of the patch clamp technique for the study of electrophysiology by *Erwin Neher* and *Bert Sakmann* opened a whole new era of science for not only studying the underlying pathophysiology of epileptic seizures but also the underlying mechanisms of how many drugs worked to suppress seizure activity. In the early 1970s, *Dr. Terrell Holliday* contributed significantly to the understanding of the canine EEG associated with paroxysmal central nervous system disorders. The contributions of *Dr. Wolfgang Löscher* and *Dr. Dawn Boothe* continue to advance our understanding of canine and feline anticonvulsants and have prevented an incalculable number of toxic reactions of dogs and cats to common drugs used to treat seizures in humans. *Dr. Michael Podell* continues to advance our understanding of the clinical application of new antiseizure medications, and *Dr. Fiona James* is paving the way for new applications of the EEG. An entirely new syndromic classification of feline epilepsy has been uncovered by *Dr. Akos Pakozdy*. Advanced imaging techniques combined with various forms of EEG, the identification of new syndromes of epilepsy, and, most importantly, a desire to not only advance the field but also help animals, are driving the application of surgery for epilepsy, thanks to some of the pioneering work of *Dr. Daisuke Hasegawa* and his associates.

One of the most significant advances in the diagnosis of the causes of epilepsy was in the form of advanced imaging of the brain. *J.M. Cobb* described the technique of pneumoencephalography in the dog in 1960. While performed decades earlier in humans, this radiographic technique allowed for the first time the *visualization* of structures of the brain in a minimally invasive way (compared to vivisection) (Cobb, 1960). The 1980s brought computed tomography (CT) into clinical use for imaging the canine and feline brain. In the 1990s, magnetic resonance imaging (MRI) of companion animal brains was introduced, which "opened the door to the brain." MRI quickly became the gold standard of imaging the brain and today is used clinically in almost all veterinary schools and veterinary private practices by specialist veterinary neurologists.

SIX THOUSAND YEARS LATER

A quarter way into the 21st century, we find that the diagnostic tests and treatment modalities for seizures in dogs and cats are in step with those employed for humans just as they were 6000 years ago. Certain limitations continue. While there is no lack of sophistication or desire to investigate the causes of seizures in dogs and cats, those limitations, discussed in further chapters, are slowly being overcome. Epilepsy is one of the oldest afflictions documented in human history, and it is interesting that references to dogs and cats having seizures are, for the most part, absent. Comparative medicine receives little mention in the historical perspectives of human epilepsy other than the use of animals in experiments to further the advancement of our understanding of epilepsy, as it affects humans. Perhaps this is due to the notion that our predecessors found little difference between species and therefore have no need to *compare* them. While dogs and cats certainly have never suffered from the psychosocial stigma of epilepsy (as far as we can tell), they have undoubtedly

suffered in other ways, particularly through a lack of understanding of epileptic seizures as it applies to their species. We are lucky to be surrounded by investigators who continue to make important advances in the study of veterinary and human epilepsy. The *applied knowledge* of these researchers in a clinical setting is the duty and obligation of the practicing veterinarian.

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The Biology of Seizures

CHAPTER 2

KEY TAKEAWAYS

An understanding of the fundamentals of how the brain works allows us to better appreciate the many ways it can go sideways.

Knowing the target areas of therapeutic options may help the clinician choose an antiepileptic drug.

Basic knowledge of the inner workings of the brain will help the clinician communicate complex subjects to pet owners and colleagues.

QUICK JUMP

Conditions which may look like seizures. . . . . .page 19

Mechanisms leading to an abnormal neuronal discharge (Table 2.1), ...page 20

Introduction 17
The Neuron 20
Neurotransmitters 32
The Neuronal Environment 40
Organization of Brain Connections 46
Nonbrain Influences of Epileptic Seizures 54

Myelominutia: The sodium/potassium ATPase pump is considered an enzyme as it catalyzes the movement of ions, using ATP—the defining characteristic of an enzyme.

INTRODUCTION

When most people think of seizures, they tend to think of *chaotic* brain activity. In fact, epileptic seizures are often just the opposite. Normally, neurons fire singularly or in short bursts. If we look at a normal animal's electroencephalogram (EEG) during slow-wave sleep, it is easy to recognize there is a distinct pattern to the electrical activity being recorded from the brain; however, in the event of an epileptic seizure, synchronous activity predominates (Figures 2.1 and 5.11).

A seizure occurs when neurons, which have a natural tendency to "want" to fire, form oscillating or reverberating hypersynchronous discharges. The summation of several neurons discharging at one time creates an environment where a local abnormality may influence nearby neurons to spontaneously fire, leading to the further discharge of more neurons at even more

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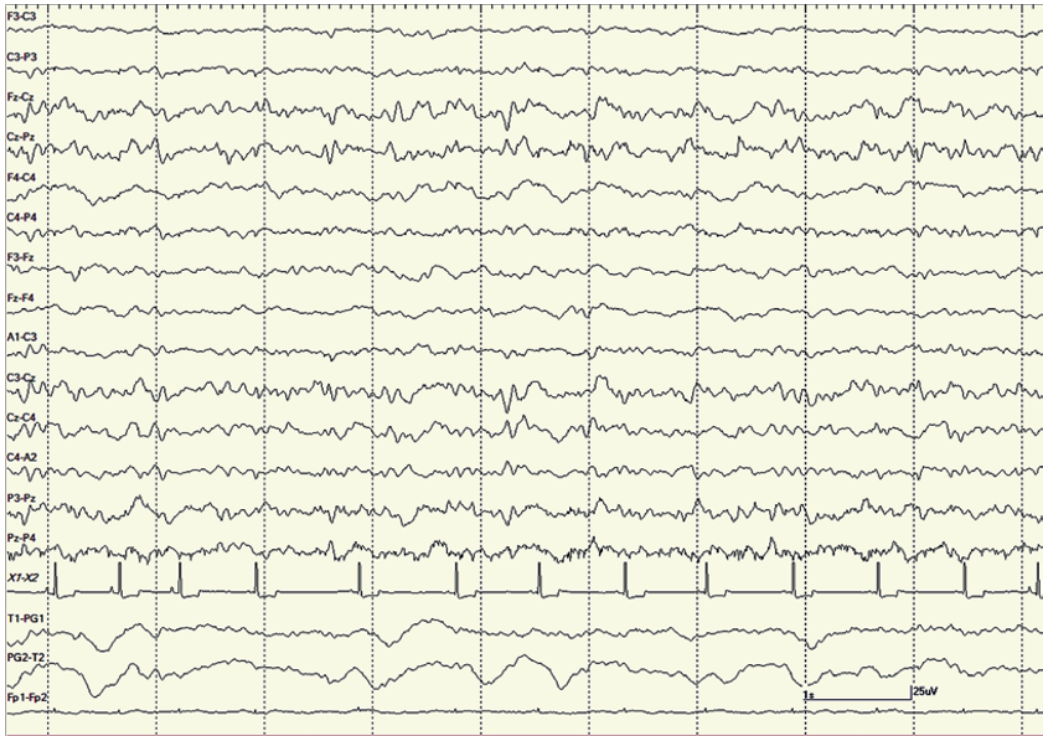


FIGURE 2.1 Above is an EEG of a dog with a typical slow-wave sleep pattern, a "normal EEG." Courtesy of D. Colette Williams, PhD., William R. Pritchard Veterinary Medical Teaching Hospital, Clinical Neurophysiology Lab, University of California, Davis.

distant sites from the point of epileptogenesis (a sort of domino effect—think of the "wave" in a stadium at a football game). Certain areas of the brain, such as the thalamus, possess natural *pacemaker* activity. Thalamic neurons contain a specific variety of voltage-gated ion channels, which allow for the generation of rhythmic self-sustaining action potentials without any external influence. As these electrical signals propagate throughout the brain, they travel within normal anatomic conductive pathways (e.g., corona radiata, internal capsule, etc.), eventually reaching areas such as the motor cortex, resulting in the manifestation of, in several cases, a *generalized motor seizure*, or the limbic structures of the brain, where *focal motor or psychomotor* epileptic seizures are more likely to manifest.

An epileptic seizure is a sudden, involuntary, synchronous discharge of brain neurons. Epileptic seizures are sometimes referred to as arrests, convulsions, spasms, attacks, fits, or an ictus. The outward manifestation of a seizure is dependent on which area of the brain it originates in or propagates to. For example, if the seizure originated from or propagated to the visual center of the brain, the manifestation may be visual hallucinations. *Epilepsy* is a term specifically referring to chronic, recurrent seizures or the propensity for an individual to have more than one seizure (Blume *et al.*, 2001).

Most clinical veterinarians will be presented with numerous cases of dogs with a history of seizures every year (Kay, 1989; Podell *et al.*, 1995). Epileptic seizures are much less common in cats; however, the same approach to a patient having epileptic seizures can be made for cats as well as dogs. The incidence of seizures within the general canine population is estimated at about 0.6–1% of dogs (Kearsley-Fleet *et al.*, 2013; Heske *et al.*, 2014). When compared to the general human population, it is a close approximation, however, in certain purebred dogs, the incidence may be

significantly higher (e.g., Belgian Shepherd at 9.4%) and epidemiological studies are continuing to classify and identify the genetic prevalence of epilepsy amongst different breeds (Berendt *et al*., 2015). As in human medicine, epilepsy is the most common neurological condition a veterinarian will be presented with. The first step the clinician should take in evaluating an animal whose owners are complaining of seizures is to figure out if the animal is indeed having *epileptic* seizures. Other conditions commonly mistaken for epileptic seizures may include:

- Syncope/cardiac disease (collapse)
- Vestibular disease
- Myasthenia gravis
- Cervical pain
- Tremor syndromes
- Exercise-induced collapse or weakness
- Feline estrus behavior
- Myoclonus (episodic shock-like contractions/muscles)
- Behavioral abnormalities/OCD (including normal behaviors such as "scooting")
- Periodic weakness
- Narcolepsy/cataplexy/parasomnias
- Gastric distress
- Paroxysmal movement disorder—stereotypic movement disorder
- Paroxysmal dyskinesia

Technically, the term "seizure" could mean any medical condition resulting in a sudden cessation of normal activity. In the context of our discussion, we will assume the term "seizure" is in reference to an *epileptic seizure*. It is very important before proceeding with an extensive diagnostic workup to determine if the animal is experiencing a true seizure or a "seizure-like" event. A patient questionnaire and videos of the event can be very helpful (see Appendix 2). There is no etiological significance to a seizure. An epileptic seizure simply represents a *sign* or *symptom* of brain dysfunction. In a sense, a seizure is the brain's way of "limping." A limp only tells you there is a problem with the leg but not *what* the problem is. Similarly, a seizure only tells the clinician there is a problem with the brain but not what the problem might be. The brain is a fundamentally excitatory organ, and it is in the animal's best interest, for survivability, to be able to take in as much information from its environment as possible but at the same time be able to filter and focus on a refined amount of information. In a simplistic manner, it helps to think of the brain as a car waiting at a stoplight with the driver having their foot on the gas *and* the brake at the same time—ready to go at a moment's notice but being held back until necessary.

Following a volley of information, the brain will discharge its various responses. Those responses, when considered in aggregate form, will produce a *behavior*. A basal level of excitation can be seen in several areas of the nervous system. For example, the brain is processing proprioceptive information on an almost continuous basis. When we stumble or fall, this basal activity is quick to activate extensor muscles on the side we are falling to. The vestibular system is "primed" for the potential of a fall at all times. The brain is in a constant balance between inhibition and excitation. Neurons want to fire, and it is up to a fine balance between the inhibitory and excitatory components of the central nervous system to keep neuronal activation and

Table 2.1 Mechanisms leading to abnormal neuronal discharge.

- Alterations in inhibitory/excitatory homeostasis
- Changes in transmembrane ion concentrations
- Alterations in neuronal homeostasis
- Alterations in the function of neurotransmitters
- Factors leading to spontaneous firing of large groups of neurons
- Alterations in glucose or oxygen metabolism

synchronization in check. If isolated from their surroundings, neurons will fire spontaneously (Roberts, 1984). When the neuron is placed in an environment such as the brain, its firing potential is influenced by other nearby neurons and components of the extracellular environment. The primary means of *quieting* the brain or holding activation in check is through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), synthesized from the amino acid glutamine.

The epileptic properties of a specific area of the brain are determined by *hyperexcitability* and *synchronization*. Many theories have been postulated as to the generation of epileptic seizures and why some areas of the brain have epileptogenic properties. One of the earliest theories was a lack of inhibition, leading to a *hyperexcitable* environment. Another theory supports the notion that seizures are secondary to a regional area of unusual concentrations of strong or dense excitatory interconnections. With either theory, there is an excess of "gas" in the brain and not enough "brakes." The brain is out of balance.

Most of the mechanisms thought to contribute to the generation of epileptic seizures are centered around the idea of either alterations in the inhibitory or excitatory homeostasis of the brain, changes in transmembrane ion concentrations, alterations in neuronal homeostasis, alterations in the function of neurotransmitters, factors that cause a large group of neurons to fire spontaneously, and alterations in either glucose or oxygen metabolism (see Table 2.1). In the end, many factors are involved in the generation and propagation of seizures. There is no one single cause of epileptic seizures just like there is no one *single* cause for a limp. Most treatments for epileptic seizures are directed at their prevention and not necessarily the cause (with the exception of surgery, see Chapter 10). With an increased understanding of the basic pathophysiology of seizures, more targeted therapies toward the cause of seizures, as opposed to the suppression of seizures, will be possible.

THE NEURON

The neuron is the primary functional information-processing unit of the brain. Collections of neurons and glial cells form aggregates, which allow for the generation of specific brain-derived behaviors such as simple reflexes to complex cognition. Each singular element is essential for overall brain function. The neuron is a highly specialized cell that has the natural ability to create a communicating signal in the form of an *action potential*. A detailed description of underlying neurophysiology is beyond the scope of this book; however, an elementary description of the neuron may help in understanding how various elements of the nervous system come together to either suppress or potentiate epileptic activity. Neurons come in several different forms, evolved for a specialized function relating to the area of the brain where the neuron resides. Neurons create synaptic connections with other neurons. This is the second aspect of neural communication. There are approximately 86 billion neurons in the human brain (16 billion in the cerebral cortex) (Herculano-Houzel, 2012). Added to another 85 billion, nonneuronal cells in the brain combine to form approximately 1 trillion synapses. The dog brain is estimated to have approximately 530 million cortical neurons, whereas the cat brain has about 250 million (Jardim-Messeder

et al., 2017). The brain is more than a just a fancy computer. It is a *physical connection* between matter *and* energy. This collection of biological tissues, is able to create *action*, *thought,* and *conscious awareness*. This amazing organ is responsible for generating great works of art, scientific theories, and complex emotions. An infinite variety of neural connections are possible, resulting in an incomprehensible amount of diversity. It is no wonder things occasionally go wrong. In fact, when considering all of the potential for mistakes, it is amazing the brain actually works so well.

Most neurons are comprised of a cell body, dendrites, and an axon. The dendrites are highly branched extensions of the cell body, which radiate outward, creating a large surface area for contact or *synapses* with other neurons. Think of a large tree with multiple branches and subbranches intermixed with similar trees. A significant variety of specialized dendritic forms exist in the nervous system (Figure 2.2). The axon leaves the cell body at the *axon hillock*. The axon hillock is the point of the neuronal cell body where the summated change in membrane potential results in the propagation of the action potential. The action potential is a self-generating electrical wave. The action potential spreads through the axon as an orthodromic (i.e., one-way) impulse in an anterograde (i.e., away from) manner from the cell body. The axon is often covered by segments of myelin. The segmental nature of this covering allows for *saltatory conduction*. Saltatory conduction is a mechanism of action potential propagation where the electrical charge "jumps" from one unmyelinated (i.e., nodes of Ranvier) segment to another. Think of it in this way: would it be faster to walk from point A to point B or to skip (note: the answer is *skip*) (Figure 2.3)? Once the action potential reaches the terminus of the axon, the signal (information) encoded by the action potential opens ion channels, which then trigger the events leading to synaptic vesicles (containing neurotransmitters) to dock with the cell membrane and release their contents into the extracellular space. The neurotransmitter diffuses across the synaptic junction, where it then comes into contact with receptors on the surface membrane of another neuron. The neuron *releasing* the neurotransmitter is referred to as the *presynaptic cell*, and the neuron *receiving* the

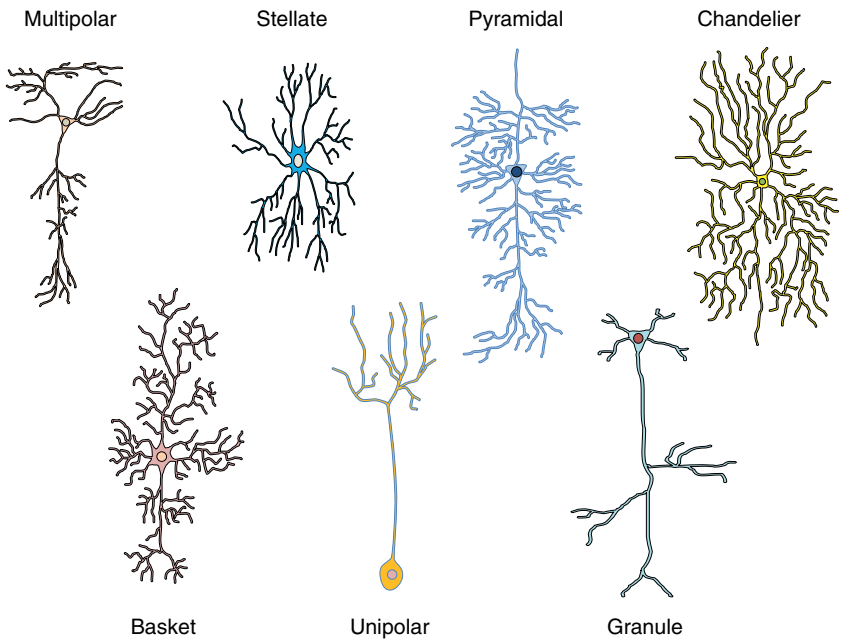


FIGURE 2.2 The brain contains a wide variety of morphologically different neurons, each with its own form to follow function. Neurons may be inhibitory or excitatory. They may have a local environmental influence or send their axonal projections over great distances to affect remote areas of the brain or spinal cord.

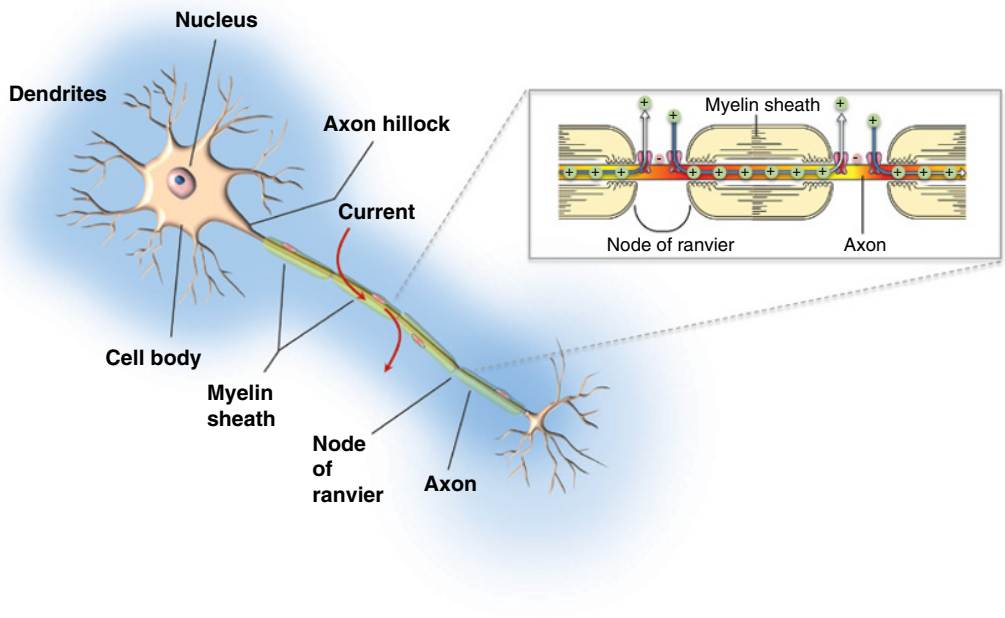


FIGURE 2.3 Anatomy of a "typical" neuron. The action potential is generated at the axon hillock due to the presence of a large number of "leaky" sodium channels. The inside of the cell is negatively charged relative to the outside. Once the membrane depolarizes, the electrical charge propagates down the axon toward the synapse through a process known as *saltatory conduction*. The electrical signal, in the form of positively charged sodium ions, passes through the axon, held inside the axon by the insulating myelin sheath, which prevents the ions from leaking out (inset). At the Node of Ranvier, sodium ions leak out in response to the voltage change, and the membrane is depolarized. Voltage-gated sodium channels open in response to the voltage change and sodium ions flow inward into the axon and the process begins again, propagated toward the synaptic connection.

neurotransmitter is referred to as the *postsynaptic* cell. The connection between the two neurons is the *synapse* (Figure 2.4). Transmitted signals may be inhibitory or excitatory. This is an example of a *chemical synapse* because chemical neurotransmitters are released.

ELECTRICITY 101

Electrical potential or *voltage* (V) is the force exerted on a charged particle (i.e., ion). It is the difference between the cathode (positive) and the anode (negative). The greater the difference, the more force is applied to the ion, which makes it move toward its opposite charge. Opposite charges attract each other and like charges repel one another. The flow of these ions is referred to as *current* (I). If the ions are prevented from flowing toward their opposite charge, they are meeting *resistance* (R). If they move toward their opposite charge, they have *conductance* (g). The greater the conductance (or the lower the resistance), the higher the *current*. This relationship is known as *Ohm's law* and can be expressed as:

$$\text{Current}(I) = \text{conductance}(g) \times \text{voltage}(V)$$

In this simple equation, if conductance is zero (no movement of ions), no current will flow even if there is a high potential (voltage). In the model of a cell membrane, ion channels allow ions to move back and forth across the membrane (Figure 2.5). The ion channels reduce the resistance

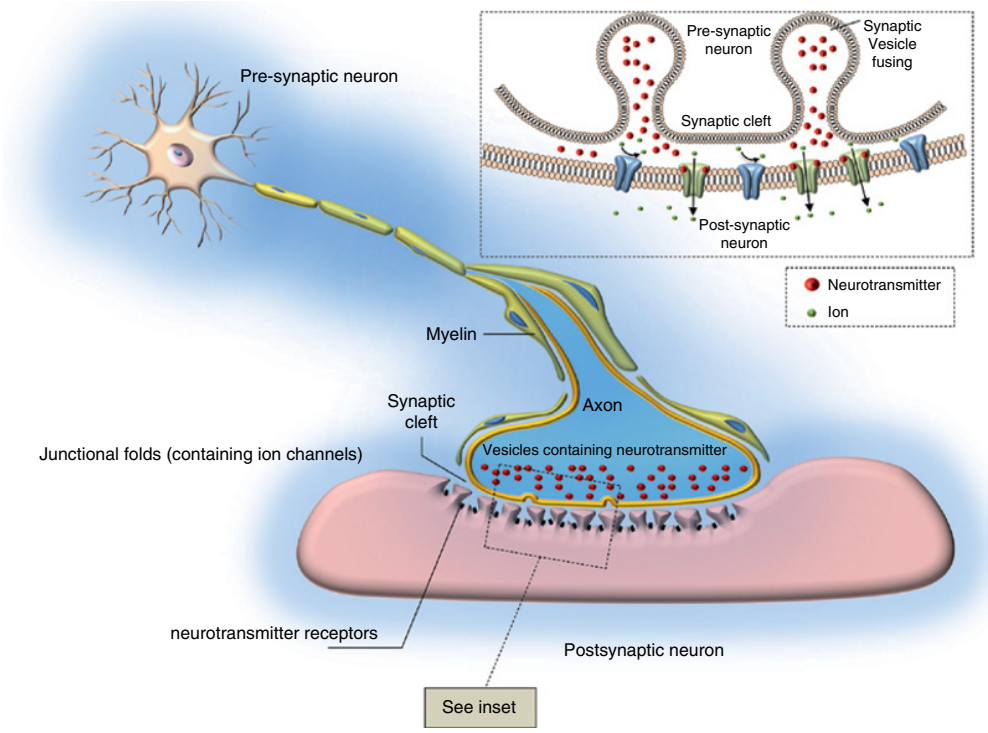
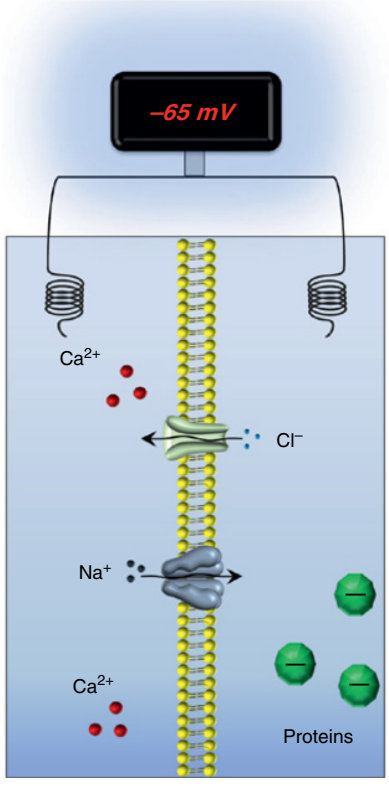


FIGURE 2.4 Example of a typical chemical synapse. The axon terminates near the postsynaptic neuron creating a synaptic cleft. Synaptic vesicles, containing neurotransmitter, fuse to the presynaptic membrane, and their contents are released into the synaptic cleft. The neurotransmitter then diffuses to junctional folds, where it binds to chemical receptors causing these *ligand-gated* ion channels to open allowing ions to pass resulting in either hyperpolarization of the postsynaptic membrane (inhibition) or depolarization (excitation).

FIGURE 2.5 A membrane separates two compartments. Ion channels permeable to chloride and sodium ions are present, allowing the free flow of those ions across the membrane. The movement of ions is referred to as *current* measured in *amps*. Calcium ions are also present but there is no way for them to move across the membrane. Therefore, there is high *resistance* to calcium ions (or no *conductance*). Similarly, the chloride and sodium ions have high conductance and low resistance. The calcium ions provide an electrical gradient for the oppositely charged chloride ions to move toward, while the negatively charged proteins on the opposite of the membrane will attract the sodium ions.



(or increase the conductance), which allows current to flow. By opening or closing ion channels, the *potential* of the cell membrane will change. The presence of other oppositely charged ions or proteins will also create electrical potential (i.e., a draw of the oppositely charged ion across the membrane).

HOW A NEURON "FIRES"

An understanding of what makes neurons fire can be very helpful in not only explaining why a seizure may occur but also why certain medications help prevent seizures and why excessive activity of the brain (in the form of seizures) can lead to brain damage. A single neuron is an amazing, highly evolved, and complex structure, which by itself has the propensity to generate a *signal* (i.e., *action potential*). The neuronal membrane and its associated ion pumps and ion channels are the structures responsible for this characteristic. This structure allows certain ions to be pumped and concentrated on one side of the membrane and others to diffuse across the membrane along a concentration gradient. When a difference of charge exists on opposite sides of the membrane, a potential is present, measured as a *voltage*. However, the ability to generate a signal must be coupled with interconnections involving other neurons to form *circuits*. These circuits, when considered as an aggregate, create a *system* (e.g., visual, auditory, olfactory, and motor) responsible for a certain behavior, reflex, or sensation. Communication depends on an element to generate a message (i.e., signal), transmission of the message (i.e., "wires" or axons), and receipt of the message (i.e., postsynaptic neuron). Billions of neurons making an infinite number of connections and subsequent circuits create the most complex structure known to humans, the brain. These micro- and macro-circuits are responsible for the behavior of the brain. This may be a simple two- to three-neuron circuit, which allows for a reflex or memory, to a collection of macro circuits, which allow for cognition.

A neuron is activated through a highly evolved and specialized electrical gradient. A well-balanced flux of ions across the neuronal cell membrane is responsible for the electrical gradient, which makes up the resting membrane potential (Figure 2.6). To create a membrane potential, we need *ions* (charged molecules such as sodium, potassium, and calcium) on each side of a cell membrane. The movement of those ions is highly regulated. In addition, charged *proteins* help to maintain the potential. The resting membrane potential is the difference in voltage between the inside and outside of the cell. The flow of ions across the membrane is variable through conductance and resistance. The easier it is for an ion to move through a membrane, the higher its conductance and the lower its resistance. When a neuron is quiet, the inside of the cell is electrically negative (hyperpolarized) and the outside is positive. This potential is maintained through an active process using adenosine triphosphate (ATP) to pump ions in and out of the cell and through a passive process whereby ions continuously "leak" down their concentration gradient. Think of this potential as similar to a windup toy. You use energy to turn a crank, which coils up a spring. The spring stores that energy as a *potential* to do work. When you reach a certain point or *threshold*, the energy is released as the behavior of the toy (like a "jack in the box"). When the membrane potential of a neuron reaches the *threshold*, there is an all-or-none firing of the neuron.

Potassium and negatively charged proteins are concentrated inside the cell, whereas sodium, calcium, and chloride are concentrated outside of the cell. Potassium ions readily cross the membrane when the cell is "at rest." The driving force to "attract" the positively charged potassium ions is the negatively charged proteins inside the cell. The proteins cannot cross the cell membrane; however, the potassium ions can (i.e., they have high conductance). This attraction of opposites creates an ionic concentration gradient. Since, sodium, chloride, and calcium ions are concentrated outside of the cell, their conductance through the membrane is very low (and conversely resistance is high). The concentration gradients arise through the actions of ion pumps located in the cellular

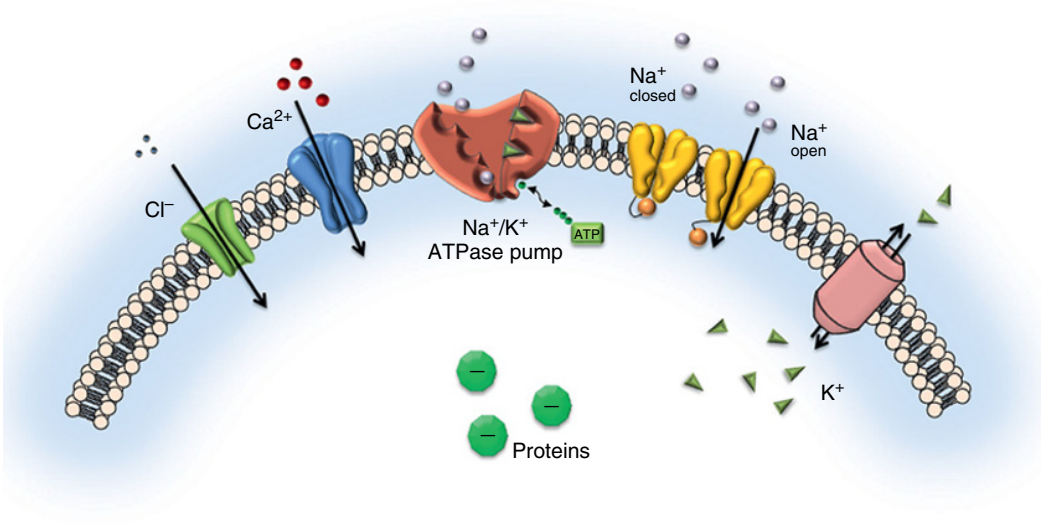


FIGURE 2.6 The typical neuronal membrane is comprised of many elements that allow for a voltage potential. Chloride, calcium, and sodium ions are concentrated outside of the cell, while potassium is concentrated inside the cell. Potassium ion channels allow free movement of potassium across the membrane. Negatively charged proteins confined to the interior of the cell draw potassium ions into the cell. The sodium/potassium ATPase pump pumps sodium and potassium against their concentration gradients (potassium in and sodium out).

membrane and the continual leaking of ions through the cellular membrane. The two most important ion pumps are the sodium/potassium pump and the calcium pump. In the presence of intracellular sodium, the enzyme pump hydrolyzes ATP, and the energy released *exchanges* three intracellular sodium ions for two extracellular potassium ions. The purpose of this very important pump is to concentrate sodium outside of the cell and concentrate potassium inside the cell (Figure 2.7). These processes lead to a *resting membrane potential* of the inside of a typical neuron at −65 mV. For a neuron to fire, the membrane potential must reach a *threshold* (the point where the switch is automatically flipped). The action potential is an *all-or-none* phenomenon. It cannot be graded. The neuron either fires an impulse or is at rest. This potential is primarily due to the conductance of sodium and potassium ions.

Voltage-gated ion channels are transmembrane proteins that allow specific ions to pass through the cell membrane while excluding others. These proteins form pores in the cell membrane. The pores open or close based on the electrical potential of the cell membrane; thus, they are voltage-dependent. The neuronal membrane at rest is very permeable to potassium. When ion channels open, positively charged ions flow to areas where they are less concentrated. Because sodium is concentrated outside of the cell, it will flow into the cell when ion channels are opened (down its concentration gradient). As sodium concentration inside the cell increases, the membrane potential becomes more positive. The threshold for depolarization occurs at roughly −55 mV. Small changes in potassium concentration outside of the cell will lead to depolarization, and the neuron will "fire" once it reaches a threshold. *Ligand-gated ion channels* will become porous to certain ions based on the binding of various neurotransmitters (i.e., ligands) to the extracellular protein surface. Neurotransmitters such as dopamine, GABA, and serotonin will have various excitatory or inhibitory effects depending on their location, receptor subtype, and local microenvironment. Each one of these systems works to create a balanced network of neural activity. It is easy to imagine how a simple defect in a membrane protein could lead to any one of a multitude of genetic forms of epilepsy. The first channelopathy recognized in humans to result in genetic epilepsy is a missense mutation of the

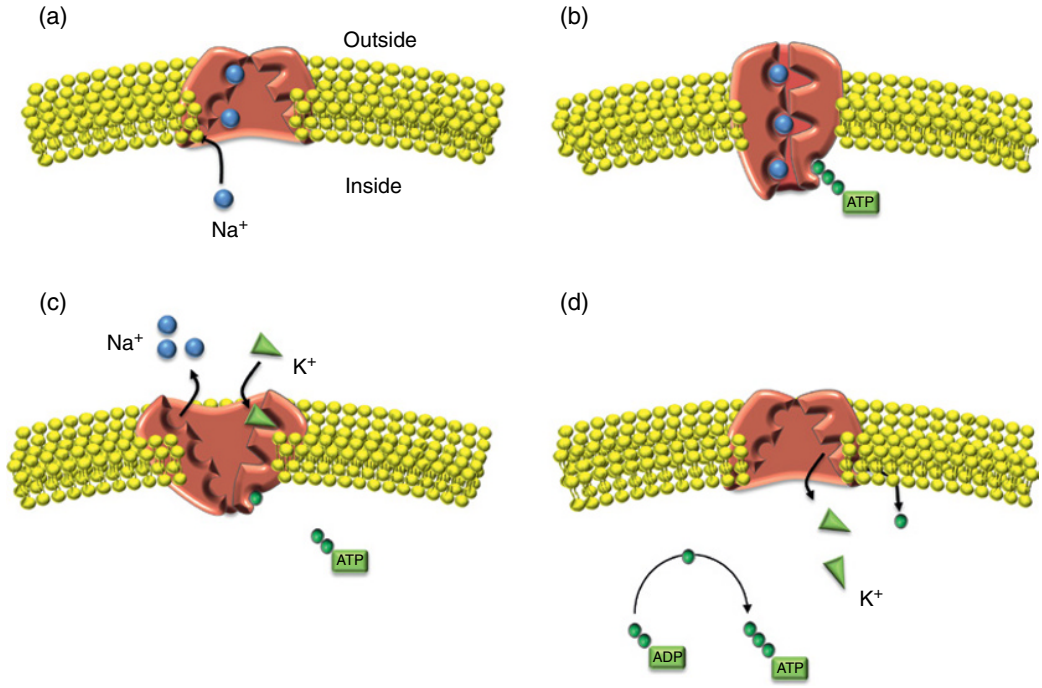


FIGURE 2.7 The sodium/potassium ATPase pump is an enzyme, which hydrolyzes ATP in the presence of intercellular sodium (a). The conformation of the pump changes, (b) releasing three sodium ions to the extracellular environment in exchange for two extracellular potassium ions (c). When the potassium ions bind, another conformation change occurs, releasing potassium to the intracellular environment. The inorganic phosphate ion is released, which allows it to combine with ADP to form ATP and the cycle occurs again (d). The action of this pump ensures sodium is concentrated outside the cell and potassium inside the cell. The pump uses ATP energy to work against the concentration gradient of the ions.

genes Kv7.2 and Kv7.3, which code for the KCNQ2 and KCNQ3 potassium channels. This condition results in the syndrome of *benign familial neonatal seizures*. A protein associated with voltage-gated potassium channels (VGKCs) in the hippocampus (*leucine-rich glioma-inactivated 1 protein* or LGI-1) is known to be associated with temporal lobe epilepsy (TLE) in people and cats (Glantschnigg-Eisl *et al*., 2023). Cats with suspected autoimmune encephalitis can be tested for the presence of LGI-1. Mutations to the leucine-rich glioma-inactivated 2 protein (LGI2) and ADAM23 (a disintegrin and metalloproteinase) protein are known to cause genetic epilepsy in dogs (Seppälä *et al*., 2011, Koskinen *et al*., 2015). The genetic mutation to LGI2 in the *Lagotto Romagnolo* dog has been identified as the cause of *benign familial juvenile epilepsy* or *focal remitting juvenile epilepsy* in the breed (Jokinen *et al*., 2007; Seppälä *et al*., 2011). The mutation interferes with a protein necessary for normal synaptic function. This is one of the first veterinary epileptic syndromes described with characteristic development of focal epileptic seizures between 5 and 9 weeks of age which tend to resolve by 13 weeks with a predisposition of the dogs to develop a behavioral disorder similar to attention deficit hyperactivity disorder (ADHD in humans), later in life (Jokinen *et al*., 2015). In the Belgian Shepherd, mutations of the ADAM23 gene, an important protein associated with VGKCs, neuronal development, and connections of presynaptic and postsynaptic neurons; and of the RAPGEF2 gene which is important for regulating β-catenin gene transcription have been identified (Seppälä *et al*., 2012; Cayabyab *et al*., 2024). These investigations are important as they may help identify targeted therapies. Other investigations are underway to identify genetic defects responsible for the numerous genetic (idiopathic) epilepsies of dogs (Ekenstedt and Oberbauer, 2013).

Buffer systems are also in place to prevent wide swings in ionic concentrations. For example, calcium-binding proteins inside the cell and intracellular organelles can sequester calcium ions. A special potassium buffering network is maintained by astrocytes. Astrocytes are a form of neural glial cell, which serve as supporting cells of the brain and form the bulk of brain tissue. Many of the mechanisms for maintaining the ionic gradient are dependent upon ATP, and therefore, any change that alters either ATP synthesis or utilization, may cause a disruption in the resting membrane potential. If the pumps fail due to any number of reasons (blocked by chemicals, antibodies, exhaustion of energy, etc.), the inside of the cell becomes more positive (e.g., leakage of sodium ions into the cell), and the membrane potential will approach the threshold necessary for the cell to spontaneously fire. Therefore, damage to neurons may lead to a propensity to "fire." A propensity to fire leads to synchronization, which may lead to a seizure.

THE ACTION POTENTIAL

The *action potential* is a self-generating electrical signal originating at the axon hillock, which is propagated toward the axon terminal. It arises from a brief change in membrane potential due to the rapid opening and closing of voltage-gated ion channels. Action potentials serve to transmit information throughout the nervous system from one point to another via a "wavelike" movement (think of ripples in a pond when a stone is cast into it). They can only move away from their source. When a neuronal membrane depolarizes, a wave of subsequent depolarized areas of the membrane is propagated down the axon to the axon terminal, where a neurotransmitter is released into the synapse (Figures 2.3 and 2.4). The neurotransmitter may be excitatory, prompting the next neuron to fire an action potential (i.e., more gas), or inhibitory, causing the next neuron in line to be less likely to fire (i.e., more brakes). A typical action potential lasts about 2 milliseconds (ms). An action potential is triggered when the membrane potential reaches a critical level of depolarization known as the *threshold*. This depolarization can be triggered by many different means in different cells of the nervous system. For example, sensory neurons may be triggered through stretch mechanisms, such as touch or pressure, light, or volatile chemicals (i.e., smell or taste). When the membrane of a neuron is stretched (such as a pinprick on the finger), sodium channels pop open, and the positively charged sodium ions rush into the cell, causing the charge of the inside of the cell to become more positive toward the depolarizing threshold. Once the threshold is reached (about −55 mV), the action potential is triggered. The slower VGKCs open at about the same time as the sodium channels close, causing potassium to rush out of the cell, resulting in hyperpolarization and the cell "resetting" itself (back to −65 mV) for the next action potential. A *refractory period* ensues as sodium channels are inactive and potassium channels are in the process of closing. During this time, another action potential cannot be generated (Figure 2.8). It helps to think of the generation of an action potential as if pressing a doorbell button. You apply gradual pressure with no effect until it reaches a point (threshold) where contact is made and the bell rings. Pressing softer does not make it ring quieter; it just takes longer to generate enough pressure to trigger the bell. Multiple action potentials can be generated through varying degrees of stimulus. This can be directly related to the extent of the depolarizing current. A gentle stimulus may not create enough action potential to cause the neuron to reach the threshold, whereas a strong and continuous stimulus may result in repetitive action potentials (Figure 2.9). In clinical practice, lidocaine is used as a local or topical analgesic by exploiting its pharmacological properties associated with the blocking of fast-gated sodium channels. By preventing the opening of these sodium channels, the action potential is not propagated, and the "pain signal" to the brain is never generated. Theoretically, if the firing of neurons can be attenuated or made more difficult to propagate, any condition (i.e., epileptic seizures) requiring rapid propagation of action potentials to be initiated may be blocked. Through binding to the $GABA_A$ receptor, many antiseizure medications

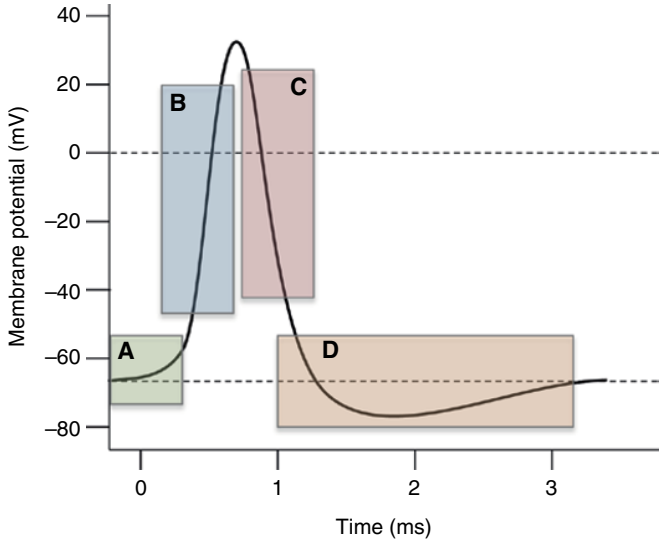


FIGURE 2.8 The action potential. *A. Rest*. When at rest, the conductance of sodium across the neuronal cell membrane equals that of potassium. This equilibrium results in a resting membrane potential of approximately −65 mV for the typical neuron. *B. Rising Phase*. A stimulus occurs, causing sodium channels to pop open. The positively charged sodium ions enter the cell, causing the membrane potential to move toward the threshold for spontaneous firing (approximately −55 mV). At the threshold, the more rapidly opening sodium channels allow a greater conductance of sodium ions into the cell. *C. Falling Phase*. As the sodium channels close, the potassium channels open (about 1 ms after the sodium channels). Potassium exits the cell, causing the membrane potential to become negative again. *D. Undershoot and Refractory Period*. Membrane permeability favors potassium, and the membrane potential approaches that of the equilibrium of potassium (slightly negative relative to rest). Sodium channels are inactivated when the membrane is highly depolarized. As potassium channels close, the membrane potential slowly reaches rest. At rest, sodium channels are once again ready to be activated, and another action potential is possible.

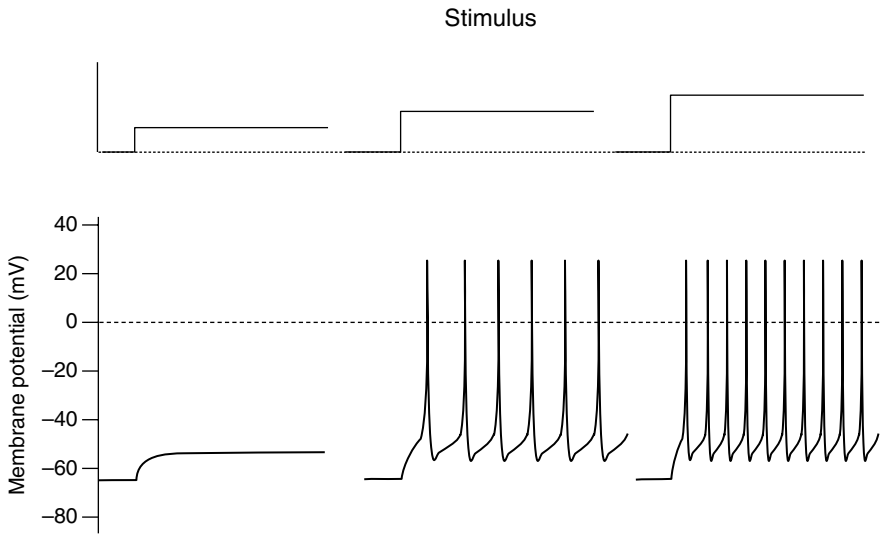


FIGURE 2.9 Dependence of action potential on degree of stimulus. In the first example, too little stimulus is given to reach threshold and generate an action potential. In the middle panel, if the stimulus is great enough, action potentials will be generated. In the final panel, prolonged action potentials will be generated with increased stimulus.

(e.g., benzodiazepines and phenobarbital) open chloride channels, allowing the negatively charged chloride ions to enter the cell, making the interior more negative (hyperpolarized) and therefore less likely to reach threshold to fire (Figure 2.10). Conversely, defects in the genes that code the formation of ion channels (channelopathies), such as the K_{V7} family of genes, which codes for potassium channels responsible for *M-current*, can lead to the generation of epileptic seizures (Engel, 2013). Drugs and toxins that either block (antagonist) or potentiate (agonist) ion channels can have a variety of effects on an organism from inducing seizures such as scorpion toxin blocking potassium channels (so the cells are naturally closer to threshold and more likely to fire) to causing complete paralysis such as the neurotoxin in puffer fish (tetrodotoxin), which, through blockage of voltage-gated, fast sodium channels, blocks all action potentials and results in complete paralysis (the sodium channels cannot open, so the action potential is never generated). On the other hand, we can use these effects to our advantage. Through antagonism of certain potassium channels in the heart, class III antiarrhythmic drugs act to prolong repolarization and prevent reentrant

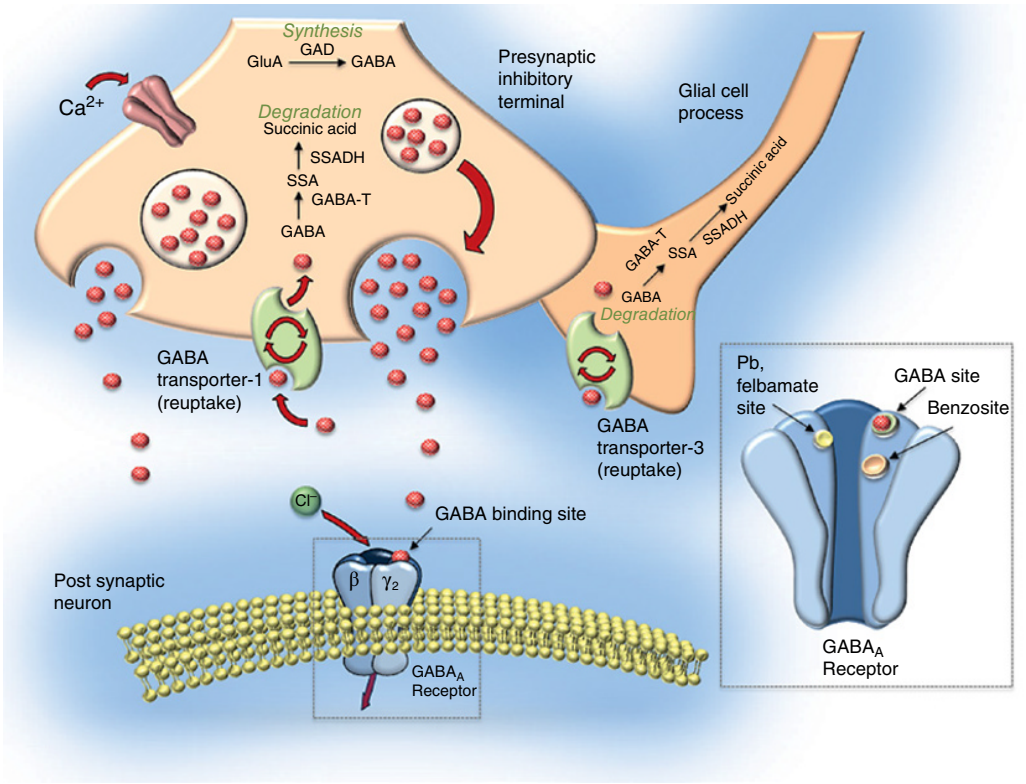


FIGURE 2.10 Typical GABAergic inhibitory synapse. γ-Aminobutyric acid (GABA) is synthesized at the axon terminal from glutamate (GluA) by glutamic acid decarboxylase (GAD). GABA is packaged into synaptic vesicles and stored. An action potential reaches the axon terminal, voltage-gated calcium channels open, causing calcium to enter the nerve terminal. The influx of calcium initiates exocytosis of the synaptic vesicles. GABA is released and diffuses across the synaptic cleft where it binds to the $GABA_A$ receptor, causing the receptor to open and chloride ions to enter the postsynaptic neuron. The negatively charged chloride ions hyperpolarize the cell membrane taking it further from threshold and causing inhibition of neuronal firing. GABA is taken back into the presynaptic nerve terminal through GABA transporter-1. GABA is also removed from the synaptic cleft by the GABA transporter-3 on nearby glial cells. Once in the cell, GABA is degraded to succinate semialdehyde (SSA) by GABA transaminase (GABA-T). SSA is further degraded to succinic acid by the enzyme succinate semialdehyde dehydrogenase (SSADH).

arrhythmias. Numerous genetic abnormalities have been identified in humans, which result in epileptic seizure syndromes. It would certainly be reasonable to assume similar if not identical clinical syndromes exist in dogs and cats, especially when we consider the prevalence and phenomenology of naturally occurring epilepsy in dogs and cats are similar to humans (Steinmetz *et al*., 2013). Knowing how action potentials are generated helps us to understand many of the mechanisms through which antiseizure drugs work.

An incredible diversity of neuronal firing patterns is present because many different types of ion channels and combinations of ion channels have evolved to allow for this variety. For example, the stellate cell of the cerebral cortex will create a relatively steady frequency of action potentials when exposed to a stable depolarizing current. These patterns of action potential discharge can range from fast and repetitive to slow and repetitive to rhythmic (Figure 2.11). While various ion channels and their combinations may lead to differing firing patterns, other variables such as the local environment and presence of inhibitory interneurons, excitatory neurons, and even neuronal circuits can combine to create an unlimited variety of individual neuronal characteristics.

The transmission of an action potential from the nerve cell body to a synapse with other cells occurs through the nerve's axon. As mentioned before, the action potential is initiated at the axon hillock, a region of the cell body where there is a large concentration of voltage-gated sodium channels. This area is often referred to as the *spike initiation zone*. One way to think of the action potential is like a row of dominos falling in succession. The first domino is slowly tipped to the point where it falls (threshold), whereby the fall triggers the next domino to fall. This process continues in one direction to the end of the line. It cannot go backward and cannot start again (i.e., the relative *refractory* period) until the dominos are again set up. Each domino has the same ability to knock over the next domino; therefore, there is no *degradation* in signal strength. Other analogies are "ripples in a pond" spreading out from a rock dropped in the water

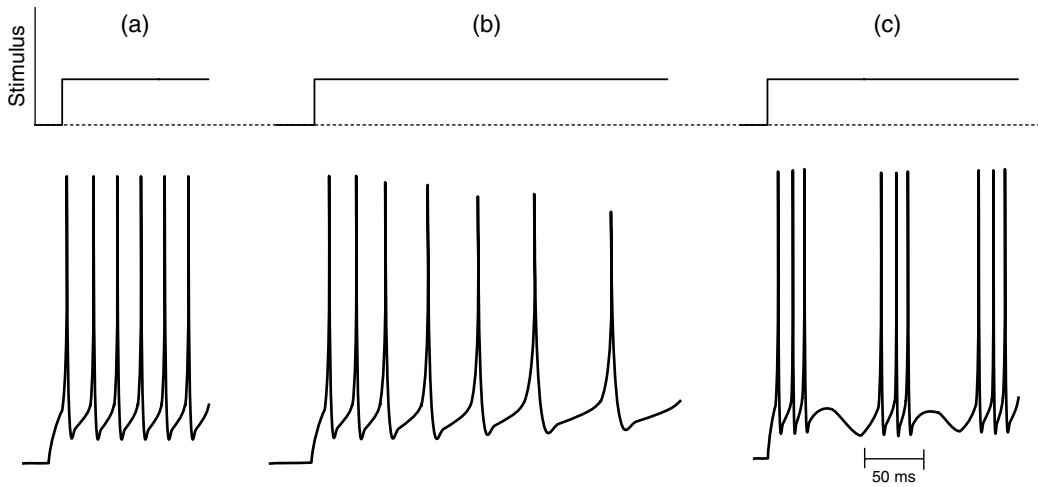


FIGURE 2.11 Neurons not only differ in morphology but also in firing patterns and response to the local environment from which they reside. This diversity adds to the functional differences of the brain. For example, in (a), the steady rate of action potential firing from a cerebral cortex stellate neuron is differentiated from the adaptation to a sustained depolarizing current seen in cerebral cortex pyramidal cells (b). These neurons cannot sustain a consistent firing rate and will quickly demonstrate spike-frequency accommodation. In (c), a burst pattern is observed in response to a depolarizing current (stimulus). Firing patterns are dependent on a multitude of factors such as the type of ion channels, number of channels, dendritic morphology, and back-propagating action potentials, which ultimately create a particular firing pattern, modulation of neuronal function, and synaptic plasticity. Adapted from Agmon and Connors, 1992.

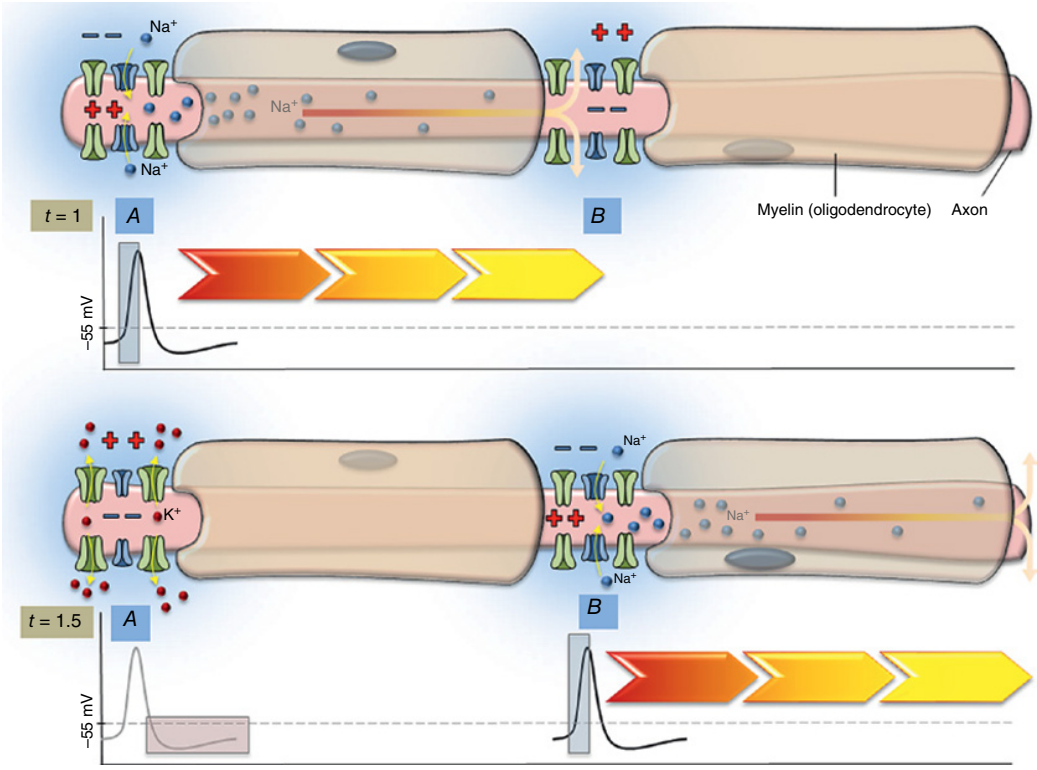


FIGURE 2.12 Saltatory conduction (from Latin meaning *to hop* or *to leap*). The myelin sheath, which surrounds some axons acts like insulation preventing ions from leaving or entering the axon. High concentrations of voltage-gated sodium channels are located between myelinated segments at the *Nodes of Ranvier* (refer to Figure 2.3). A stimulus triggers sodium channels to open at $t = 1$. At that instance of time, the intracellular environment becomes positively charged (depolarized) and an action potential is created (point *A*). The electrical charge (sodium ions) propagates down the axon to the next node being contained within the axon by the myelin. Once the sodium ions reach the next node, they cause voltage-gated ion channels to open ($t = 1.5$ at point *B*), resulting in a repeat depolarization and the propagation of another action potential. Within 0.5 ms of the sodium channels opening at point *A* ($t = 1.5$), the slower-to-activate potassium channels open, causing the membrane to become more negative and hyperpolarize. The segment is now ready for another action potential. Myelination allows the electrical signal to skip from node to node increasing conduction velocity by up to 150 times that of an unmyelinated axon.

or a fuse that has been lit (Figure 2.12). Once the signal reaches the end (synapse), synaptic transmission occurs, typically through the release of neurotransmitters or the opening of voltage-gated ion channels.

THE PAROXYSMAL DEPOLARIZATION SHIFT

The paroxysmal depolarization shift (PDS) is the cellular manifestation of epilepsy. It is a prolonged depolarization, which is transmitted throughout regions of the brain, recruiting other areas of the brain into the seizure discharge zone. High-amplitude, regenerative calcium currents have the effect of inducing rapid, successive, sodium-mediated action potentials at the axon hillock. During individual cell recordings, these appear as high-amplitude spikes occurring in bursts. On an EEG recorded from the scalp, these bursts appear as a "spike." This *burst* firing of sodium action potentials, mediated by calcium and calcium-dependent potassium currents, is followed by a

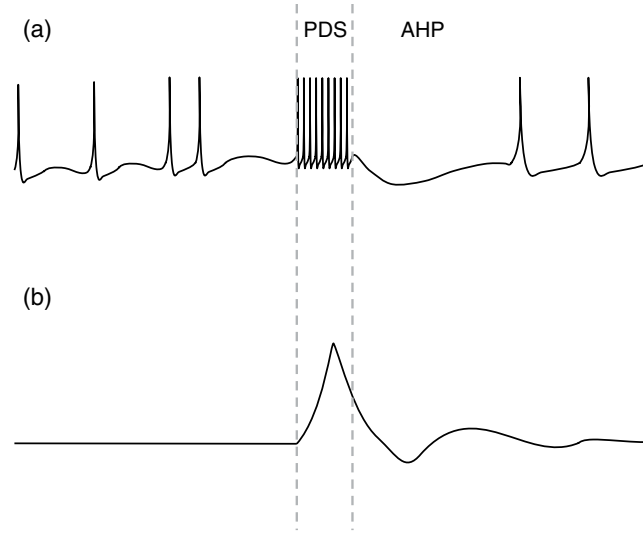


FIGURE 2.13 The paroxysmal depolarization shift (PDS) and afterhyperpolarization (AHP). (a) Single cell recording showing individual spikes followed by a PDS after large numbers of calcium channels open resulting in a burst firing of the neuron. Following the burst firing, the summation of IPSPs and prolonged opening of potassium channels results in a hyperpolarization wave. (b) Scalp electrode recording measures a summation of electrical fields created by the EPSPs and IPSPs from the area the electrodes reside over. A "spike" and "wave" complex is the EEG manifestation of a PDS and AHP.

prolonged *afterhyperpolarization* (*AHP*). On the scalp EEG, the AHP appears as a "wave." Between seizures, interictal spikes, spike waves, and spike-and-slow-wave complexes may be observed (Figure 2.13). In a normal neuron, the summated excitatory postsynaptic potentials (EPSPs) will generate a very brief action potential, lasting only a few milliseconds. If a single neuron is recorded from an epileptogenic site, the abnormal neuron has the potential to create a sustained PDS, which will produce rapid, successive action potentials, lasting up to 100 ms. The combination of the PDS, loss of normal inhibitory influences (such as specialized ion channels), and feedforward and feedback mechanisms (inherent to principal neurons), along with potentially many other variables leading to an abnormal environment, allows neighboring neurons to be influenced and recruited into a pattern of synchronous firing.

NEUROTRANSMITTERS

The classic definition of a neurotransmitter is a chemical (i.e., ligand) released at the presynaptic membrane, typically at the end of an axon terminal, which then activates a postsynaptic receptor. The major neurotransmitters in the brain are GABA, glutamate, acetylcholine (Ach), serotonin, epinephrine, dopamine, and histamine. The main inhibitory neurotransmitters of the brain are GABA and glycine. The main excitatory neurotransmitter in the brain is glutamate. There are multiple subtypes of the various ligand receptors, each possessing different agonist/antagonist properties as well as specific ion permeability (Figure 2.14). A *voltage-gated* ion channel will open and close based on various phases of membrane potential (Figure 2.14a). *Ionotropic* receptors are usually closed until a ligand (neurotransmitter) binds, causing the receptor to open and ions to flow through (Figure 2.14b). A *metabotropic* receptor is a membrane receptor linked to a G-protein (Figure 2.14c). The glutamate (excitatory) receptor is a metabotropic and ionotropic receptor. When glutamine binds to a metabotropic receptor, a G-protein on the inside of the cell is activated. The G-protein travels to a separate site to trigger a signal. Sometimes, the distant site is an ion channel in the cell membrane. In other cases, the G-protein may activate a cellular process, such as the activation of vesicles containing neurotransmitters, allowing them to fuse to the cell membrane and be released into the extracellular space. Metabotropic subclasses of the glutamate receptor utilize this *second messenger* system through the G-coupled protein to activate calcium ion channels indirectly. These receptors are associated with slow synaptic activity because the receptors themselves do not contain an ion pore. The ion channel is activated through the

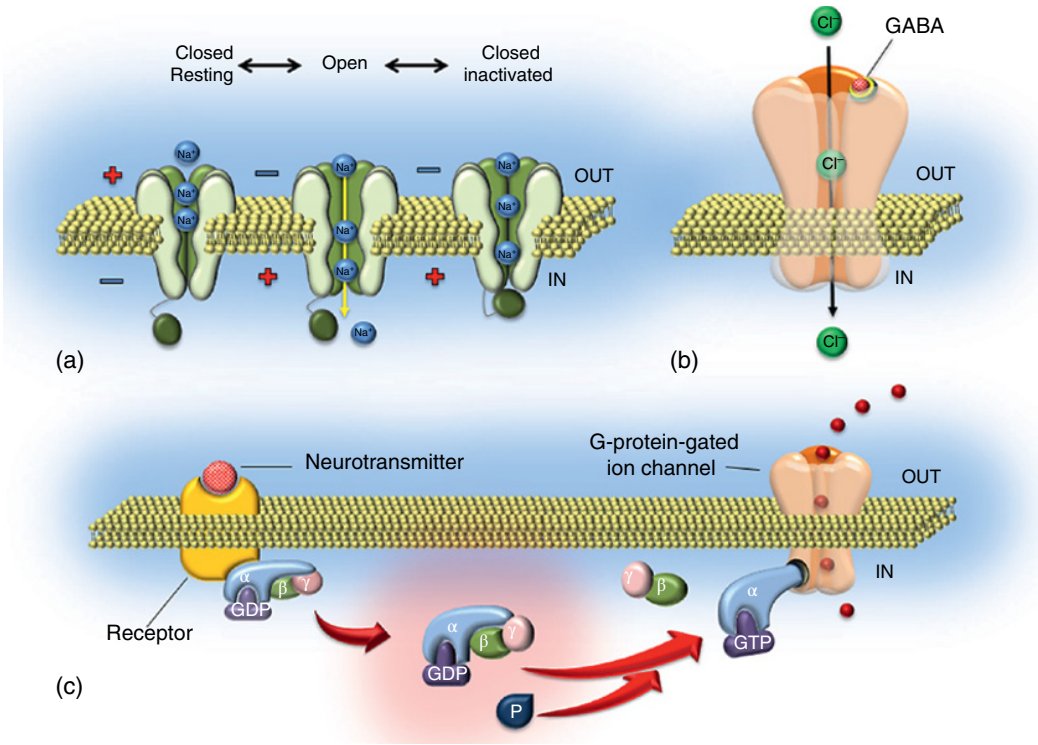


FIGURE 2.14 Examples of receptor types. (a) A voltage-gated sodium ion channel in different conformational states is dependent on the membrane potential. (b) Example of the $GABA_A$ ionotropic or ligand-gated ion channel. GABA binds to the receptor, opening the channel pore, which allows the chloride ion to pass into the cell, causing the membrane to become more negative (hyperpolarize), resulting in inhibition of the postsynaptic neuron. Benzodiazepines, barbiturates, propofol, and alcohol (along with many other substances) also interact with the $GABA_A$ receptor, lowering the threshold for neuronal firing. (c) Simple example of a metabotropic receptor. A neurotransmitter binds to a metabotropic receptor, which is associated with a G-protein. The activation of the receptor allows guanine diphosphate (GDP) to bind with a phosphate ion (P), releasing the β and γ subunits. The α subunit is then free to interact with ion channels, effector proteins, or second messenger systems.

second messenger system. *Ionotropic* subclasses of the glutamate receptors combine ligand–receptor binding with cation channels and include alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate receptors. These are potassium and sodium cation channels associated with fast-acting synaptic transmission. The NMDA receptor allows for the influx of *calcium* into the cells, which under certain conditions (e.g., status epilepticus) may lead to excitotoxic neuronal cell death (Fujikawa, 2005). Agonists of AMPA, NMDA, and kainate will induce seizures in experimental studies, while *antagonists* of the substances will attenuate or suppress seizures (e.g., ketamine and *maybe* propofol). Ionotropic receptors act very fast. Metabotropic receptors take longer for their effect, although the effect can influence distant sites. To further add to the diversity, presynaptic metabotropic glutamate receptors are inhibitory, and postsynaptic metabotropic glutamate receptors are excitatory (Engel, 2013). Many other chemicals such as hormones and neuropeptides also play a more minor role in brain communication, behavior, and disease. As we learn more about these interesting compounds in regard to their ability to either induce or suppress epileptic seizures, we will likely gain more therapeutic options.

GABA is the major inhibitory neurotransmitter in the brain. There are two types of GABA receptors: $GABA_A$ and $GABA_B$. *$GABA_A$* receptors are located on the postsynaptic nerve terminal and play a major role in the inhibition of neuronal firing. When a $GABA_A$ receptor is activated, an ion channel opens, allowing negatively charged chloride ions to enter the cell. This influx of anions hyperpolarizes the cell membrane, inhibiting the action potential (Figure 2.14b). Postsynaptic *$GABA_B$* receptors produce slow inhibition through potassium currents. *Presynaptic* $GABA_B$ receptors reduce calcium current through the *guanosine triphosphate* (GTP)-binding protein second messenger system, leading to reduced neurotransmitter release. The location of the $GABA_B$ receptor allows for modulation of presynaptic and postsynaptic functions. Benzodiazepines (i.e., valium-like drugs), barbiturates (e.g., phenobarbital), and alcohol all bind to the $GABA_A$ receptor, leading to an overall reduction in neural activity (therefore reducing the potential for seizures). $GABA_A$ autoantibodies have been identified in a dog's cerebrospinal fluid (CSF) and serum with refractory epilepsy, who after failing conventional antiepileptic drug therapy, eventually responded to corticosteroid treatment (Huenerfauth *et al.*, 2022).

Autoimmune encephalitis is recognized as a drug-resistant form of epilepsy, at least to traditional anti-seizure medications. Antibodies may be directed at surface antigens or intracellular antigens (characteristic paraneoplastic antibodies) (Xie *et al.*, 2021). Neuronal surface receptor antibodies include the following:

- Anti-$GABA_A$ and $GABA_B$ receptors
- Anti-NMDA receptor
- Anti-AMPA receptor
- Anti-contactin associated protein-like 2 (CASPR2)
- Anti-leucine-rich glioma inactivated 1 and 2 (LGI1 and LGI2)

In human medicine, it is fairly well recognized that each antibody/antigen interaction will commonly manifest with a distinct clinical syndrome. The veterinary ability to recognize these syndromes is just beginning to develop. For the most part, we agree that cats with LGI1 autoantibodies will typically present with orofacial automatisms (chewing gum fits), which often secondarily generalize. In humans, a similar syndrome exists with characteristic fascio-brachial dystonic seizures (strikingly similar to cats), with characteristic magnetic resonance imaging (MRI) changes to the temporal lobe and hippocampus—which may also be seen in cats, however, recognized MRI changes in cats are rare (possibly due to size of the feline brain and magnet strength of the MRI) (Glantschnigg-Eisl *et al.*, 2023). Finally, a response to immunomodulatory therapy appears to be a possible treatment option in both species (as well as dogs). Humans typically also present with cognitive impairment, sleep disorders, refractory hyponatremia, and confusion—signs we might need to anthropomorphize to a cat or dog. Genetic mutations resulting in LGI1 protein dysfunction present very differently and respond very differently to treatment compared to autoantibodies directed at LGI1 (Fels *et al.*, 2021). Humans with LGI1 mutations develop a form of TLE, whereby seizures may be triggered by audio stimuli (such as a bell ringing) (Michelucci *et al.*, 2007). These patients tend to respond very well to AED, while those with autoantibodies respond to corticosteroid treatment, especially if treated early in the course of their disease.

LGI1 indirectly regulates postsynaptic AMPA receptor surface expression and *loss* of LGI1 increases excitatory postsynaptic transmission (Figure 2.15) (Fukata *et al.*, 2006; Zhou *et al.*, 2009). This paradoxical reaction (AMPA is an *excitatory* neurotransmitter receptor) is thought to be due to changes in presynaptic function, such as altered neurotransmitter release (Baudin *et al.*, 2021). However, it is suspected the altered modulation of the presynaptic Kv1.1 potassium channel, by disrupted LGI1, is what leads to epileptic seizures, not necessarily any changes to AMPA function (D'Adamo *et al.*, 2020). LGI1 modulates VGKCs at the presynaptic neuron by

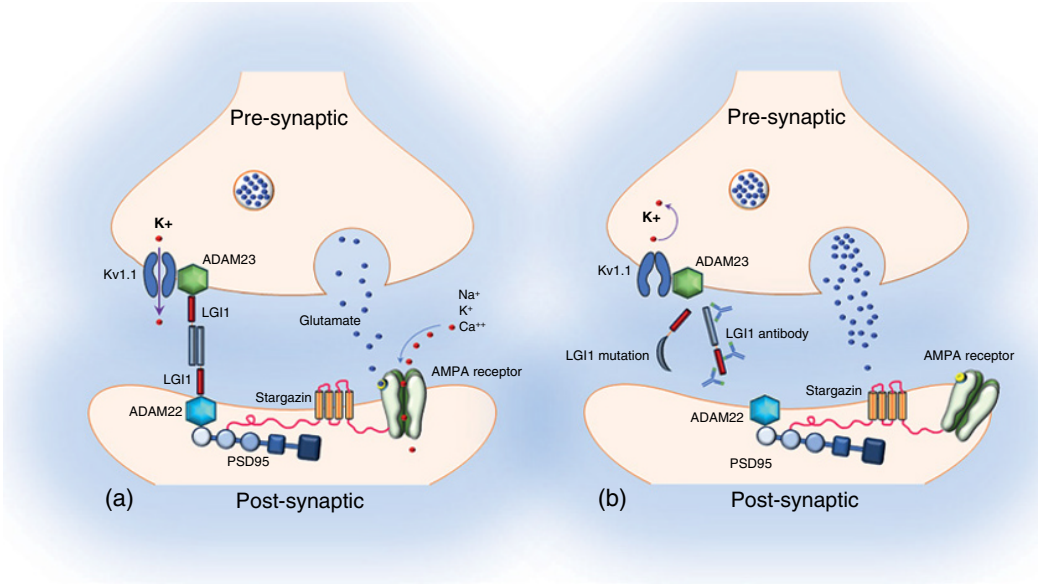


FIGURE 2.15 (a) The leucine-rich glioma inactivated 1 protein (LGI1) is a secreted neuronal protein, which is highly concentrated in the nervous system and highly expressed in the hippocampus. The protein interacts with the presynaptic ADAM23 and postsynaptic ADAM22 transmembrane proteins. At the level of the presynaptic neuron, LGI1 modulates the voltage-gated, Kv1.1 potassium channel, by preventing its rapid inactivation and influencing neurotransmitter release. At the postsynaptic neuron, LGI1 influences the surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA). (b) Loss of function of LGI1 due to mutation or binding with autoantibodies (i.e., limbic encephalitis) leads to increased excitatory synaptic transmission due to a decrease in ADAM22 expression, as well as alterations to Kv1.1 modulation and AMPA expression. Mutations of the LGI1 genes as well as autoantibodies directed to the protein result in epileptic seizures, however, patients present with different clinical syndromes. Adapted from: Baudin, P., Cousyn, L., & Navarro, V. (2021). The LGI1 protein: molecular structure, physiological functions and disruption-related seizures. *Cellular and molecular life sciences: CMLS*, *79*(1), 16. https://doi.org/10.1007/s00018-021-04088-y. Fig. 2. With permission from Springer publishing.

preventing their rapid inactivation and therefore preventing hyperexcitability through the delay of neuronal firing. This fine-tuning function helps to control the action potential timing, frequency, and shape, which also modulates neurotransmitter release from presynaptic nerve terminals. Autoantibodies directed at VGKCs have been demonstrated in 5/14 cats with limbic encephalitis and out of the five positive cats, four cats also had autoantibodies to the LGI1 protein complex (Pakozdy *et al*., 2013; Binks *et al*., 2022). Mutations to the LGI1 gene result in cortical dysplasia another recognized cause of epilepsy (Silva *et al*., 2019). LGI1 plays an important role in early central nervous system (CNS) development, particularly in the brain where one of its primary functions is the pruning of neural networks. Additionally, it has other diverse roles such as control of myelination in the central and peripheral nervous systems (Silva *et al*., 2019).

Anti-NMDA receptor antibodies have been demonstrated in a polar bear and in dogs diagnosed with meningoencephalomyelitis of unknown origin (MUO) (Prüss *et al*., 2015; Stafford *et al*., 2019). Until commercial tests are available on a routine and cost-effective basis, the clinician may consider trying immunomodulatory doses of corticosteroids if the index of suspicion for autoantibodies is high.

The phenothiazine sedative, *acepromazine*, has long been implicated in potentiating epileptic seizures in veterinary patients. The biogenic amines (e.g., dopamine) are known to inhibit epileptic activity depending on which receptor subtype is activated and what area it resides in or projects to

(Boison, 2012; Bozzi and Borrelli, 2013; Li *et al*., 2013). Phenothiazines are biogenic amine *antagonists* and potentiate epileptic seizures (Ruffmann *et al*., 2006). The aliphatic phenothiazines (chlorpromazine and its close relative acepromazine) have uses ranging from antipsychotic effects in humans (chlorpromazine) to sedation in veterinary patients (acepromazine) and treatment of allergic reactions (chlorpromazine acting as an antihistamine). The aliphatic phenothiazines are the most potent inducers of epileptic activity, and reports of generalized seizures following treatment for psychosis in humans are well documented (Schlichther *et al*., 1956; Ruffmann *et al*., 2006). While numerous veterinary textbooks warn against the use of acepromazine in patients who might have a predisposition to epileptic seizures, references to support these warnings are lacking. It is suspected the concern stems from the early observation of epileptic seizures in humans following the use of chlorpromazine and induction of seizures in dogs (with a history of seizures) following rapid infusion of chlorpromazine (Holliday *et al*., 1970). Other literature does not support this concern with the use of acepromazine (Tobias *et al*., 2006; Drynan *et al*., 2012). Theoretically, phenothiazines could promote epileptic seizures; therefore, if there is the possibility of potentiating an epileptic seizure (especially in known epileptics), a safer alternative should be considered.

CONNECTIONS

Neurons must form connections to make something happen (i.e., sensation, behavior, and memory). Neurons do not function in isolation. They form dense connections through chemical and electronic (gap junction) synapses. As previously mentioned, a single neuron may make up to 10,000 synapses with other neurons. At a microscopic level, this may appear similar to a dense tangle of tree branches in a thick forest. An incredible amount of diversity is created through the various combinations, numbers, and morphologically different connections inherent to the nervous system. Combined, the dense thicket of neurons, axons, dendrites, and glial cell processes forms the matrix or substance of the brain known as the *neuropil*. Beyond synapses, neurons will be organized into *circuits*. However, from this point forward, our traditional way of thinking about how the brain is further organized is starting to change. A simple paradigm, where one discrete area of the brain was responsible for one function (auditory cortex, visual cortex, somatosensory, and motor cortices, for example) was based on those neural circuits being organized into *systems*. *Epileptogenicity* is the pathological tendency of neuronal circuits to generate spontaneous epileptic seizures. Circuits are groups of neurons, which form to create a common function or pathway to a behavior, sensation, or process. *Efferent* neurons are those carrying information away from the nervous system. *Afferent* neurons carry information to the nervous system, and *interneurons* are neurons that form connections between different nerves or are only involved in a local circuit. Circuits formed to create a common process or behavior were organized into systems such as the auditory or visual systems. These systems were then further grouped into primary *sensory*, responsible for taking information into the brain regarding our environment, and primary *motor*, responsible for executing behavior and processes. Additionally, other functions such as memory and emotion are potentially very simple or complex interactions between neural circuits and the various systems.

With advances in functional neural imaging, along with electrical stimulation studies, a new model of a meta-networking brain, where microscale neural connections, of an individual neuron-to-neuron interaction all the way to the macroscale of cognition, allow for processing of high-level cerebral functions, based on distributed subnetworks and their functional integration with each other. For example, the visual subnetwork may integrate with memory, learning, and other associated stimuli (e.g., olfactory and auditory) along with emotion, conation, and cognition to form individualized and independent unique reactions to a visual stimulus. Those reactions, whether generated for the first time or the millionth time, will never be the same because the

spatiotemporal associations are continuously in a dynamic state. This model accounts for the amazing neural plasticity of the brain, whether from injury or dysgenesis. The model depends on brain representations, which naturally change over time and are in a continuous process of evolving. Therefore, how does this model impact our understanding of epilepsy, and how can that understanding help us with treatment? Epilepsy is now viewed as a *network disorder* as opposed to a specific region of the brain where dysfunction resides alone (Sinha *et al*., 2022). The dynamic and distributed aberrant network as a whole is responsible for the generation of epileptic seizures, whether generalized or focal, as opposed to a discrete seizure focus (Geier *et al*., 2015). Long-term EEG studies in humans have shown changes in the seizure onset zone throughout a macroscale epileptic network, leading to predictive information regarding impending seizures (Rings *et al*., 2019). Furthermore, many of the predictive nodes have no association with focal epileptic areas and never play a role in the evolving epileptic network, emphasizing their peripheral but fundamental role in epileptogenesis. We currently treat epilepsy with medications that target the entire network (i.e., nonspecific pharmacology). Investigators are looking into node-specific pharmacology, optogenetics (genetically engineered, light-sensitive proteins used to control the functions of cells—how cool is that?), gamma knife, high-intensity focused ultrasound, laser thermotherapy, and focal cooling (to name a few) modalities applied to specific (not necessarily epileptic seizures zones) areas of the brain, identified to have an impact on the generation, spread, or cessation of epileptic seizures. Predictive modeling may identify a *vertex* (individual cell up to a region(s) of the brain) and *edges* (areas where vertices connect) that influence but are not wholly responsible for epileptic seizures. Understanding the model and knowing the problem that needs to be solved gives investigators a road map to use predictive modeling along with newly developed therapies to target the implicated node(s) that contribute to the disorder.

Synapses

Neurons need connection(s). A synapse is a connection between neurons. Nerve cells have the ability to communicate through synaptic connections. The synapse is composed of the axon terminal (presynaptic element) and the membrane of the adjacent dendrite or cell body (postsynaptic element). The space between the two elements is the *synaptic cleft*. This space is typically between 20 and 40 nm in the case of a chemical synapse and approximately 3–4 nm for electrical synapses or gap junctions (Hormuzdi *et al*., 2004). *Electrical synapses* allow for very rapid communication utilizing the passive flow of ions and chemicals through channels or pores, which connect two cells (Figure 2.16). Chemical synapses are slower than electrical synapses and utilize the secretion of neurotransmitters, which then diffuse the distance from the presynaptic terminal to the postsynaptic membrane where they then interact with receptors to elicit a response (Figure 2.4).

Neurotransmitters are either synthesized or packaged in the presynaptic axon terminal into synaptic vesicles. The building blocks of neurotransmitters arrive at the axon terminal either through anterograde axonal transport or the recycling of neurotransmitter elements at the axon terminal via the presynaptic membrane. When an action potential reaches the axon terminal, voltage-gated calcium channels open, allowing calcium influx into the presynaptic terminal. Calcium binds to intracellular proteins, resulting in phosphorylation and the activation of protein kinases. This complex interaction of multiple proteins activates vesicle trafficking at the presynaptic terminal. Vesicles containing neurotransmitters undergo a highly coordinated sequence of events leading to the docking of the vesicle to the presynaptic membrane, fusion, and release of neurotransmitters into the synaptic cleft. A single protein abnormality in this process may lead to the failure of neurotransmitter release, reduced uptake of neurotransmitter components, or miscommunication in the vesicle trafficking process leading to *increased* excitability. *Levetiracetam* (Keppra®) is an antiseizure drug that has the unique characteristic of selectively targeting epileptogenic neurons (i.e.,

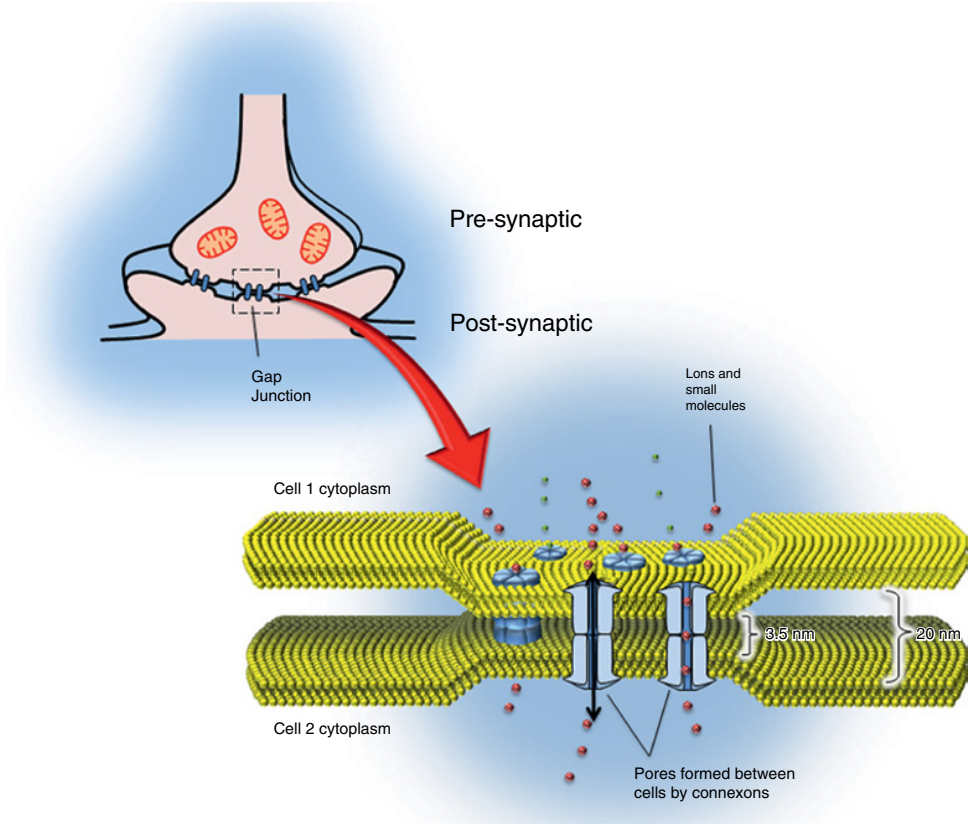


FIGURE 2.16 An electrical synapse. In this example, a presynaptic neuron and a postsynaptic neuron are connected via *gap junctions*. In the enlargement, protein subunits called *connexins*, which are present at the gap junction within the plasma membrane, join together to form *connexons*. Connexons from each cell interact with one another forming pores through which small molecules and ions can readily move from cell to cell in both directions.

hypersynchronous), thereby resulting in a more specific antiepileptic effect and fewer side effects through a narrower mechanism of action and subsequently more-broad therapeutic window (i.e., more specificity and fewer side effects). The mechanism of action is not completely understood; however, it is known to bind to *synaptic vesicle protein 2a* (*SV2a*) and modulate its activity (Lynch *et al.*, 2004). SV2a is involved in vesicle trafficking at the axon terminal where it binds to synaptotagmin-1 (Syt1), a protein that regulates synaptic vesicle activity. Upregulation of the gene that encodes for SV2a has been associated with the kainate-induced seizure model of epilepsy (Winden *et al.*, 2011). However, loss of SV2a is associated with reduced inhibitory neurotransmission, and its expression is decreased in cases of chronic epilepsy (Janz *et al.*, 1999; van Vliet *et al.*, 2009). Knockout mice lacking the SV2a protein have severe seizures and die within a few weeks of being born (Lynch *et al.*, 2004). The SV2a protein plays an important role in regulating the size of the neurotransmitter pool to be released, as well as interacting with numerous proteins involved in neurotransmitter release. Levetiracetam selectively binds to the SV2a protein, although the molecular basis of its action is unknown (Wu *et al.*, 2024). SV2a overexpression is as problematic as underexpression—so this little rascal seems to be a bit of a "Goldilocks" protein (Nowack *et al.*, 2011). The SV2a protein and other proteins involved in vesicle trafficking are new targets for the development and identification of more specific-acting antiseizure drugs.

After neurotransmitters have bound to the target receptor, they are released back into the synaptic cleft and recycled via reuptake receptors on the presynaptic membrane, degraded via enzymatic processes (i.e., acetylcholine), or removed through reuptake by nearby glial cells (Figure 2.10). Abnormalities in synaptic reuptake may also lead to excessive "excitatory" neurotransmitters (such as glutamate) remaining in the "neighborhood" of a neuron, predisposing the neuron to fire again and again and again; potentially leading to a seizure. One of the many mechanisms of action of *zonisamide* (Zonegran®) in preventing seizures is through the downregulation of the glial cell GABA reuptake transporter (GAT-1), resulting in more GABA (inhibition) in the extracellular environment (Engel, 2013). Alterations in the synthesis or degradation of neurotransmitters can influence epileptogenesis. Valproic acid exerts some of its antiseizure effects through the inhibition of GABA *transaminase* (GABA-T), which is necessary for the metabolism and breakdown of GABA (Löscher, 1999).

Gap Junctions

Electrical synapses are formed by gap junctions. Gap junctions are low-frequency filtering, bidirectional, rapidly transmitting passive pores formed between two adjacent cells. Gap junctions provide a direct cell-to-cell continuity. *Connexins* are the transmembrane proteins, which form gap junction pores. These pores are formed from two hemichannels, known as *connexons*, each comprised of six connexin subunits. The channels of one pore will connect to an adjacent pore in another cell membrane to create a gap junction or connecting conduit between the cytoplasm of two adjacent cells (Figure 2.16). Gap junctions allow free passage of ions and molecules up to 1 kDa in size between cells due to a diameter of approximately 16–20 Å. Connexons are expressed in different cells, at different times of development and maturity, and are thought to play a very important role in the developing brain and especially the development and maintenance of neural *super-networks* (Hormuzdi *et al*., 2004). Gap junctions occur in all cells of the nervous system and allow direct communication between cells of similar function (glial to glial) and of dissimilar function (neuron to glial or astrocyte to oligodendrocyte). The interconnectivity of one glial cell to another creates the ability to send signals over vast distances of the nervous system. Because the coupling of two cells allows for very rapid communication, gap junctions allow for a very precise, temporally synchronized, signal transmission. This characteristic has been identified in several areas of the brain as the ability to generate very *rhythmic* activity. Neural networks, which contain a large number of gap junctions transmitting electrical signals, will fire in a more temporal, homogenously synchronized manner (White *et al*., 1998).

The maintenance or propagation of *failure of disassociation* of gap junction connections in the mature brain, may be one of the underlying causes for enhanced synchronous activity associated with epilepsy. Non-synaptic epileptiform activity is more common in the immature brain, and gap junction connections are more common in the immature brain as well (Roper *et al*., 1993). Experimental models that block gap junction communication show suppression of spontaneous, synchronous events in the C1A region of the rat hippocampus, and conversely, models that enhance gap junction communication result in enhanced spontaneous activity (Perez-Velazquez *et al*., 1994). Gap junction communication can be augmented through intracellular alkalization and suppressed through intracellular acidosis. This mechanism may explain why hyperventilation, which results in systemic alkalosis, is used clinically to induce seizures and why certain systemic acidifiers, such as the ketogenic diet, are recognized as anticonvulsants (Perez Velazquez and Carlen, 2000), although any changes in systemic pH, intracellular pH, or the neuronal microenvironment are likely to result in a wide variety of possible effects to epileptogenesis. Carbenoxolone, a drug used to treat gastric ulcers, is a gap junction blocker at high concentrations and may provide future use as an antiseizure medication (Liu *et al*., 2022) (see Chapter 7). A gap junction could represent the form of communication between friends in a stadium who are

physically close to one another (gap junction). When one friend (neuron) starts to chant (fire spontaneously), the nearby "familiar" friend is more likely and quicker to join in the chant (temporal synchronization) than a complete stranger (chemical synapse) several seats away. The gap junction communication would not only be stronger but also more likely to be temporally synchronized (less delay). Cells connected through gap junctions, firing in synchrony, will also change the microenvironment through temporally enhanced extracellular potassium accumulation further leading to increased excitability and local increases in pH (alkalosis). This *depolarization shift*, beginning at the level of connected gap junction communicating neurons, can lead to increased neuronal firing through more distant chemical synapses.

THE NEURONAL ENVIRONMENT

The nuances of the local neuronal environment can have a huge impact on the development, maintenance, and functionality of a neuron and its node. The excitability of individual neurons is governed by both intrinsic factors and extrinsic factors. *Intrinsic* factors are those having to do with the neuron itself, while *extrinsic* factors are those related to the neurons' extracellular environment. Examples of intrinsic factors include the following:

- The distribution and number of certain ion channels can lead to a multitude of variations relating to action potential propagation, speed of activation, and feedback loops.
- The biochemical modification of receptors may significantly alter the receptor characteristics. For example, ion channel protein palmitoylation is essential for quality control of ion channel expression and maturation (Shipston, 2011). The clustering and cell surface stability of $GABA_A$ receptors is regulated by palmitoylation of intracellular cysteine residues (Rathenberg *et al*., 2004). Alterations in this clustering through disorders of protein palmitoylation may lead to attenuated inhibition.
- The modulation of gene expression can significantly alter the ion selectivity of an assembled ion channel. For example, a single neurotransmitter may have different effects through the modulation of mRNA encoding for a specific protein subunit of the receptor. The "new" receptor built from the altered protein subunit may have completely different ion selectivity.
- The activation of second messenger systems leads to an elaborate sequence of biological reactions and processes, resulting in the downstream activation of specific enzymes, which alter neuronal function and cellular metabolism. This slow form of signal transduction can have the advantage of signal amplification. A single neurotransmitter binding to a G-coupled membrane protein has the capability to influence the activity of multiple ion channels. The possible influences on neuronal activity are extremely diverse and complex.

Examples of extrinsic factors include the following:

- Changes in the extracellular environment, including ion concentration, glial cell populations, and local neuron populations. The number of glial cells in the extracellular environment can have a dramatic impact on the buffering of extracellular ion concentrations. If the concentration of sodium in the extracellular environment is altered through damage to glial cells or overproduction of glial cells (such as gliosis associated with glial scarring secondary to brain injury), the nearby neuron the glial cells are serving may be more likely or less likely to fire based on the changes in the local ion concentration.
- Changes in glial cell modulation of neurotransmitters. If the local and regional glial cells alter their uptake of a neurotransmitter, which would normally serve to excite a neuron, the glial cells are in effect causing inhibition of neuronal firing through the increased reuptake of excitatory neurotransmitters. Less glutamate leads to inhibition through *lack of* excitation.

- Alterations in synaptic contact or synaptic firing. For example, a single presynaptic action potential may not lead to threshold-triggered firing of the postsynaptic action potential; however, multiple presynaptic action potentials can lead to *spatial summation*, or an increased frequency of postsynaptic action potentials by a single dendritic connection resulting in *temporal summation* may result in a postsynaptic axon reaching threshold (Figure 2.17). Long-term potentiation and long-term depression are other mechanisms a neuron may develop to become either more efficient or less efficient at firing, which, depending on the output of that neuron, may lead to either more excitation or more inhibition (Figure 2.17).
- Alterations of the blood–brain barrier (BBB). Disruption of the BBB has been shown to be both a *cause* and an *effect* of epileptic seizures. Magnetic resonance imaging (MRI) studies utilizing dynamic contrast enhancement can help investigate disruption of the BBB, which has been shown to affect up to 37% of dogs diagnosed with idiopathic epilepsy (IE) (Hanael *et al*., 2019). However, is this a cause or an effect? It seems to be a possibility with both. Experimental studies purposely causing an alteration in the BBB have shown to induce epileptic seizures, much like any other

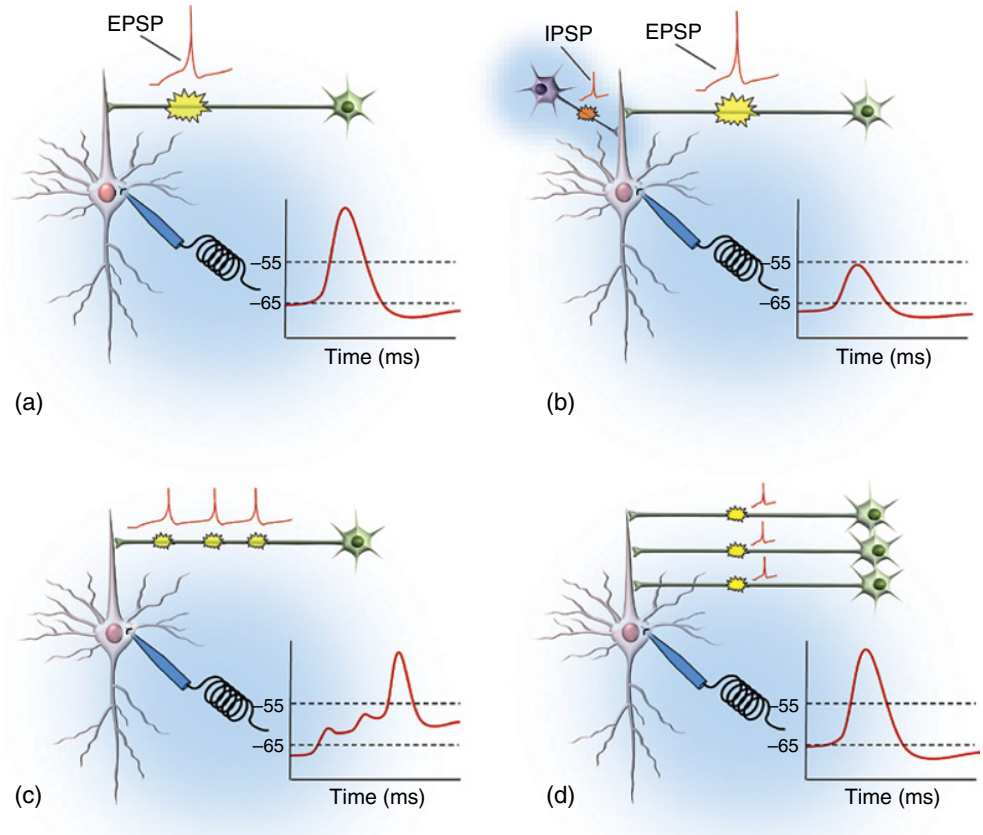


FIGURE 2.17 (a) A presynaptic neuron stimulates a postsynaptic neuron with an excitatory postsynaptic potential (EPSP), which has enough strength to generate an action potential. (b) An inhibitory postsynaptic potential (IPSP) occurs shortly after an EPSP preventing the postsynaptic neuron from reaching threshold. The action potential is blocked by the IPSP. (c) An example of *temporal summation*. Three small EPSPs are generated in succession, having a summative effect on the membrane potential, allowing it to reach threshold and an action potential to be created. (d) When two or more EPSPs are generated at the same time, they can have the effect of *spacial summation*. Individual EPSPs are too weak to cause the membrane to reach threshold, but when combined at the same time, they have a summative effect.

known injury to the brain (Friedman *et al*., 2009). Additionally, alterations in the BBB as a secondary effect of an insult, for example, organophosphate toxicity and subsequent neuroinflammation, can then lead to the development of epileptic seizures following neuroinflammation, secondary astrogliosis, and neurofibrosis, which leads to an alteration in the extracellular environment (Bernardino *et al*., 2024). Both levetiracetam and topiramate have been shown to be protective against seizures in experimental models of BBB disruption (Kaya *et al*., 2012).

THE WIRING OF THE BRAIN (NEURAL NETWORKS)

The ultimate biological example of order from chaos is the functional wiring of the brain. Just over half a billion neurons in the adult canine brain (about half that in the feline brain—sorry cat people) form interconnections, relationship patterns, and continuous modification of the processes governing nearly every action an animal performs, sensation it experiences, or emotional/cognitive event, whether it is purposeful or automatic. A single scent detected by the entorhinal cortex of a dog can trigger not only a behavioral response but also the formation of memories, analysis of consequences of actions, and ultimately voluntary or reflex action relating to the collective experience associated with the scent. As mentioned before, that reaction is unique every time due to the influence of a multitude of distributed subnetworks within the brain. It is challenging and awe-inspiring to grasp the complexity of the brain and the fact that with such a complex biological machine, so little goes wrong. Perhaps what we view as "normal" is actually a subbasement level of potential functionality. Patterns of circuit development in the brain occur before birth, based on cell-to-cell communication, physical contact of cells, and diffusible signals. This unabashed "grab as much as you can get" behavior of neurons occurs for a significant amount of time in the early years of a developing mammal as growing neurons compete for synaptic connections. A natural lack of inhibitory circuitry in young animals leads to the reinforcement of repetitive neural patterns of activity, resulting in the "hard wiring" of the developing brain. This lack of inhibitory activity also helps to explain why younger animals are more susceptible to epileptic seizures. In addition, excitatory connections develop before inhibitory connections, there is a significant difference in the ionic microenvironment between the mature and immature brains, and the young are more susceptible to potentially epileptogenic stimuli such as hypoxia, fever, and infection (Holmes *et al*., 2012). These known developmental mechanisms explaining neural wiring are applicable to epileptogenesis. As the brain ages, neural plasticity declines, glial cells propagate, inhibitory synapses develop, and epileptiform activity becomes more organized (synchronous), although less likely to develop (reach threshold) because of age-accumulated inhibitory influences. This may explain why some animals (and people) stop having seizures once they reach maturity.

Neurons undergo a remarkable process of cell proliferation via the creation of new daughter cells from stem cells within the ventricular layer of the embryonic brain. Daughter cells migrate to the marginal layer of the brain. The process continues until all of the neurons of the cortex are created. Radial processes extend from glial cells outward from the ventricular zone like spokes on a wheel. Daughter neurons migrate from the ventricular layer to the marginal layer by crawling along the radial processes toward the surface of the brain. The first *neuroblasts* to migrate to the mantle (surface of the brain) are destined to become the innermost layer of the cortex (layer VI). There are between three and six cortical layers, with the innermost (and first produced) layer being referred to as layer VI. Once these neuroblasts have found their target, layer V cells migrate past them, and so on. In this manner, the brain develops from the inside out. Disorders of neuronal migration, such as focal cortical dysplasia, are the most common causes of focal refractory epilepsy in humans (Kuzniecky *et al*., 1991; Palmini *et al*., 1991). The disorder, although rarely found clinically, has been reported in dogs and cats (Casey *et al*., 2014; Cooper *et al*., 2015; Cocchetto *et al*., 2022). Given the similarities between human and veterinary epilepsies, it would be logical to

assume the disorder is significantly underdiagnosed in veterinary patients. Gross lesions may be visible on MRI, as reported in the Cooper paper but oftentimes, when the diagnosis is made in humans, the lesions are extremely subtle on MRI examination (Su *et al*., 2024).

Cell differentiation is the process a neuroblast undergoes to take on the physical and functional characteristics of its future self. Differentiation is both programmed into the neuron before it leaves the ventricular layer and dependent on local environmental cues once it reaches its target. For example, a layer III neuroblast will continue to differentiate even if it is removed from the brain and kept in cell culture; however, its final characteristics will not be exactly the same as those left in the local environment. As a neuron undergoes differentiation, it continues to grow, develop pathways, reach its target, and ultimately form a synapse. The young neuroblast is composed of dendrites and axons that are fairly similar to one another and, at this stage, are collectively referred to as "neurites." The growing end of a neurite has footlike processes called *lamellipodia*, which probe the surrounding extracellular environment for cues to lead its growth. Within the extracellular matrix are specialized proteins, which both guide and attach to the axons, providing an integrated "highway" for the axons to travel to their target destination. *Netrins* are proteins secreted by the embryonic cells of the developing brain, which act like homing beacons for the axons to travel to. Numerous chemical signals are at play to both promote and inhibit axonal growth in the central nervous system. One large family of trophic proteins is the neurotrophins. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) were the first two proteins discovered in this group promoting the growth, survival, and synaptic contacts of neurons. Once the lamellipodia reaches its target, it collapses and forms a synapse. As synapses are formed, further refinement of the nervous system takes place through the orderly elimination of cells and synapses (*pruning*). The brain initially starts by painting with broad strokes and then fills in the details through several more refined mechanisms. Understanding these mechanisms may also help to explain some of the characteristics of epileptogenesis and epileptogenic tissue.

A process of naturally occurring cell death begins almost as soon as a neuron reaches its target. One of the most profound causes of this normal scaling back of neurons and synapses is through competition for nutrients. As many neurons reach a finite number of target cells, a limited amount of trophic factors are available to the arriving neurons. They compete for these nutrients and trophic factors, which allow the precise synapses to form. This is evolution at a cellular level. *Only the strong* (and functional) *will survive*.

Another common feature of the developing nervous system and of ongoing neural plasticity is the notion of "use it or lose it." Electrical and chemical connections refine synaptic capacity; however, each neuron only has a limited amount of *synaptic capacity*. The developing mammal has its greatest synaptic capacity early in life, usually reaching a peak by the time of sexual maturation. From then on, synaptic capacity takes a rapid decline. If, for example, a neuronal synapse is electrically active, the synapse will be preferentially retained or become more specific to the particular message, which is continually being reinforced. Those synapses remaining functionally quiet retain a polysynaptic nature. Neural activity also results in *synaptic rearrangement*, which is reinforced through synaptic transmission. In this regard, a neuron will "select" the connections necessary to deliver the message. Of the billions of neurons in the brain, each will form roughly 10,000 synapses with other neurons—and that is a lot of zeros (Holmes *et al*., 2012).

Hebbian Theory

Synaptic segregation is a process whereby those synapses active at the same time become reinforced through a form of *synaptic stabilization*. Canadian psychologist Donald O. Hebb proposed what would later become known as the *Hebbian Theory* in his 1949 book *The Organization of Behavior*. The Hebbian Theory can be used to explain why certain neural pathways are reinforced, which, ultimately, can lead to increased efficiency in neuronal firing. This theory may also explain the phenomenon of *kindling* where there is an increased chance a neuron will fire with fewer stimuli

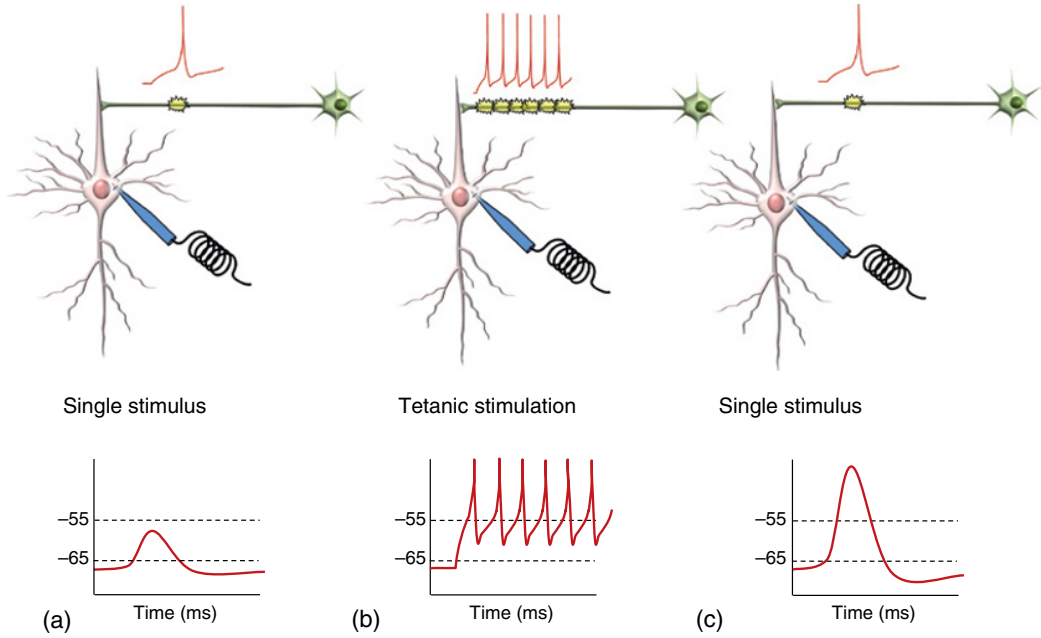


FIGURE 2.18 Long-term potentiation. (a) The neuron is stimulated with a single EPSP but does not result in a postsynaptic action potential. (b) The same neuron is subjected to repetitive (*tetanic*) stimulation. (c) The same neuron is now receptive to the initial degree of EPSP, creating a postsynaptic action potential. The neuron has "learned" to fire with less stimulus.

over time. The brain is an inherently plastic structure. One of its most unique features, the ability to "learn," is also one of its most detrimental when seizures are manifested. When neural pathways are strengthened, actual neuronal processes are rearranged to complete a new circuit for that particular event. Neuron "A" forms a synapse with neuron "B," which inhibits neuron "C" and so forth to the point where a "circuit" forms the basis for the event. Neurons learn. We know if a neuron is stimulated repeatedly to fire, upon further stimulation, after a period of rest, it will actually take less stimuli to generate the same response. The Hebbian mechanism explains the properties of classic long-term neuronal potentiation (Figure 2.18). Specifically, Hebb postulates:

> *When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.*
>
> (*Hebb, 1949*)

The Hebbian Theory provides a very adequate, although most likely not complete, mechanism for many of the underlying features of the excitable brain. The above description of neural efficiency has been summarized as "neurons that fire together, wire together."

Long-Term Potentiation

What allows us to remember? How is it that a short-term memory, such as the phone number of a stranger, is quickly forgotten while a person's own name will be remembered even if they go for years without hearing it? One of the major contributing concepts to neural plasticity is *long-term potentiation* (LTP). Simply defined, LTP is the persistence of synaptic strength based on past

patterns of activity. The fundamental notion is one where a particular neuron may "learn" to fire in a more efficient manner after being asked repeatedly to fire in the past. For example, neurons in the CA1 region of the hippocampus (an area involved with memory) receive collateral projections from the CA3 region of the hippocampus. Electrical stimulation of a CA3 neuron will generate an EPSP to the CA1 neurons. The summation of these potentials can be recorded; however, individual potentials can also be elucidated. If the stimulus is slow and steady (such as two to three times a minute), the size of the EPSP generated by the CA1 neurons is consistent. However, if a high-frequency burst of stimulation is provided, the recorded EPSP in the CA1 neurons will be longer lasting and of greater amplitude. Long-term potentiation is mediated through increases in intracellular *calcium* and the subsequent second messenger systems it activates. The calcium makes its way into neurons through *NMDA* receptors. NMDA is a glutamine receptor (recall the primary excitatory neurotransmitter of the brain). Seizures frequently arise from the hippocampus, and the hippocampus is arguably one of the most sensitized areas of the brain for the generation of seizures (see later in the chapter under *Limbic connections*). Seizures activate NMDA receptors, and LTP is suspected to play a role in potentiating seizure activity. This may explain why seizures generated in one area of the brain may be propagated to another area. The phenomenon of *kindling* is supported by the involvement of LTP. In experimental models of seizures in rats and cats, a constant low rate of a weak stimulus over a long period of time will eventually result in generalized seizures and epilepsy, which is essentially permanent and irreversible (Burchfiel, 1981). Thus, the phenomenon of kindling, whereby one minor seizure triggers another, results in more difficult seizure control. This has significant implications when we consider anticonvulsant therapy in later chapters (pro tip: treat epileptic seizures early and effectively to help avoid kindling).

GLIA

About half of the brain matter is comprised of glial cells. The two main types of glial cells in the central nervous system are *astrocytes*, which contain radiating processes allowing them to interweave between neuronal cell bodies and *oligodendrocytes*, responsible for forming the myelin sheath, which wraps around neuronal axons allowing for the rapid transmission of the action potential. In addition, *microglia* are present as a representative of the immune system (Jessen, 2004). Microglia do not originate from the brain but are derived from blood macrophages. These macrophage-like cells aid in the regulation of the immune system. If neurons are the rock stars of the brain, glial cells are the roadies. Glial cells have a highly developed control mechanism in place to regulate neural activity and synchronization. They provide an integral supporting role to the neurons and their local environment including (but certainly not limited to):

- Provide elements for the synthesis of neurotransmitters (glutamate, glutamine, D-serine, ATP).
- Act as a buffer for neurotransmitters, with active transport of glutamate and GABA from the extracellular space.
- Regulate interstitial (extracellular) homeostasis through the expression of inward rectifying potassium channels and *aquaporin-4*, the water channel.
- Modulate the immune system through the expression of cell surface molecules and anti-inflammatory factors (Carson *et al*., 2006).
- Maintain the BBB.
- Regulate neuronal development.
- Myelinate. A single oligodendrocyte can myelinate between 30 and 40 axons in the central nervous system.

The density of potassium channels on glial cells is much greater than sodium channels, which prevents glial cells from being able to generate an action potential. However, their lack of ability to generate an action potential does not prevent them from cell signaling and communication. Glial cells create a vast communication network through gap junctions. Their membranes contain neurotransmitters and other chemical receptors. At the synapse, neurotransmitter activity releases glutamate from nearby astrocytes, which has an inhibitory effect on neuronal excitability (Haydon, 2001). This occurs with an increase in intracellular calcium. Intracellular calcium can form a sort of long-range signaling system, as *waves* of calcium will spread from one astrocyte to another, through electronic gap junctions, in response to synaptic activity. This allows one astrocyte to influence synaptic activity at distant sites (Cornell-Bell *et al.*, 1990; Guthrie *et al.*, 1999). Furthermore, the release of ATP by astrocytes (as an extracellular messenger) allows the calcium waves to "jump" over cell-free regions (<120 μm), creating the brain's own "wireless network" (Hassinger *et al.*, 1996; Stamatakis and Mantzaris, 2007).

The inhibitory influence of glial cells may also contribute to hypersynchronization as regulation of action potentials may create a situation whereby multiple neurons are inhibited at the same time, allowing for greater recruitment of primed and ready-to-fire neurons.

ORGANIZATION OF BRAIN CONNECTIONS

If excitability is considered at the level of the neuron, the synchronization of neurons (the functional form of excitability) must involve neural networks. Synchronization and excitation may be enhanced through propagation. The propagation of neuronal signals occurs through recruitment, augmentation, and anatomical connections of various areas of the brain. The notion that epileptic seizures are exclusively a forebrain-mediated event or result only from forebrain dysfunction is incorrect. Generally speaking, the telencephalon (cerebral cortex and hippocampus) is the location of epileptic excitable tissue; however, epileptic seizures may be generated from subcortical structures, such as the amygdala. Diencephalic structures and brainstem projections, such as the pontine reticular formation, also influence cortical excitability. Connections between the various structures of the brain (i.e., the brain's own highways) allow a focal, potentially controlled disturbance to be propagated to distant sites, recruiting other neural networks to fire spontaneously and in synchrony.

There are inherent properties of certain local anatomical connections between brain structures, which lend to ictogenesis. The two main epileptogenic networks of the brain involve the neocortex and the limbic system.

NEOCORTICAL CONNECTIONS

For the most part, the neocortex receives information from the thalamus and other cortical structures (e.g., the primary olfactory cortex, which bypasses the thalamus—see Figure 9.3). Feedforward and feedback inhibition are the most common electrical interactions of the central nervous system (Figure 2.19). When large pools of neurons are all inhibited at the same time or with the same frequency, they become "primed" to fire simultaneously with the right excitatory input, leading to the potential for synchronization. It seems counterintuitive that *inhibition* can result in *excitation* (but then the brain is cool that way—just when you think you understand it . . .) (Trevelyan and Schevon, 2013). A naturally occurring post-excitation inhibition due to rebound depolarization of neurons coupled with inhibitory input further increases the chance for synchronization of neuronal pools to develop. If these neurons are subjected to an excitatory input at the right time and right frequency, they will contribute to the collective pool of a *synchronous excitatory discharge*, which may propagate to other areas of the brain (Figure 2.20). GABAergic

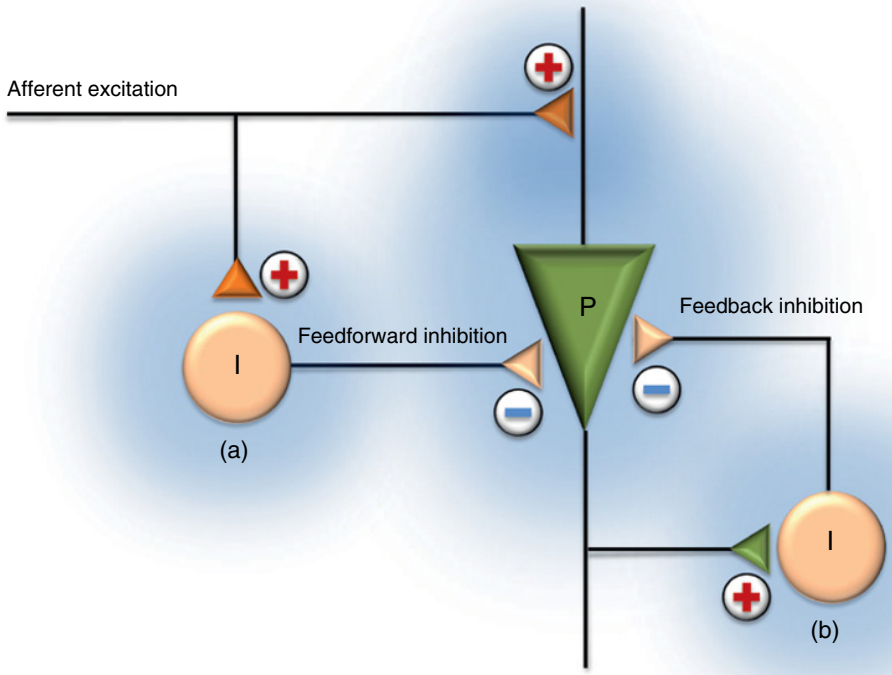


FIGURE 2.19 Feedforward and feedback inhibition. P, principal neuron. I, inhibitory interneurons. Afferent excitatory input activates both the principal neuron and the inhibitory interneuron. The inhibitory interneuron (a) then inhibits the principal neuron in a *feedforward* manner. When the principal neuron is activated by afferent input, it excites inhibitory interneuron (b), which then inhibits the principal neuron in a *feedback* manner.

interneurons are important elements providing feedforward and feedback inhibition in both the neocortex and the hippocampus. This inhibition is what strengthens an individual neuron's response to afferent synchronizing input. By being continually suppressed, more neurons are ready to "step up to the plate," often collectively at the same time. Neurons, which have the ability to spontaneously fire in bursts, are present in layers IV and V of the neocortex. These neurons may operate as neocortical *pacemakers* if the burst firing becomes synchronous. Burst firing is possible because of dendritic *T-type* calcium currents present in the vicinity of the axon hillock. Repetitive action potentials are created as a result of continuous depolarization at the axon hillock. Local inhibitory interneurons and calcium-dependent potassium currents eventually suppress the firing of these neurons. Burst firing of neurons is normally random; however, if they become synchronous, they have the potential to create high-frequency oscillations (HFOs). These HFOs may be normal (referred to as *ripples*) at frequencies between 100 and 200 Hz but can be indicative of epileptogenic tissue at frequencies between 200 and 600 Hz (*pathological* HFOs [pHFOs]). The ability to form synchronized discharges and HFOs may lead to recruiting and augmenting responses from subcortical input to the neocortex. This *normal* afferent input has the potential to induce epileptiform activity if acted on an abnormal epileptogenic area of the neocortex, as opposed to being propagated from abnormal thalamic relay tissue (Gloor *et al.*, 1977). HFOs may spread throughout the brain through gap junction-mediated calcium waves (Traub et al., 2001). Gap

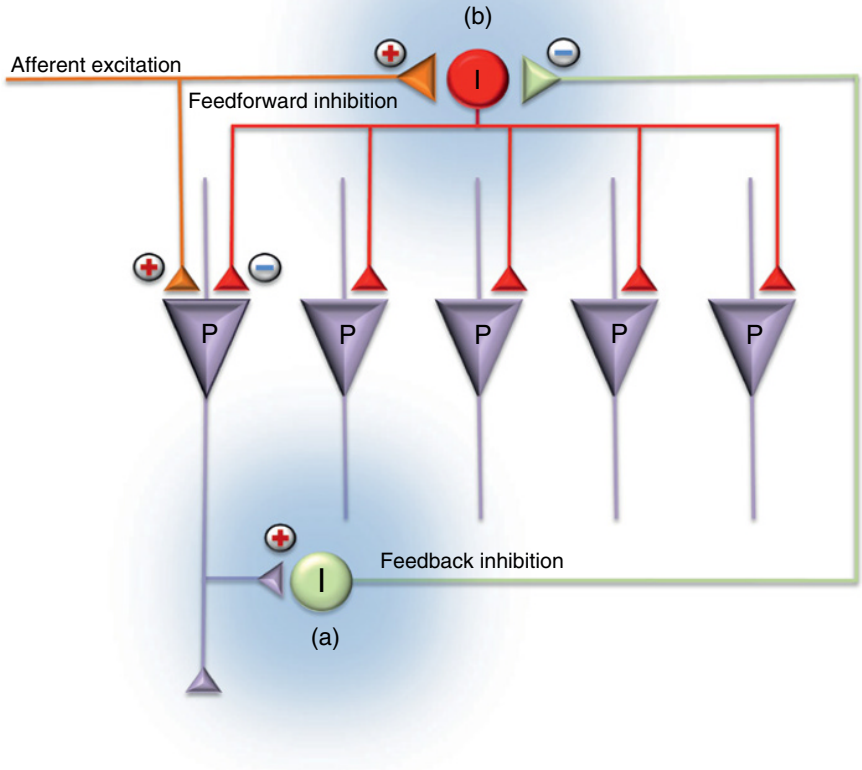


FIGURE 2.20 Synchronization. In this example, a large group of principal neurons (P) are inhibited by an interneuron (I) in a feedforward mechanism. At (a), the principal neuron excites an inhibitory interneuron, which feeds back to the original inhibitory interneuron (b). In this manner, large groups of excitatory neurons may be "primed" and ready to fire through inhibitory processes.

junction blockers, such as *carbenoxolone*, may have a future role in stopping seizures (Sefil *et al*., 2012).

Kindling is the subconvulsive stimulation of neuronal populations leading to progressive intensification of neuronal firing and culminating in generalized seizures. Kindling is suspected to be one of the primary means subcortical neurons can spread their epileptic potential to distant sites through normal anatomical connections. Some of these anatomical connections are through normal central nervous system "highways" such as *association fibers* (connections between different areas of the cerebral cortex within the same hemisphere—think *cingulum*), *commissural fibers* (connections between cerebral hemispheres—*corpus callosum* is an example), and *projection fibers* (connecting subcortical and spinal cord areas with the cerebral cortex—like the *internal capsule*) (Figure 2.21). Epileptic seizure propagation may also be made through *aberrant neural connections*. In the GEPR-9 model of audiogenic brainstem-derived generalized seizures, kindling creates an expanded seizure network involving the medial geniculate body, amygdala, and cerebral cortex. Once this occurs, *cortical* epileptiform activity can be demonstrated on EEG recording (Faingold, 2012).

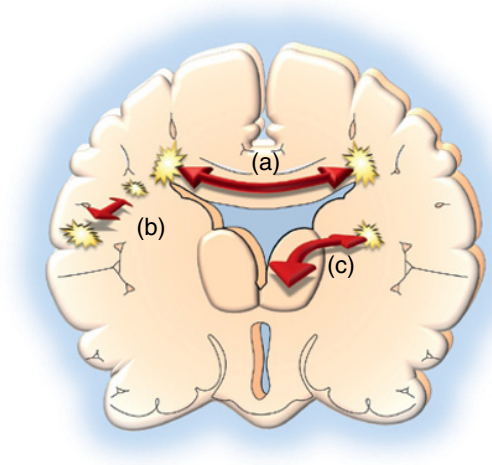


FIGURE 2.21 The spread of epileptic discharges through the brain via (a) *commissural fibers* connecting one hemisphere to the other, (b) *association fibers* connecting areas of the same hemispheres, and (c) *projection fibers* connecting the brain to areas outside of the cerebral cortex. (a) The corpus callosum acts as a "superhighway" in the brain, whereby epileptogenesis can spread to the contralateral hemisphere creating a *mirror focus* or propagating a focal seizure to a generalized seizure.

SUBCORTICAL CONNECTIONS

The amygdala is anatomically related to the basal nuclei. There is a poorly organized collection of neurons and axons, which "pass through" the amygdala to other areas of the brain. Experimentally kindled seizures have long been generated through stimulation of the amygdala. The amygdala has efferent and afferent connections to the hypothalamus, septal area, forebrain olfactory areas, and brainstem. If the amygdala is stimulated rhythmically, a recruitment response will be elicited in the hippocampus resulting in status epilepticus, which persists even after the stimulus has ceased (McIntyre *et al*., 1982). *Kindling* is classically demonstrated in the hippocampus through the stimulation of the amygdala to create subthreshold focal seizures, which eventually lead to progressive, reliable, permanent increases in epileptic response to a given stimulus (Goddard *et al*., 1969). Destruction of cell bodies in the amygdala by kainic acid, which preserves fibers passing through the structure, does not prevent kindling. It is therefore suspected the epileptogenic effects of the amygdala are due to the *fibers transiting through* it to the hippocampus as opposed to the intrinsic cells present within the amygdala (Kaneko *et al*., 1981).

The neocortex also receives input from other subcortical structures, organized by the primary neurotransmitter involved (Figure 2.22):

- Dopaminergic: Substantia nigra and ventral tegmental area
- Noradrenergic: Locus coeruleus and nucleus subcoeruleus
- Serotonergic: Raphe nucleus
- Cholinergic: Lateral dorsal tegmental, pedunculopontine reticular, and basal forebrain nuclei

Excitatory amino acids are involved in reciprocal connections from the neocortex to the brainstem. GABAergic connections predominate from the neocortex to the subcortical structures. Subcortical and brainstem connections to the neocortex have different potentials to either *induce* or *suppress* epileptiform activity. For instance, noncholinergic projections from the brainstem and diencephalic nuclei will *increase* cortical synchronization similar to their ability to influence slow-wave sleep patterns. Epileptogenicity is more likely to happen during slow-wave sleep when synchronicity predominates in the brain. On the other hand, cholinergic input to the neocortex has an effect on arousal, desynchronization, and REM sleep (i.e., less epileptogenic). While generally true, *serotonergic* input from the brainstem will *suppress* epileptic activity, even though it helps to

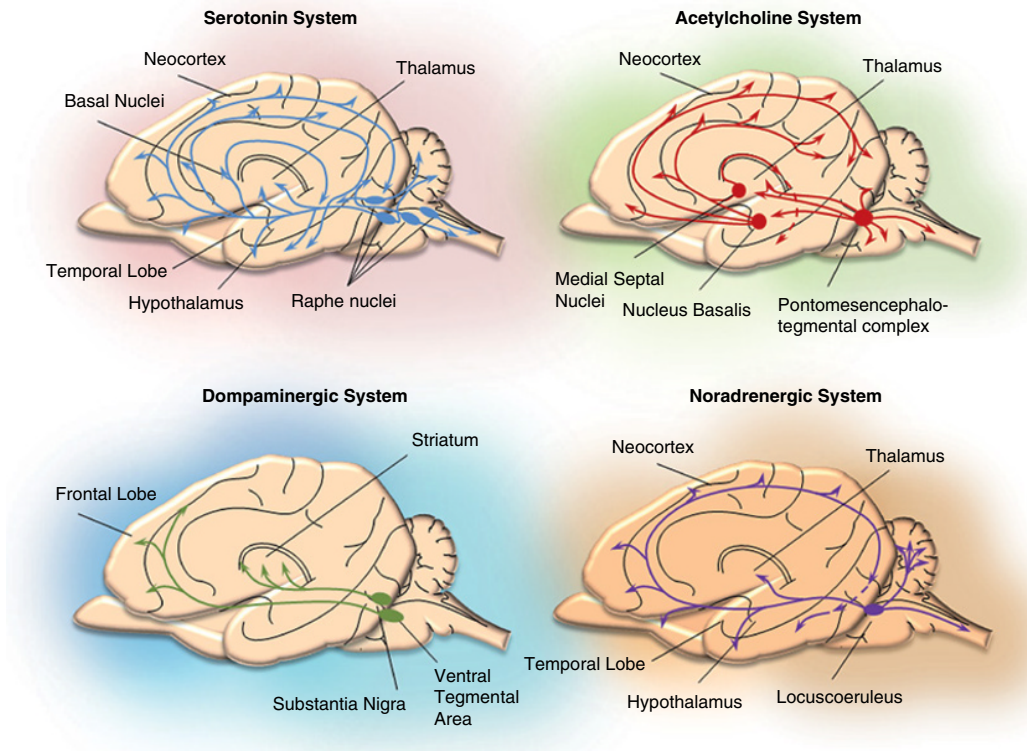


FIGURE 2.22 Simple graphic representation of neurotransmitter origination and projection/innervation within the brain.

initiate slow-wave sleep. Noradrenergic and dopaminergic input to the cortex will also suppress epileptogenicity.

The cerebellar output to the deep cerebellar nuclei is inhibitory. The deep cerebellar nuclei have connections to the neocortex and the hippocampus. Stimulation of the cerebellum experimentally has produced mixed results with some studies showing suppression of seizures, others having no effect, and still others potentiating epileptogenic activity (Graber and Fisher, 2012).

CONNECTIONS BETWEEN HEMISPHERES

A *mirror focus* is a point of epileptogenic tissue in a homotopic location in the contralateral hemisphere. Interictal spikes first show up in the area of the brain where the primary lesion is located (McCarthy *et al*., 1997). If allowed to continue, a secondary location of interictal spikes appears in the contralateral cerebral hemisphere in a *mirror* location to the primary side of epileptogenic tissue. The development of mirror foci is thought to arise from continuous epileptic activity crossing interhemispheric connections such as the corpus callosum (Figure 2.21). If the primary site in one hemisphere is allowed to continuously be active, a mirror focus may develop in the opposite hemisphere, which matures to the point where it can generate its own *asynchronous* (relative to discharge relating to the progenitor site), epileptic activity, independent of triggering from the progenitor site. Transection of the corpus callosum has been used to prevent the development of mirror foci experimentally in animals and to help treat severe forms of epilepsy in humans, dogs, and cats (see also Chapter 10) (Asada *et al*., 2021; Hasegawa *et al*., 2021). However,

there are reports where *callosectomy* resulted in worsening of seizures in patients with independent foci of epileptogenic activity on EEG, suggesting in certain circumstances the corpus callosum may play a part in contralateral inhibition of seizure activity (Spencer *et al*., 1984).

BRAINSTEM CONNECTIONS

Penfield and Jasper originally proposed the *centrencephalic* system of brainstem involvement in the ictogenesis of generalized seizures (Penfiled and Jasper, 1954). The ascending reticular activating system is thought to play a critical role in the synchronization and spread of generalized seizures. The notion that a generalized seizure may be propagated from a location in the brainstem reticular formation has since been demonstrated, primarily utilizing genetically epilepsy-prone rats (GEPR-9). The GEPR-9 rats are susceptible to audiogenic triggered generalized seizures. Audiogenic generalized seizures may be confined to the brainstem and subcortical structures before kindling (Faingold, 2012). In this model, a sound stimulus propagated through the cochlear nucleus and the superior olivary complex reaches the inferior colliculus where a deficiency of GABA-mediated inhibition leads to excessive auditory-evoked inferior colliculus neuronal firing, subsequently leading to the audiogenic generalized seizure. Excessive neuronal firing is thought to result in activation of the regional brainstem locomotor network, which is located in the brainstem and spinal cord (Grillner and Jessell, 2009). The physical characteristics of generalized tonic–clonic seizures are a manifestation of excessive neuronal activity involving the locomotor apparatus in the brainstem. As previously discussed, there are multiple reciprocal connections from the neocortex and the hippocampus to the brainstem.

LIMBIC CONNECTIONS

The limbic system (from the Latin term *limbicus*, meaning "border" or "margin") is comprised of two incomplete ring structures in the shape of a "C" located opposite to one another bordering the lateral ventricles (medially). An excellent description of its anatomical development can be found in de Lahunta *et al*. (2021). The limbic system is generally considered to be involved with the sense of smell, learning, and emotional behavior. However, it has other influences on memory formation, autonomic functions such as blood pressure and heart rate, reward, pleasure, addiction, and the decision-making process, to name a few. It has significant influence over neocortical and brainstem function, as well as being influenced by those same structures. Many of its intrinsic characteristics, both structurally and functionally, make it a common site of epileptogenesis.

The hippocampus is a gyrus of the telencephalon, which is "rolled" under the brain, medial to the lateral ventricles and diencephalon, and medial to the temporal lobe. The hippocampus proper is often referred to as "Ammon's horn" because of its appearance to the coiled ram's horns of the ancient god Amun (meaning "the hidden one"). The name hippocampus comes from the Greek words *hippos* (meaning "horse") and *kampos* (meaning "sea monster"). When dissected from the brain, the structure resembles a *seahorse*. The primary output of the hippocampus is to the hypothalamus, medial prefrontal cortex, and caudal brainstem nuclei. The limbic system is a complex aggregate of structural and functional elements, which collectively influence most brain activity. Signals flowing through the hippocampus form a loop or "circuit." This circuit is further connected to other parts of the brain forming neural networks. Structurally, the limbic system is comprised of an inner cortical ring consisting of the amygdala, the hippocampus, and the hippocampal fornix. An outer cortical ring consists of the cingulate gyrus, the cingulum (axons projecting from the cingulate gyrus to the entorhinal cortex), the septal area, the median forebrain bundle, and the hypothalamus. The parahippocampal gyrus, the corpus callosum, and the lateral ventricles border the hippocampus. It wraps around the thalamus (Figure 2.23a).

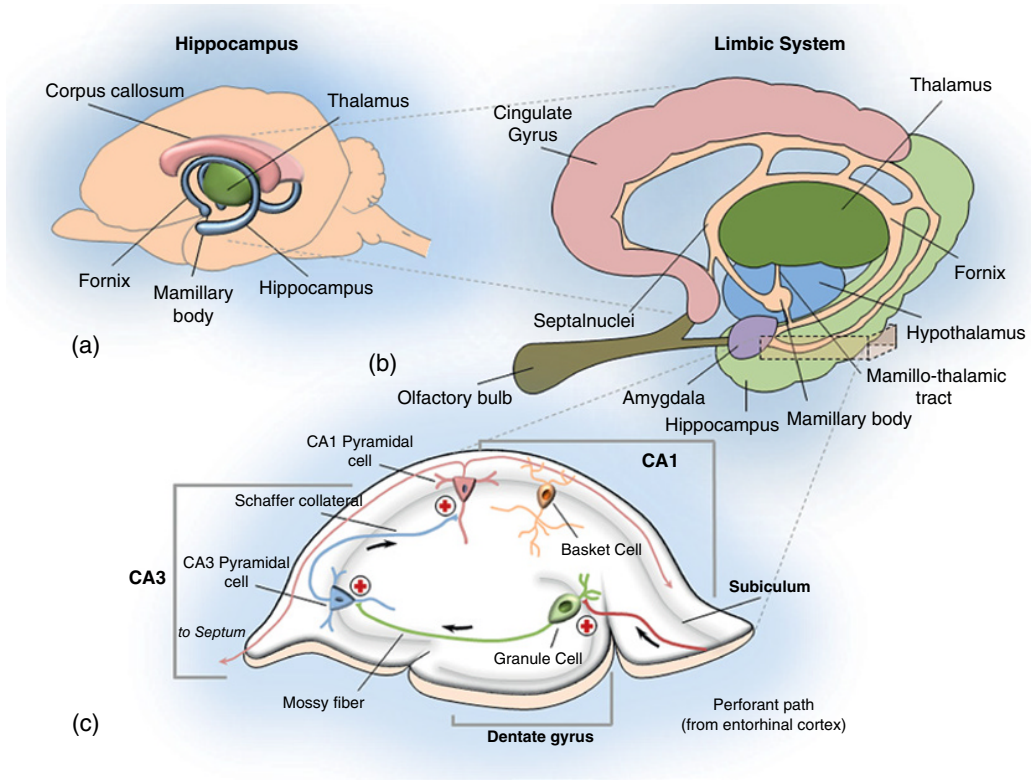


FIGURE 2.23 The hippocampus and limbic system. (a) The curved "C"-shaped hippocampus wraps around the thalamus ventral to the corpus callosum and medial to the lateral ventricles. (b) Some components of the limbic system. The olfactory bulb and olfactory tracts are not part of the limbic system but project to it. (c) Horizontal section through the hippocampus showing basic intrahippocampal connections and projections.

Microscopically, it is composed of a broad-based portion, the subiculum, a region of densely packed, large pyramidal cells referred to as the CA1–CA4 areas (the "CA" is the abbreviation for *cornu ammonis* or "horn of Ammon"), and a terminal portion wrapped around the hippocampal gyrus, known as the dentate gyrus (Figure 2.23b and c). Axons from layer 2 of the entorhinal cortex enter the dentate gyrus and synapse on granule cells. This external input to the dentate is known as the *perforant path*. Granule cells in the dentate send projections as *mossy fibers* to pyramidal neurons and interneurons in the CA3 region. The inhibitory interneurons of the CA3 area feed back to the ipsilateral and contralateral inner molecular layers of the dentate gyrus to provide braking action to entorhinal input. The pyramidal neurons of CA3 send collateral projections (aka *Schaffer* collaterals) bilaterally to the CA1 area. The neurotransmitters thought to be involved in the perforant path to CA1 are excitatory—in particular, glutaminergic. Pyramidal neurons in the CA1 region send their axons to the *subiculum* (the most ventral aspect of the hippocampus), the deep layers of the entorhinal cortex, and adjacent structures in the temporal lobe. This is referred to as the *alvear path*. In addition, CA1 axons course through the fornix to the septum, mammillary bodies, and contralateral hippocampus (through the *hippocampal commissure*). Moreover, in the CA1 area, inhibitory interneurons (i.e., *basket* cells) receive excitatory input from afferent projections into the hippocampus and collaterals from efferent neurons exciting the hippocampus (Brodal, 1981). These interneurons play a major role in the feedforward and feedback mechanisms of synchronization. With repeated stimulation, the inhibitory neurons (GABAergic) have a reduced

effect (disinhibition), leading to greater excitation of CA1 pyramidal neurons. Subicular neurons also send projections to the entorhinal cortex. Afferent connections to the dentate gyrus (cholinergic) also arise from the subcallosal area (i.e., diagonal band of Broca) and the septal area traveling in the fornix of the hippocampus to enter the dentate gyrus. Whew . . . that's a lot of hippocampal neuroanatomy.

Similar to the neocortex, simultaneous inhibition of large pools of pyramidal neurons creates a "primed" state where larger numbers are available to fire in synchrony with the right excitatory input to the hippocampus. Neurons in the CA3 area and the subiculum are also capable of *burst firing*, further adding to the potential of the hippocampus to result in epileptogenicity. Normal burst firing in the CA3 area is asynchronous. However, if the burst firing in the CA3 area becomes synchronous (due to feedback or feedforward inhibition), it can induce CA1 neurons to burst fire. Oscillatory patterns are favorably created by neurons in the CA3, CA1, dentate gyrus, and subiculum during states of arousal, active motor movement, and REM sleep. Cholinergic input from the septum is responsible for these 4–6 Hz oscillations, known as the *theta rhythm* on EEG recordings. Buried within the EEG (sample rates greater than 2000 Hz), HFOs have been identified as potential *biomarkers* of epilepsy (Zijlmans *et al*., 2012). HFOs probably originate from populations of neurons firing in synchrony and spread through calcium waves, mediated by electronic gap junction connections. HFOs may be normal electrical activity of the brain (Frauscher *et al*., 2018). This activity is referred to as *ripples* when frequencies are between 80 and 250 Hz (100–200 Hz depending on source). When they occur in the mesiotemporal area, they are thought to be associated with memory. When they arise from the extratemporal neocortex, they are thought to be associated with information processing. Pathological HFOs (pHFOs) are associated with frequencies of 250–600 Hz (200–600 Hz depending on the source) and are referred to as *fast ripples*. HFOs have caught investigators' attention as they are observed before seizures, during seizures, and in between seizures. They require special EEG recording techniques to detect. It is thought that HFOs represent small groups of principal cells (i.e., projecting neurons), which have become synchronized and are pathologically interconnected. If brain tissue is damaged or alterations in the cell population or local environment occur, neurons may be more likely to fire in response to subthreshold stimuli. Recruitment and augmentation are secondary to the propensity for inhibition in these areas and also contribute to the ability of this abnormal tissue to become spontaneously active and recruit interconnected cells in the local vicinity. HFOs have been shown to be a reliable marker of the future development of seizures in rats (Bragin *et al*., 2004). HFOs also provide a more accurate representation of the epileptogenic seizure zone (Cai *et al*., 2021). The inherent characteristics of the hippocampus (e.g., burst firing, oscillatory patterns, large amounts of potential inhibition, and extreme interconnectivity with other areas of the brain) allow the structure to have a profound influence over epileptogenicity. It is no wonder hippocampal sclerosis is the most common pathological substrate of epilepsy in humans and becoming increasingly recognized in veterinary patients (Engel, 1996; Klang *et al*., 2018; Chambers *et al*., 2022; Zilli *et al*., 2022).

New methods of determining structural and functional relationships in the brain are aiding in the understanding of aberrant neuronal connections, their role in the ability of neurons to spontaneously fire (i.e., epileptogenicity), and the spread and progression of epilepsy (i.e., epileptogenesis). These new techniques hold significant promise in furthering our understanding of the underlying pathophysiology of epilepsy. MRI diffusion imaging (diffusion tensor imaging) allows the delineation of whole-brain three-dimensional maps of fiber pathways throughout the brain (see Figure 5.6). Functional MRI looks at areas of the brain, which are functionally related either through influences by each other, on the other, or through another site influencing both regions (see Figures 5.13 and 5.14). The metabolism-based structural information can be very helpful especially when combined with structural MRI and EEG recordings of brain activity (see Figure 10.8).

NONBRAIN INFLUENCES OF EPILEPTIC SEIZURES

If the maintenance of the electrochemical gradient is dependent on the sodium/potassium ATPase pump, then any systemic alteration of normal cerebral oxygen or glucose metabolism may lead to membrane instability. Recall potassium has a strong conductance through the neuronal membrane. Failure of the sodium/potassium ATPase pump leads to the membrane potential approaching threshold and subsequent hyperexcitability.

Electrolyte disturbances such as hypocalcemia, hyperkalemia, hypernatremia, hypochloridemia, and hypomagnesemia have the potential to induce epileptic activity. Increases in toxic by-products of metabolism not cleared from the body through normal mechanisms (hepatic or renal) also have the ability to disrupt the neurons' microenvironment. Imbalances in systemic acid–base status can lead to disruptions of the highly regulated cellular microenvironment. Glial cells act to buffer changes in the acid–base status through the use of carbonic anhydrase, which acts to catalyze the hydration and dehydration of carbon dioxide (Silverman and Lindskog, 1988):

$$CO_2 + H_2O \xleftrightarrow{\text{Carbonic anhydrase}} HCO_3^- + H^+$$

In this simple reaction, carbon dioxide is combined with water to form a bicarbonate ion and a hydrogen ion. The bicarbonate ions are excreted in the urine and the hydrogen ions are retained. Carbonic anhydrase inhibitors, such as acetazolamide, will cause retention of carbon dioxide by preventing its breakdown (acidosis) and subsequent reduction in neuronal excitability. Changes in cerebral circulation, renal disease, hepatic disease, polycythemia, and hypertriglyceridemia all have the ability to create a more epileptogenic environment in the central nervous system. Alkalosis causes neuronal hyperexcitability, and acidosis is inhibitory to neurons (Casey *et al*., 2010; Ruusuvuori *et al*., 2010).

Mechanisms thought to contribute to the generation of epileptic seizures revolve around several key concepts. These include disruption in the balance of inhibitory and excitatory signals in the brain, changes in concentrations of ions across cell membranes, and alterations in neuronal homeostatis. Additionally, variations in neurotransmitter function, factors leading to the spontaneous firing of large groups of neurons, and changes in glucose or oxygen metabolism can also play significant roles in the development of seizures. Ultimately, epileptic seizures are likely due to a multifactorial alteration in normal brain homeostasis, and unfortunately at this time, the majority of therapies are directed at the prevention of seizures, not necessarily the cause. This is slowly changing.

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Epileptic Seizure Classification and Syndromes

CHAPTER 3

KEY TAKEAWAYS

If we are all speaking the "same language," we avoid confusion and mistakes related to misunderstanding.

Classification can help with diagnosis, treatment, and prognosis.

Classification may prevent premature euthanasia.

The primary goal is to achieve an etiological cause of epilepsy.

A syndromic classification is the most utilitarian in lieu of an etiological classification.

Understanding human semiology may help us to better recognize and understand the semiology of dogs and cats.

QUICK JUMP

Veterinary Seizure Classification Schemes Table 3.1

Conditions Mistaken for Seizures Table 3.2

Classification of Seizure Type (descriptive) Tables 3.4 and 3.5

Diagnostic Model Table 3.6

Veterinary Seizure Syndromes Tables 3.3, 3.7, and 3.11

Breeds Reported with Genetic Epilepsy Table 3.8

Introduction 62
Terminology 62
- Seizure 63
- Epileptic Seizure 63
- Epilepsy 65
- Epileptic Syndrome 66
- Elements of an Epileptic Seizure 66
- Status Epilepticus 69
- Cluster Seizures 70

Classification 70
- Historical and Current Perspectives 70
- Patient Assessment 72
- The Approach to Classification 80

Phenomenological Seizure Types 85
- Focal Seizures 87
- Generalized Seizures 92
- Unknown or Unclassified "Seizures" 97

Epileptic Syndromes 100
Summary 109

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Myelominutia: Why seizures are more likely to occur during sleep...p. 107

INTRODUCTION

The purpose of classification is to organize items into their functional (practical) relationships in order to provide a *common reference framework*. In regard to epileptic seizures, a common terminology for ictal semiotics (descriptive signs) and classification is the end goal. Seizure semiology is the study of the clinical signs and their descriptions relative to epileptic seizures. This is especially relevant in veterinary medicine, where our patients have to *show* us the problem rather than tell us about it. Specifically, the description allows the clinician to classify the disease into categories, which relay important, consistent, relevant information within the medical and research communities. These descriptive terms can provide us with much more valuable information than artificial terms gleaned from human descriptions of seizures, as in many cases the underlying etiology, disease substrate, and progression are unknown. A classification scheme can provide valuable information regarding possible causes, treatment, and prognosis, even when the underlying etiology is unknown (especially common with veterinary patients and surprisingly common in human patients). That being said, the basis or foundation of the veterinary classification scheme of seizures should be modeled to and closely resemble that of human classification schemes. A consensus statement was created by the International Veterinary Epilepsy Task Force (IVETF) to help us speak in a "common language" (Berendt *et al.,* 2015). This current recommended classification system mirrors that of the International League Against Epilepsy (ILAE) but accounts for certain particularities associated with veterinary medicine. An adaptation of the human *Glossary of Descriptive Terminology for Ictal Semiology* is presented in Appendix 1. Considering the similarities between species and the use of comparative physiology and pharmacology in research and teaching, being able to communicate on a comparative level enhances collaboration and understanding among researchers and clinicians. Additionally, for pet owners, a classification scheme provides a name for the condition and enhances understanding of the diagnosis. Progress made in either the understanding of the underlying pathophysiology or treatment of epileptic seizure disorders, whether in veterinary medicine or human medicine, will be easier to identify and apply comparatively. Of even greater importance, the categorization or classification of epileptic seizures and epilepsies is an essential component of the successful diagnosis and treatment of epileptic disorders.

TERMINOLOGY

Prior to the discussion of a classification scheme, a basic understanding of common definitions and terms associated with seizures and epilepsy is necessary. The *ILAE* was formed in 1909, consisting of physicians and other health professionals to:

> *Ensure that health professionals, patients and their care providers, governments, and the public worldwide have the educational and research resources that are essential in understanding, diagnosing and treating persons with epilepsy.*
>
> (*ILAE Mission, Goals and Strategy, www.ILAE.org*)

It makes perfect sense that the classification of seizures and epilepsies as well as definitions of terms used in the classification and description be modified and adapted to veterinary patients based on the foundations laid by the ILAE. Much of the research and investigation regarding epilepsy is comparative in nature among species affected by the condition. Furthermore, the vast majority of research regarding epilepsy and epileptic seizures is based on animal models of the disease. The dog and cat share similar etiologies, pathophysiology, electroclinical patterns, and responses to treatment for epilepsy as humans. The ILAE's classification scheme is understood to be a continuing work in progress filled with controversy and revision; however, the organization, composed of the world's leading epilepsy specialists, is generally accepted as the preeminent expert source on this subject.

SEIZURE

The word "seizure" is derived from the Greek word *epilambanein*, which literally means "to take hold," "to be seized," or "to be attacked." It is derived from a mystico-religious concept, which dominated prehistoric and early written understandings of disease, whereby one who experienced seizures (or any other disease affliction, for that matter) was being possessed or attacked by evil spirits, usually as a form of punishment (see Chapter 1). In modern days, however, the term is not uniformly specific to *epileptic* seizures (Fisher *et al*., 2005). A "seizure," in the true sense of the word, may not even involve a pathological process. Therefore, the word "seizure" has been modified and should be referred to as an "*epileptic* seizure" as opposed to simply "seizure" in order to avoid confusion with non-epileptic seizures such as syncope (a physiological condition resulting in fainting) and psychological causes, a group of disorders not present in animals. A *seizure,* as a pure reference to the medical application of the, word is defined as "to attack or afflict suddenly" (e.g., *to be seized with pain*). A *seizure* could refer to any sudden onset, a transient event that usually lasts only a short period of time. To avoid confusion, we will infer that the intended meaning of seizures in this text is *epileptic* seizures.

EPILEPTIC SEIZURE

The current definition of an *epileptic seizure* by the ILAE (as of 2017) is:

> *A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.*
>
> (*Fisher et al., 2014*)

Previous definitions focused on the notion that an epileptic seizure was due to an imbalance of electrical activity in the brain, resulting in an excessive degree of excitation either as the primary source or secondary to a lack of inhibition of brain activity. The analogy of "too much gas and not enough brakes" in the brain could be used to simplify neuronal activity to the layperson. The new definition reflects current advances in the understanding of neuronal networks and focuses on the *synchronous* activity of neurons in addition to excessive activity and lack of inhibition. An *operational* definition of a seizure may also have its place, especially when one is clinically trying to decide if the described event meets the criteria of an epileptic seizure. In veterinary medicine, in particular, the *epileptiform* (a characteristic electroencephalograph [EEG] abnormality often seen during or in between epileptic seizures) is not easily measured. EEG recordings are considered fundamental criteria for the definition of many forms of epileptic seizures in human medicine, but not all EEG abnormalities result in epileptic seizures. The practical difficulties in obtaining EEG data in veterinary patients dictate we work around this deficiency in a more pragmatic way. To this end, we may employ an *operational definition* of a seizure in order to guide our judgment. An operational definition of an epileptic seizure would describe the incident in question based on specific observable events or conditions that must be present, from which any observer (layperson, clinician, or researcher) can independently use to come to the same conclusion. A consensus operational definition for an epileptic seizure has been defined as:

> *Manifestation(s) of excessive synchronous, usually self- limiting epileptic activity of neurons in the brain. This results in a transient occurrence of signs which may be characterized by short episodes with convulsions or focal motor, autonomic or behavioral features and due to abnormal excessive and/or synchronous epileptic neuronal activity in the brain.*
>
> (*Berendt et al., 2015*)

The above event would be described as self-resolving (transient) signs with potentially short episodes of convulsions, focal motor (face twitches or automatisms), autonomic

(urination, defecation, salivation, etc.), or behavioral signs (anxiety, aggression, fear, affection, etc.). Observationally, we would not be able to know if there was excessive synchronous epileptic activity of neurons (without an EEG), and we are assuming the observed signs are due to an *abnormal excessive and/or synchronous epileptic activity in the brain*. Many clinical manifestations of epileptic seizures could potentially fall outside of this definition, such as atonic seizures (drop attacks), nonconvulsive epileptic seizures, and non-motor signs such as attention-seeking behavior. Not all focal seizures consistently display autonomic signs or changes in consciousness. Furthermore, EEG is not a 100% accurate method of detecting synchronous activity in the brain (Brauer *et al*., 2012). *Essentially*, with veterinary patients, we may never be able to "see" the retinue of seizure manifestations a human would describe, which means we need to keep a very open mind as to what may or may not be a seizure. Later in this chapter, I will cover some of the more common human manifestations of epileptic seizures. It may be helpful to imagine what a dog or cat may be experiencing if it were to have an *epigastric* or other elementary sensory seizure. As we look at our patients (or more commonly videos of the patients) during a potential seizure event, we usually gain confidence in saying "we know it when we see it." I personally think the *stereotypic* nature of the vast majority of episodes we evaluate squarely places them in the category of epileptic seizures. That is, the repetitive and usually self-resolving, similar symptomology, broken up by periods of normalcy, is a very good starting point to determine if what you are presented with are indeed epileptic seizures. You can ask these questions:

- Does the event spontaneously and suddenly occur (paroxysmal or a paroxysm)?
- Does the event resolve on its own (transient)?
- Does the event look like similar episodes or events in the past (stereotypic)?
- Does the patient appear to be experiencing an involuntary action (motor, autonomic, or behavioral)?
- Is the patient non-responsive to your verbal or visual cues?

Answering yes to the majority of those questions would certainly make me more likely to consider an epileptic seizure as the event; however, this is not absolute. For example, a behavioral disorder may look very similar. Furthermore, many of the paroxysmal dyskinesias and other commonly mistaken cases of epileptic seizure will also answer "yes" to the above questions. When you are presented with a case that is not as clear as to whether or not the episode is an epileptic seizure, you have to dig a little deeper. You may ask:

- Can you influence the behavior by trying to grab the patient's attention? Some animals with paroxysmal movement disorders may have their episodes interrupted by an owner petting them or asking them if they want to "go for a walk."
- Is there a breed predilection for the disorder (e.g., idiopathic head tremor of Dobermann Dogs)?

Paroxysmal movement disorders are often described as occurring or reoccurring spontaneously (paroxysmal), self-resolving (transient), and with similar symptomology each successive time (stereotypic). During the event, there would be an indication the subject is not in complete control of its movements and/or behavior. This description is purposely subjective in regard to the time of the event, as not all epileptic seizures are *brief*. Additionally, not all epileptic seizures are transient or self-resolving, as in the case of status epilepticus (SE), but SE may be defined and addressed as a potential consequence or variant of epileptic seizures. Certain forms of epilepsy in humans (e.g., epilepsia partialis continua) may produce epileptic seizures, which can last for days to years but are not recognized in veterinary patients, at least not yet (Cockerell *et al*., 1996). Additionally, it is now well recognized that epileptic seizures may arise from cortical as well as subcortical structures and the brainstem in humans and animal models. A *symptom* is a subjective feeling, which is *observed*

by the patient and cannot be measured with direct means. Technically, our patients are not capable of communicating symptoms. They do, however, show us *clinical signs*. A clinical sign is a direct measurement of the *observed* patient. Therefore, veterinary patients have clinical signs of dysfunction and not symptoms of disease or dysfunction. A syndrome is a collection of clinical signs or observations that share common characteristics with known disease or dysfunction entities. Notice we refer to it as disease *or dysfunction*. Finally, not all seizures are spontaneous. Some can be induced or triggered, as in *reflex* epilepsies. Later in the chapter, we will see the first step in the diagnostic process is to determine if the event is an actual epileptic seizure or something else.

EPILEPSY

In the past, epilepsy was considered to be not a disease but rather a disorder of aberrant neural connections (Engel, 2013). Furthermore, epilepsy was not a single disorder but rather a collection of disorders, which may be referred to as *the epilepsies* (Engel and Wiebe, 2012). The contemporary accepted definition of *epilepsy* is somewhat different from previous definitions, and as of 2014, the ILAE now considers epilepsy a "disease" and not a "disorder" for the sole reason of alerting society, patients, and clinicians to the importance and impact of epilepsy (Falco-Walter *et al*., 2018). The most recent definition of epilepsy is:

> *A disease of the brain characterized by a predisposition to generate epileptic seizures and practically specifies more than one epileptic seizure over any particular unit of time (for instance, at least two epileptic seizures, at least 24 h apart).*
>
> (*Berendt et al., 2015*)

This would also include a single epileptic seizure along with an alteration in the brain that *sustains and increases the likelihood of future epileptic seizures*, as well as any epileptic syndrome (think—brain tumor, developmental abnormality, or encephalitis) (Fisher *et al*., 2014). Along with those criteria, include any associated neurobiological, cognitive, psychological, and social disturbances (Fisher *et al*., 2005). The sustained alteration of the brain would be a *condition increasing the chance of a future epileptic seizure*. The last aspect of the definition (neurobiological, cognitive, psychological, and social disturbances), as it relates to veterinary patients, would be difficult to validate, and the current conceptual definition of epilepsy by the ILAE purposefully acknowledges the consequences of epileptic seizures (psychological and social disturbances). With the exceptions of a neurobiological condition and interictal or postictal cognitive dysfunction, psychological and social disturbances (i.e., the stigma associated with epilepsy in humans) would be difficult to apply to veterinary patients. However, we do see certain consequences in our patients of potentially having epilepsy, such as a trend toward signs associated with obsessive–compulsive disorder (OCD), fear and anxiety-related behaviors, or attention deficit hyperactivity disorder (ADHD) (Peek *et al.,* 2024). Furthermore, long-term associated comorbidities, either from the disease itself (e.g., cognitive decline) or medications used to control the disease, are often encountered (James *et al.,* 2024). A neurobiological condition may include permanent changes to the brain secondary to trauma, encephalitis, neoplasia, degenerative disease, and anomalies, as well as any temporary changes to the brain, which allow a permanent alteration in the organization or function of the neural networks. For practical purposes, an operational definition of epileptic disorders may simply include:

> *A history of at least one epileptic seizure, an enduring alteration of the brain that increases the likelihood of another seizure and any neurobiological or behavioral disturbances secondary to the epileptic seizure.*

One of the major considerations of the ILAE was to prevent the common practice of dismissing a single event as not important. By avoiding the dismissal of a single event and therefore pursuing diagnostics earlier in the course of the disorder, there may be a more likely chance of preventing or reducing the possibility of multiple epileptic seizures. Essentially, if the clinical picture "fits," those patients who present for a single seizure have a greater chance of having multiple further seizures, and a clinical workup is warranted. The simplified version of the definition of epilepsy as "*recurrent unprovoked seizures*" is practically more useful for veterinary patients.

EPILEPTIC SYNDROME

The definition of an *epileptic syndrome* may help in selecting diagnostic tests, medications, and predicting prognosis. An epileptic syndrome would be defined as:

> *A collection of clinical signs, including one or more seizure types, along with characteristic EEG patterns (if applicable), genetic defects, pathological abnormalities, etiologies, response to medications and prognostic factors considered together with the signalment of the patient, to which the patient fits in the category of other pateints with similar clinical signs.*

For veterinary patients, the practical application of an epileptic syndrome may be the syndromic classification, where we make a presumptive diagnosis based on factors such as the age of onset, presence of interictal deficits, certain responses to treatments (e.g., steroids), and the time course of the clinical signs. However, unlike a specific disease, there may not be a consistent etiology, treatment, or prognosis due to the multivariate nature of epilepsy. When an underlying cause is not determined, the *syndromic classification* provides the clinician with important insights into the management and prognosis of epilepsy and epileptic seizures.

ELEMENTS OF AN EPILEPTIC SEIZURE

To aid in the clinical discussion of epileptic seizures, the entire process of a seizure has been defined to occur in different elements or phases. Observers of animals having epileptic seizures may not readily identify all of these elements. However, knowledge of the components of an epileptic seizure may provide insight into classification, diagnosis, prognosis, and treatment. Additionally, recognition of pre-seizure activity may provide an opportunity for early intervention with medications whose aim is to halt the progression of the seizure. The classic and well-defined progression of an epileptic seizure event can be divided into:

- *Prodrome*
- *Aura (focal seizure)*
- *Ictus (seizure)*
- *Postictal*
- *Interictal* elements

Humans describe the *prodrome* as a "feeling" or mood change, which precedes an epileptic seizure several minutes to days prior to the event. There are no EEG changes identified during a prodrome. In veterinary patients, this may be observed by the animal's caretaker as a behavioral change in the patient, such as anxiety, restlessness, attention seeking, or specific behaviors common to the situation or event (e.g., eating carpet or hiding) (Berendt *et al.*, 1999).

A prodrome is considered a "pre-seizure" activity and usually occurs in the pattern of a stereotypic event (i.e., eating carpet every time, not just once). Some humans report headaches as part of the prodrome. If we anthropomorphize this to a veterinary patient (which we should consistently be thinking about), the patient may be withdrawn or restricting its own activity, appear somnolent, or take a posture where the head and neck are held in a neutral position (again, try to think about what it would look like if the patient had a "headache"). An astute owner may comment their pet "seems off" and is needy, clingy, or anxious. Some animals become withdrawn from their family or hide. They may also behave differently to other members or pets in the household. Many prodromal events are quite obvious, whereas others may be inferred or implied based on pattern recognition. A prodrome reflects an increase in excitability of an epileptic focus, and its possible manifestation may reflect what area of the brain the focus is dominating (Gastaut, 1973). If a prodrome is recognized through its specific pattern of behavior or activity, a pet owner can be instructed to give medication for a defined period of time (several hours to days) in order to suppress the potential of the epileptic seizure continuing to develop (see Chapter 6). This short-term medication can be a very powerful tool in the long-term management of an epileptic pet.

The *aura* is commonly thought of as a warning sign that a seizure is about to occur when, in reality, the aura is assumed to be the *beginning* of an epileptic seizure. Auras were formally classified as a partial seizure after the 1981 International Classification of Epileptic Seizures by the ILAE. Typically, they were considered focal seizures without the impairment of consciousness (formerly, "simple partial seizures"), which may or may not secondarily generalize (i.e., go on to develop into a generalized seizure). They have come full circle to now be regarded, once again, as *focal* seizures in the most recent (2022) classification by the ILAE (see classification section) (Beniczky *et al.,* 2022). An aura may not result in detectable EEG epileptiforms, although they commonly do, which is why they are regarded as epileptic seizures. Not all auras will secondarily generalize, in which case they are referred to as *sensory seizures* (Thomas, 2010). Most of the subtle and subjective experiences humans describe may not be observable in veterinary patients; however, many observers will be able to see distinct changes either in the behavior of the animal or motor changes, including automatisms. An *automatism* is a relatively specific, repetitive, or coordinated motor activity, which usually occurs when cognition is impaired. They often resemble a voluntary movement (although they are themselves involuntary) and are thought to be a continuation of inappropriate, preictal motor activity (Blume *et al*., 2001). Once again, if we apply an anthropomorphic standard to what is observed when veterinary patients have epileptic seizures, one may describe *oroalimentary* signs (lip-smacking, bruxism, and swallowing), hyperkinetic movement, hypokinetic movement, and vocalizations as automatisms. Certain automatism described in humans simply do not occur in veterinary patients, such as gelastic (inappropriate bursts of laughter or giggling) and dacrystic (inappropriate bursts of crying) events, whereas others may be inferred, such as vocal utterances (grunts or shrieks) and dyspraxia (i.e., loss of the ability to perform learned movements on command despite adequate comprehension). Nonmotor descriptors are also commonly used with veterinary patients to help communicate events such as fear, anxiety, panic, aggression, affection, and restlessness. Some of the motor signs may be interpreted as visual hallucinations (fly-biting), auditory hallucinations (head turning, staring into space, looking for objects that are not present), gustatory or oroalimentary sensations (lip-smacking, licking, swallowing, and bruxism), and olfactory hallucinations (certain posturing such as nose to the sky as if sniffing), to name a few. More classic and apparent signs of an aura may include rhythmic contraction or flexion of a particular limb, head tremor, tonic opening of the jaw, trembling, incoordination, ataxia, and losing tone in the pelvic limbs (pelvic collapse). Many of the semiological terms used to describe human epileptic seizures do not have a place in veterinary medicine simply because they do not exist (e.g., verbal utterances and dysphasic or impaired communication,

spitting). *Autonomic* signs (originating from the autonomic nervous system) may include pupil changes (dilation, anisocoria), drooling, vomiting or retching, cardiovascular changes (tachycardia), piloerection, and thermoregulatory abnormalities. An aura or focal seizure may end suddenly (isolated) or secondarily generalize (i.e., progress to a generalized seizure). When it secondarily generalizes, it becomes the *ictus*. Berendt demonstrated that 85% of dogs diagnosed with partial seizures (focal) went on to develop secondary generalized seizures, making them the most common form of seizure (Berendt and Gram, 1999). An *aura* has a significant degree of subjectivity associated with it. Because the aura is actually a focal seizure, in the 2015 consensus statement from the IVETF, it is recommended to not use the term *aura* and instead refer to the instance as a focal seizure (Berendt *et al*., 2015).

The *ictus* is the epileptic seizure itself, which may be a continuation of an aura (focal event) or the evolution of a focal seizure into a generalized seizure. *Ictal*, *postictal*, and *interictal* are terms used to describe the distinct stages of a seizure event; however, the exact point from where one phase transitions to another may be difficult to distinguish. The ictus can last from minutes to days and may manifest as an obvious epileptic seizure (classic "convulsion") or the less obvious signs such as blindness, aimless wandering, confusion, salivation, and periods of affection or aggression. There is no correlation between the severity of the ictus and the length and severity of the postictal period. Many animals with severe epileptic seizures will recover quickly, and conversely, many animals with mild seizures will have debilitating postictal periods lasting for hours to days. The physical damage to the body secondary to a sustained epileptic seizure, however, is often proportional to the length of time of the event, as sustained muscle contractions, apnea, hypertension, and disorders of metabolic processes (e.g., acidosis) can result in secondary physical damage to the body. Therefore, we should be careful about labeling seizures as "mild" if that labeling potentially delays treatment. I personally believe all epileptic seizures should be treated *quickly and aggressively*, assuming they have the potential to become "severe."

The *interictal* phase is the time between the end of the postictal abnormality and the next ictus. This stage is only used when describing patients who have regularly recurrent epileptic seizures. There may be no easily distinguishable transition between postictal and interictal stages. Within the interictal phase, the patient may exhibit abnormal symptomology suggesting a recent seizure. These signs may be proprioceptive deficits, behavioral changes, mentation changes, and individual or combined cranial nerve abnormalities (although less common). In general, interictal deficits are assumed to resolve within several hours to days after an epileptic seizure; however, some seizures may result in structural damage to the brain with subsequent, permanent postictal or interictal deficits (although this too is uncommon). It is important to recognize this peculiarity, as the presence of *persistent* interictal deficits (greater than 5–7 days after the last epileptic seizure) is a distinguishing characteristic, which may be used to aid in a syndromic classification (see under Epileptic Syndromes). To use interictal deficits as a prognostic factor, one should consider the *progression* of deficits related to the brain rather than the simple *presence* of deficits. Progression, as it relates to specific disorders of the brain, implies an underlying etiology, which is *growing* or *changing* (Figure 4.4). Postictal deficits may be indistinguishable from permanent interictal deficits. There is no correlation between the type, intensity, or duration of an epileptic seizure and the duration of the postictal phase (Berendt and Gram, 1999). A presumed *permanent deficit* may resolve over time as the brain has an incredible ability for neuronal reorganization (i.e., plasticity), resulting in the potential reversal of these clinical signs (either alone or with focused rehabilitation). Disease progression over time is an important element to consider in veterinary classification schemes, as opposed to human schemes. Because the underlying cause of the epileptic seizures is often not known (i.e., pet owners may not allow diagnostics or diagnostic testing fails to identify the cause of the seizure), being able to determine if new clinical signs associated with brain dysfunction are developing over time (independent of seizures) will aid the clinician in syndromic classification, therapy choices, and prognostication.

STATUS EPILEPTICUS

There is no single standard, universally accepted definition of *status epilepticus*. According to the *Glossary of Descriptive Terminology for Ictal Semiology*, status epilepticus is defined as:

> *Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.*
>
> (*Trinka et al., 2015*)

This is an example of a *conceptual* definition, whereby the general lack of knowledge regarding the pathophysiology of status epilepticus results in a vague attempt to define the state. It contains two *operational* parameters. The first is the term *t1* or the time point at which the seizure is considered an "abnormally prolonged seizure." The second is *t2* or the length of time of prolonged seizure activity where there is a risk of long-term enduring consequences of the epileptic activity. The ILAE considers *t1* to be 5 min and *t2* to be 30 min. A more contemporary, simplified, mechanistic but still conceptual definition is

> *An epileptic seizure that is so frequently repeated or so prolonged as to create a fixed and lasting epileptic condition.*
>
> (*Engel, 2013*)

As the scientific community elucidates the underlying pathophysiological mechanisms leading to status epilepticus, the mechanistic definition will be refined. For now, it is reserved for primarily research uses. Numerous *operational* definitions have been proposed in order to place a defined time point within the definition of status epilepticus. Over the years, this has been modified from a general acceptance of an event lasting at least 30 min (Gastaut, 1973) to a more shortened time period of 5–20 min depending on the age of onset and the type of seizures (Lowenstein *et al.*, 1999). The 30 min time point proposed by Gastaut was based on the notion that within animal models of status epilepticus, neuronal injury usually begins to occur after a sustained epileptic seizure of 30 min or more. Studies have shown patient mortality increases with seizure duration (Jull *et al.*, 2011; Arrol *et al.*, 2012; Monteiro *et al.*, 2012; Weissl *et al.*, 2012). Additionally, cognitive and behavioral impairments in humans have been shown to improve with pharmacology or surgery aimed at reducing seizures, suggesting epileptic activity itself (as opposed to any underlying disease) leads to cognitive and/or behavioral decline (Asarnow *et al.,* 1997; Skirrow *et al.,* 2011; Barry and Holmes, 2016). Therefore, from a practical aspect, all seizures should be treated as soon as possible. It would be considered a standard practice that any patient arriving at an emergency facility actively having a seizure would be treated immediately (see Chapter 8). The vast majority of generalized tonic–clonic seizures self-terminate in less than 5 min and very commonly in less than 1 min. Seizures do not stop owing to neuronal exhaustion but rather to a combination of desynchronization, increased extracellular potassium, active inhibition, and depolarization block (Engel, 2013). Operationally, one may consider status epilepticus as a prolonged seizure event continuing beyond the time the majority of epileptic seizures would self-terminate *for that particular patient*. An operational definition of status epilepticus is therefore referred to as:

> *Repeated seizure activity without an intermission consisting of either continuous seizure activity lasting at least 5 minutes or 2 or more seizures with incomplete recovery between seizures.*
>
> (*Shell, 1999; Saito et al., 2001*)

CLUSTER SEIZURES

The term *cluster seizures* refers to an abnormal grouping of seizures relative to a particular patient (or more than one seizure in <24 h). Cluster seizures imply a period of time where the patient returns to being normal between the epileptic seizures (and is therefore not in status). Without this return to normalcy, the patient would be considered to be in a state of status epilepticus. Therefore, assuming a patient is considered normal following an epileptic seizure and another occurs within an abnormal time period relative to that patient, a cluster would be considered a *group* of epileptic seizures. A cluster may be multiple seizures in an hour, hours, day, or days, or within a week or month. Beyond a month, one may assume the frequency of seizures is increasing, although, theoretically, a patient could have an increased number of epileptic seizures *relative to their previous history*, occurring within months. Determining if a patient is clustering may be helpful when formulating a therapeutic strategy by using techniques such as pulse or bridge therapies (see Chapter 6).

CLASSIFICATION

This section will define a veterinary classification model as it relates to the most currently accepted human classification as developed by the ILAE. From the simple standpoint of comparative medicine, a scheme that is as similar as possible to that used in human medicine should be employed in veterinary medicine in order to facilitate communication in regard to teaching, research, and clinical purposes. However, there are some intrinsic differences as well as practical differences between veterinary and human patients, which do not allow for an *unconditional acceptance* of the human scheme of classification. The veterinary model must be labile and will change with time, just like the human model. A consensus report was created in 2015 by the IVETF in order to clarify and focus on a common position for the classification of epilepsy and epileptic seizures in veterinary patients. The intent was to create a system that was rooted in the well-accepted veterinary terminology while at the time reflecting new thoughts from the accepted human classification schemes (Berendt *et al.,* 2015).

HISTORICAL AND CURRENT PERSPECTIVES

Previous classification systems relied primarily on observational accounts of epileptic seizures and their etiologies. Scientific advances have created a more precise pathophysiological explanation for epileptic seizures. Because of this, treatment and prognosis may now be determined in certain situations by a specific *epileptic syndrome* based on seizure type and disease progression over time (without necessarily knowing the cause). Therefore, three general classification paradigms will be addressed. The first is the *phenomenological* classification of seizures (i.e., the descriptive semiology used to categorize seizures). This is the type. The second would be the *etiological* classification of seizures (i.e., what is the underlying cause of the seizure?). This would be the *epilepsy* type. Finally, and most importantly, would be the *epileptic syndrome*, the seizure type, and etiology fall under (Table 3.1). One note to be aware of is the discussion of *metabolic* or *reactive* seizures. Technically, they are not true epilepsies if the seizures stop once the underlying disorder is removed. However, because these etiologies may pathologically alter the brain, they may create a new neural substrate, which in and of itself creates the propensity for recurrent seizures. Furthermore, recurrent seizures from a reactive cause may create an epileptogenic site in the brain, resulting in the development of epilepsy. Therefore, they should be considered within the classification schemes. Just because the underlying cause of a reactive or *provoked* seizure has been eliminated (i.e., toxin, portosystemic shunt, etc.), we cannot necessarily assume the seizures will also stop. The importance of the syndromic classification scheme

Table 3.1 Classification schemes of epileptic seizures.

Phenomenological (seizure type)	What does the seizure look like (see Table 3.4)?
	Using descriptive semiology to describe the seizure *type*. **Focal**, **Generalized,** or **Unknown**
Etiological (epilepsy type or cause)	What is the cause of the seizure?
	Making a diagnosis (presumptive or definitive) of the *cause* of the epileptic seizures. **Idiopathic**, **Structural,** or **Unknown**
Syndromic	Based on seizure *type*, signalment, history, minimal database, advanced diagnostics, the presence of interictal neurological deficits, and progression over time or remission.
	Which syndrome category does the patient fit best? **Idiopathic**, **Structural** (progressive vs. nonprogressive), **Metabolic/Provocative/Reactive** or **Unknown**

centers on the notion that we do not always discover the etiology of epileptic seizures. By being able to classify based on a syndrome, we can propose treatment and, more importantly, *prognosticate* without necessarily knowing the underlying cause. This is far more helpful than trying to treat a seizure *type* or cause, and this is the classification scheme we lean on the most in veterinary medicine. We make a "best judgment" call based on the evidence at hand but condition those recommendations on the acquisition of other bits of evidence or "pieces of the puzzle" over time. As more pieces of the puzzle are identified and the clinical syndrome comes more into focus, the presumptive diagnosis, treatment recommendations, and prognosis may change.

Classification schemes are useful when applied to research, teaching, and clinical purposes; however, a classification scheme is not needed to find the underlying cause of epileptic seizures in an individual patient. In determining how to set up a classification scheme, any relevant feature of an epileptic seizure considered useful could be employed to organize the epilepsies and their etiologies into groups based on the seizure type, the underlying etiology, and/or the epileptic syndrome. This could be specific EEG patterns (though uncommon for veterinary patients at this time), epileptic seizure types, triggers of epileptic seizures, or involvement and progression of certain motor, sensory, behavioral, or reflex pathways (i.e., the development of other signs of brain dysfunction). Berendt reported that 65% of dogs with an established clinical diagnosis of epilepsy had abnormal EEG activity (Berendt *et al*., 1999). As our understanding of the etiology of epilepsies advances, known genetic abnormalities, receptor defects, or metabolic aberrations may also be used to classify epileptic seizures and epilepsies. Therefore, we must keep any classification scheme open to reevaluation and modification to reflect a changing and developing understanding of epileptic seizures and the various epilepsies. Much confusion exists within the veterinary literature regarding the classification of seizures. This has led to inaccurate estimates of the etiological base of seizures (e.g., the incidence of *idiopathic* [i.e., genetic] epilepsy in cats is reported between 0 and 59% in the veterinary literature) (Kline, 1998; Barnes *et al*., 2004). An excellent description of the historical classification schemes in veterinary medicine is available (Mariani, 2013).

Prior to even considering a classification scheme, the clinician must first determine if the animal is having a seizure or a *seizure-like* event. Because chronic seizures (epilepsies) affect nearly 3% of the canine population (estimates range from 2 to 5%) and 2% of felines, most clinically oriented veterinarians will be presented with numerous cases of dogs and cats with a history of epileptic seizures every year (Kay, 1989; Lohi *et al.,* 2005; Schriefl *et al*., 2008). Epilepsy is the most common neurological condition affecting animals, a fact veterinary patients share with human

patients (Podell *et al*., 1995). It has been estimated that between 0.5 and 5.7% of dogs will have a single epileptic seizure event sometime in their life (Cunningham and Farnbach, 1988). Cats are not nearly affected as often as dogs; however, the same algorithmic approach to the canine patient with epileptic seizures can be made for the feline patient. The classification system used to categorize epileptic seizures should be comparative among species (dogs, cats, and humans). However, there are certain modifications that naturally need to be considered when applying a *universal* classification scheme.

PATIENT ASSESSMENT

The first step the clinician should take in evaluating an animal who is presumed to be having epileptic seizures is to figure out if the episode is truly an epileptic seizure and not a "seizure-like" event. An accurate historical description from an attentive owner, video observation, EEG findings (if available), and personal observation are essential components to making this determination. An owner/patient questionnaire can be useful (see Appendix 2 and companion website for example). Conditions that are commonly mistaken for epileptic seizures are listed in Table 3.2 (see Videos 25, 26, 28, 29, and 31–34).

Our ability to differentiate between an epileptic event and a non-epileptic event will continue to improve. Genetic testing of specific breed-related abnormalities will unlock previously undefined syndromes/conditions (the Holy Grail of diagnosis). Clinicians should continually research possible breed-related causes for any suspected movement disorder.

There is no etiological significance to an epileptic seizure. A seizure simply represents a sign of brain dysfunction. Think of a seizure as the brain's way of limping. A limp does not constitute a diagnosis or underlying etiology; it only allows the clinician to focus on the area of the body where the disorder exists. Similarly, a seizure only tells the clinician there is something wrong with the brain (dysfunction). Although epileptic seizures may be considered a disorder of the brain, epilepsy is a *disease* of the brain. Ultimately, the clinician will categorize the described seizure and use the information

Table 3.2 Conditions commonly mistaken as seizures.

Cervical pain (or other forms of pain)—usually severe
Syncope/cardiac disease/pulmonary hypertension (collapse)
Vestibular disease (including otitis), usually acute onset
Stereotypic movement disorder ("head bobber")
Gastrointestinal distress (e.g., smacking lips, licking at air, and gulping)
Fly-biting, fly-catching: May be epileptiform activity or behavior
Tremors and tremor syndromes
Exercise-induced collapse or weakness
Myasthenia gravis/neuromuscular weakness (collapse and weakness)
Behavioral abnormalities (Compulsive disorders—trigger event may be present)
Feline estrus behavior
Myoclonus (episodic shock-like contractions/muscles)
Encephalopathy (metabolic, toxic, ischemic, etc.)
Narcolepsy/cataplexy
Parasomnias
Paroxysmal Dyskinesias (Scotty Cramp, Canine Epileptoid Cramping Syndrome, etc.)

to generate a differential list of the possible etiologies (causes) for the seizure and reasonable tests to rule in or rule out items on the differential list and base treatment decisions and prognosis as well as treatment progress relative to the epileptic syndrome. Current classification schemes are designed with knowledge of different types of ictal events. This allows the clinician to characterize many different epileptic seizures based on particular and specific pathophysiological and anatomical abnormalities. By adhering to this focus, the clinician should be able to categorize the seizure disorder into a general epileptic syndrome. Categorization into a syndrome is the ultimate goal short of a definitive diagnosis. However, if categorization into a syndrome is not possible, the epileptic seizure classification will still be beneficial through inherent etiological, therapeutic, and prognostic implications, which still allow the clinician to help the patient with reasonable assumptions.

In contemplating the adoption or even alteration of current classification schemes utilized in veterinary medicine, we should ask ourselves, "why even consider a classification scheme for veterinary patients? Why not just adopt the method used for humans?" Much of the research into the pathophysiology of epileptic seizures as well as therapeutic interventions is derived from animal models, which makes a parallel, if not similar, classification scheme understandable. Furthermore, the incidence, etiology, electroclinical manifestations, diagnostics, and therapeutics are very similar between species. It only makes sense to approach the topic from a comparative medicine point of view. Unfortunately, there is continuous debate as to the best or even a reasonably organized classification scheme in human medicine. The *ILAE* is the *de facto* organizing body, which generates the "accepted" classification scheme of human seizures. The first International Classification of Epileptic Seizures was published in 1970 by the ILAE. Subsequent revisions were made in 1981, 2001, 2010, and most recently 2017. This naturally seems like a good place to start. We may not have to reinvent the wheel; however, we cannot completely accept the human classification scheme completely, simply because it is not a 100% phenomenological form of classification. A *phenomenological* basis of classification relies on *descriptive* terminology of seizure semiology to create subcategories of a general condition. In veterinary medicine, those descriptions are solely based on observation as opposed to human medicine, where the patient may be able to describe certain aspects of the epileptic seizure or events surrounding the seizures (triggers, stressors, aura, etc.) to some degree. Although still technically a phenomenological description, it utilizes the patient's own experiences to help with classification (i.e., symptoms). For example, a patient may complain of a bitter taste in the mouth prior to a generalized epileptic seizure, which would allow the clinician to classify the epileptic seizure as *focal* and *gustatory* with *secondary generalization*. In an extremely fascinating case of reflex epilepsy associated with eating only certain types of food, a woman watching a video of minced meat would first develop epigastric discomfort (changes begin to show up on EEG) and then get the feeling she had seen the video before (déjà vu) (clinical seizure onset), which then progressed to a generalized tonic–clonic seizure (the video is worth watching) (Mimura *et al.,* 2017). Or how about another case, where reflex epilepsy was triggered by the use of cutlery (Stravropoulos *et al.,* 2020)? These cases certainly make us wonder if I am asking the right questions at my initial epilepsy interviews with clients.

In veterinary medicine, the phenomenological description is based on the descriptive semiology as dictated by the observer of the seizure. Therefore, many descriptive terms used to categorize a seizure as *focal* may be missed, and the category of focal seizures is underestimated when compared to humans. Although this may have little relevance to treatment and prognosis, it may confuse or cloud our interpretation of the human literature as it pertains to dogs and cats. The closest we may come to a human classification scheme may be one that is utilized for neonates, preverbal children, and nonverbal humans. In human medicine, a significant amount of effort is placed on identifying the *epileptic syndrome* in addition to the classification of the epileptic seizure type. The human classification schemes have undergone a variable evolution over the years, from the extremely simple to the extremely complex. Neither of these, in any form, is completely accepted

among human epileptologists, hence the continued modification of the classification scheme of human epileptic seizures. The most recent iteration is purposefully designed to be a "flexible work in progress," which could be modified when needed and updated as new information becomes available. Additionally, it is intended to be "a testable working hypothesis, subject to verification, falsifications, and revisions" (Engel, 2001). If we base a veterinary classification scheme on the foundations of a human classification scheme, the goals of the classification model should be to describe and classify the seizure based on a system using standardized terminology but at the same time being flexible enough to account for certain practical and dynamic aspects of the veterinary diagnosis (as opposed to human). For example:

- Veterinary patients may not fall into a recognized syndromic diagnosis as humans do. They may have different and unique syndromes, typically hampered by a lack of diagnostic testing (e.g., EEG) and the subsequent development of categorized syndromes.
- Epileptic seizure types and epileptic syndromes specific to veterinary patients will change as new information is obtained and research is advanced.
- A complete and detailed description of the ictal phenomenology may not always be necessary in order to diagnose and treat.
- Different classification schemes or different layers of a single classification scheme may be designed for communication and teaching, therapeutic drug trials, and basic research.
- Diagnostic modalities and treatment options used in humans may not be available, practical, or safe for veterinary patients (modified from Engel, 2001).
- Not all veterinarians, and certainly veterinary neurologists, have an "interest" in epilepsy—so the motivation to stay current and contribute to the scientific community is variable.
- Veterinarians rely on a general syndromic classification, whereas human physicans aim for the specific syndromic diagnosis (i.e., structural progressive vs. Lennox-Gastaut Syndrome).

The most recent ILAE classification framework was adopted in 2017 (Falco-Walter *et al.* 2018). It now incorporates more specific, etiological causes of epilepsy along with seizure type, epilepsy types, and specific epilepsy syndromes. With the codification of epilepsy syndromes, the classification scheme utilized in human medicine, while seemingly simple at the surface, is open to complexity (Nabbout *et al.,* 2023). The currently accepted (a term used very loosely among human epileptologists) *etiological* categories of epilepsy are *genetic*, *structural*, *metabolic*, infectious, immune, and *unknown* (Scheffer *et al.*, 2017). Previously, etiological categories were divided into *primary* (later referred to as idiopathic or essential epilepsies) and *secondary* (later referred to as symptomatic or acquired epilepsies). These classification schemes had a greater commonality with veterinary classification in the past; however, an expanding gap related to the ability to fine-tune a diagnosis is creating a situation where the human classification scheme is becoming less useful to veterinarians. On the other hand, once an etiology is classified on the human side, it encourages veterinarians to look for similar etiologies in our patients. Such is the case with the autoimmune forms of epilepsy (antibodies directed at GABA or leucine-rich glioma-like 1 and 2 proteins). Veterinarians invariably will need to follow a more practical scheme for use, which will rely heavily on the syndromic classification related to *general* causes as opposed to identified and labeled specific diseases of humans (Table 3.3). This form of classification, at this time, has the most practical use.

In general, the primary (idiopathic) epilepsies were assumed to be nonprogressive, typically age related, presumed to be genetic in their origin, and the brain was considered to be "normal" or free from any metabolic or structural abnormalities. Secondary epilepsies were

Table 3.3 Underlying syndrome (type or cause) of epilepsy (veterinary scheme).

Current classification (2015 ACVIM Consensus)	Most recent classification	Former classification
Idiopathic	Genetic	Idiopathic or primary
Genetic (confirmed)		
Genetic (suspected)		
Unknown		
Reactive or provoked[a]	Reactive or provoked	Secondary
Metabolic/toxic	Metabolic/toxic	Symptomatic/metabolic
Structural	Structural	Secondary
Static[b]	Static	Symptomatic/structural
Progressive[b]	Progressive	
Unknown	Unknown	Cryptogenic

[a] Technically, reactive or provoked causes are not true epilepsy as there is no underlying substrate in the brain responsible for the seizures.

[b] Author's suggestion for practical use in prognostication.

presumed to consist of generalized seizures from the onset, poorly responsive to medications, and would not resolve with time. The signs of brain dysfunction could be progressive or static depending on the underlying etiology. As human physicians and veterinarians are quick to point out, patients with similar electroclinical syndromes (EEG recordings) do not always have the same etiology for their seizures; therefore, an overly simplified scheme is not terribly helpful in regard to diagnosis, treatment, or prognosis. The 1971 and 1981 classification schemes led to confusion between terms describing the etiologies and descriptions of EEG terms. In 1989, the ILAE introduced the term "cryptogenic" as an etiology whereby a structural cause of the seizures was suspected but could not be found. A previous etiological classification scheme (Berg *et al.*, 2010) focused on the notion that whether primary or secondary, idiopathic or structural, all forms of epilepsy are thought to be multifactorial, involving both genetic and acquired abnormalities leading to brain dysfunction. This concept may be difficult to embrace in veterinary medicine owing to a generalized lack of sophistication and resolution in the diagnostic modalities (specifically EEG and functional advanced imaging), treatment, and classification. For example, we may be content with assuming the cause of seizures in a patient with a brain tumor is the tumor itself and its secondary effects on the brain; however, we must also consider that for any particular patient, other variables may contribute to the development of seizures, their intensity, frequency, and response to medications, etc., in addition to the presence of a brain tumor. Genetic factors leading to a higher resting seizure threshold may exist prior to the development of a structural cause of seizures. This may explain why some patients with a particular problem (i.e., brain tumor) have seizures and others do not. To make matters even more confusing, among veterinary neurologists, there are different meanings to the term "idiopathic." To some, idiopathic simply means "unknown cause." If the patient were young and did not show any signs of progressive brain dysfunction, it would likely be *genetic* (although not necessarily proven as inherited but in the sense of *born with*). If the patient had progressive signs, it might be idiopathic (as in "we cannot find a cause"), but the progression of clinical signs would imply a cause that is not "benign." In the pure sense of the definition of "idiopathic," it refers to seizures in and of themselves with no identifiable underlying cause for seizures (such as structural brain disease) and is implied to be of genetic origin, as opposed to simply "unknown cause." There is a *cause*; we just lack the ability to see it at this time, just like in 1955, when neurologists "lacked" the ability to use MRI. Focal cortical dysplasia and disorders of cerebral migration are excellent examples of this. At some time, we'll figure it all out.

For veterinary medicine, we have gone back to suggesting the term *idiopathic* and then further subclassifying that group of patients (Berendt *et al.,* 2015).

- Idiopathic—Genetic: A known gene has been identified, and there is a confirmed genetic background.
- Idiopathic—Suspected Genetic: A high breed prevalence, association with a genealogical analysis, and/or a significant accumulation of related individuals with epilepsy.
- Idiopathic—Unknown: There is no indication of a structural cause (but it could still be there), no history of a potential cause or event (such as trauma), and no association with a suspected breed or pedigree.

The previously accepted and still widely used types of epileptic seizures (not encouraged) were divided between *petit mal* (from French meaning "small illness") and *grand mal* (French meaning "large illness") seizures. We should avoid these terms. A better understanding of the pathophysiology and anatomy of the brain led to the replacement of petit mal with *focal* or *local* seizures (suggesting they were "mild") and grand mal being replaced with *generalized*. Additionally, a further distinction was made with an *absence* seizure, which was classified as a generalized seizure only with a brief lapse of consciousness (therefore *not* a petit mal seizure). It is not recommended to use either term (i.e., petit or grand mal). The pursuit of improved classification schemes was begun with the purpose of trying to reduce the ambiguity of seizure descriptions while at the same time attempting to recognize all epileptic seizure phenomena in a categorical form. Ultimately, the goal of classification would be to apply an understanding of the underlying mechanisms of epileptic seizures into a pathophysiological-oriented classification of seizures. In 1981, the ILAE adopted a new classification of epileptic seizure types. At the time, it was felt the term *focal* implied a seizure, which occurred in only a distinct area of the brain. The new term *partial* was given to a seizure that developed in one hemisphere of the brain as determined by certain behavioral or EEG abnormalities. Partial seizures were further subdivided into *simple partial* seizures when there was no impairment of consciousness and *complex partial* seizures when consciousness was impaired. If a partial seizure was to evolve into a generalized seizure, then it was classified as a *secondary generalized seizure*. This is also considered a confusing term related and similar to "seizures secondary to a brain disease." *Generalized seizures* were considered seizures, which began in both cerebral hemispheres at the same time, again based on behavioral or EEG characteristics. Generalized seizures were further subdivided into *absences*, *major motor events* (tonic–clonic and generalized), *minor motor events* (myotonic, atonic, and brief tonic), and *tonic* and *clonic* seizures. Finally, a category of *unknown* was also adopted for those seizures that did not fit any particular classification. The current ILAE phenomenological classification scheme of seizures divides the description of the epileptic seizure into *focal*, *generalized*, and *unknown* (Table 3.4). The justification for dropping the previous category of *partial* seizure and going back to *focal* was based on the notion that the terms *simple partial* and *complex partial* were often misused or misunderstood (Berg *et al.*, 2010). Furthermore, *partial* implicated "part of a seizure" or "part of a syndrome" and therefore "not severe," which often delayed diagnostics or treatment (Engel, 2001). In readopting the term "focal," it is emphasized that the term *focal* does not mean a small area or well-defined area of dysfunction. On the contrary, focal seizures may be diffuse and often represent vast areas of cerebral or subcortical dysfunction as opposed to discrete areas of brain damage or dysfunction. It cannot be overstated that a descriptive classification of seizures alone does not change the treatment or prognosis, which may be employed or theorized, unless it is part of a specific syndromic diagnosis known to respond to a specific therapy.

Table 3.4 ILAE classification of **seizure type**: expanded form (phenomenological).

Generalized

Motor

- *Tonic*: Sustained increase in muscle contraction lasting a few seconds to minutes. Extensor *or* flexor rigidity (i.e., sustained muscle contraction)
- *Clonic*: Myoclonus, which is regularly repetitive involving the same muscle groups, usually prolonged at a frequency of 2–3 cycles/s. Think rhythmic, jerking movements where muscles alternatively contract and relax.
- *Tonic–clonic*: A sequence consisting of a tonic phase followed by a clonic phase
- *Atonic*: Sudden loss or attenuation of muscle tone without an apparent preceding myoclonic or tonic event lasting ≥1–2 s involving head, trunk, or limb musculature
- *Myoclonic*: Myoclonus (sudden brief, single, or multiple) contraction(s) of muscle(s) or muscle groups. Can be of variable areas (i.e., axial, proximal, or distal limb)
- *Myoclonic–tonic–clonic*: Single or multiple sudden movements (jerks), bilaterally of limbs, followed by tonic and clonic phases
- *Myoclonic atonic*: A brief, sudden movement (jerk) followed by a loss of muscle tone (sudden fall or head drop)
- *Epileptic spasm*: brief (1–3 s) events, where there is contraction or extension of the legs, arms, or head. Typically affecting infants

Non-motor (absence)

- *Typical*: Recognized as a brief (usually less than 20 s) generalized seizure with impaired consciousness and *specific EEG changes characterized by spike-and-slow-wave complexes, which are bilaterally represented in the cerebral hemispheres*. A short period of staring into space or "blanking out"
- *Atypical*: More pronounced changes in tone. An onset or cessation that is not as abrupt and more heterogeneous EEG changes
- *Myoclonic*: Characteristics of a *Typical* type but with rhythmic myoclonic movements of the upper arms
- *Eyelid Myoclonia*: Sudden movements, fluttering, flickering, or soft blinking of the eyelids, which may be associated with the head moving backward with or without an absence

Focal

***Aware* or *impaired* awareness (specification optional)**

Motor

- *Automatism*: Semi-coordinated repetitive movement
- *Tonic*
- *Atonic*
- *Clonic*
- *Epileptic spasms*
- *Hyperkinetic*: Characterized by an onset of sudden ballistic movements of the arms or body
- *Myoclonic*

Non-motor

- *Autonomic*: Arising from an area of the brain controlling autonomic functions such as blood pressure, bladder or bowel control, or heart rate
- *Behavior arrest*: Temporary total body cessation of movement or freezing of activity
- *Cognitive*: Alteration in cognitive function (a deficit or surplus)
- *Emotional*: Fear, joy, laughing, crying, euphoria, etc.
- *Sensory*: That area of the brain affecting sensation results in hallucinations, deficits, or other alterations

(*Continued*)

Table 3.4 (Continued)

Focal to bilateral tonic–clonic: A focal seizure that progresses to a generalized seizure
Unknown
Motor
• *Tonic–clonic*
• *Epileptic spasms*
Non-motor
• *Behavior arrest*
Unclassified

Adapted from Fisher *et al*. 2017.

Theoretically, any organizational scheme could be used as long as any relevant feature confers a useful benefit to a particular purpose. The continual restructuring of classification schemes is necessary to keep up with the advances of the scientific community. Research scientists and clinicians need to be able to communicate on the same level. At the same time, we have to be careful not to dismiss older classification methods, which have the risk of leaving those familiar with the use of those older schemes behind. People tend to be uncomfortable when the *known* is abandoned for the *new* (i.e., some *fear* and therefore, resist change).

In 2014, a large and diverse group of veterinary neurologists, human neurologists, neuroscientists, neuropharmacologists, practitioners, and neuropathologists formed the IVETF with the aim of creating consensus statements within the field of epilepsy in dogs and cats. The goal of developing a "common language" was in response to a vacuum within the field regarding communication among stakeholders, including pet owners, breeders, clinicians, specialists, and researchers. A consensus statement was published in 2015 in regard to epilepsy definition, classification, and terminology in companion animals (Berendt *et al*., 2015).

This consensus statement was based on a foundation created by the ILAE with particular modifications related to the nuances of veterinary medicine (e.g., a general lack of EEG data preventing an electroclinical diagnosis). The overall goal of a veterinary classification paradigm will be to create a universal classification scheme where epileptic seizure *types* will be considered important entities that enable the clinician to have diagnostic, therapeutic, and prognostic implications when a diagnosis of an epileptic syndrome is not possible. Ideally, a syndromic classification would be the goal if an underlying etiology cannot be found. Relative to Table 3.4, the veterinary classification scheme is similar (although simplified); however, the IVETF has recommended we do not try to determine or label the animal's level of consciousness (aware vs. unaware) as this determination will always be subjective and it cannot be assessed objectively. Therefore, the determination is not useful (see Table 3.5) (Berendt *et al*., 2015). This neurologist somewhat disagrees with the assessment of aware vs. unaware, as sometimes the perception of this distinction can be useful in treatment recommendations (e.g., do you treat the occasional fly-biter if they "snap out of it?"). Additionally, I would include a seizure type as "unknown" for veterinary classification. It's also important to note that any descriptive semiology may be applied to the seizure type.

The basis of using a *syndromic approach* is established on this core concept:

> *Descriptive semiology alone (i.e., what a seizure looks like) is not a reliable and accurate means of distinguishing between two completely different etiologies (i.e., causes). Seizures, which look alike, may have completely different etiologies and therefore potential treatment and prognostic differences. At the same time, two identical etiologies (i.e., brain tumor) may manifest with distinctly different seizure types.*

The approach to treating the specific etiology may be the same but applied in a different manner if only the seizure type is considered without considering the distinct etiology. A seizure is the brains way of "limping." It shows dysfunction but does not identify disease.

Table 3.5 IVETF classification of **seizure type**: simplified form (phenomenological).

Epileptic seizure type	Old	Current (2015)
Clinical signs indicate activity started in a localized area of the brain	**Simple partial/ focal seizure**	**Focal epileptic seizure**
Focal motor, autonomic, or behavioral signs (alone or combined)	consciousness unimpaired	
	Complex partial/ focal seizure	
	consciousness impaired	
Clinical signs indicate activity started in both cerebral hemispheres	**Primary generalized seizure**	**Generalized epileptic seizures**
Predominantly presents as immediate convulsions with loss of consciousness, salivation, urination, and possible defecation.		
May also present as atonic or myoclonic		
Clinical signs start in one hemisphere and spread to both hemispheres	**Focal seizure with secondary generalization**	**Focal Epileptic Seizure evolving to become generalized**
Starts with localized signs and evolves to loss of consciousness, salivation, possible urination, and possible defecation		

Adapted from Berendt *et al*. 2015.

Examples

Case 1. A 4-year-old, female, spayed Labrador Retriever presents with a complaint of sudden onset, generalized seizures for 5 months. The neurological exam is normal.

Case 2. A 14-year-old, male, Boston Terrier presents with a sudden onset of focal facial seizures, characterized by intermittent, repetitive myoclonus of the right facial muscles, which has been occurring for the last 2 weeks.

Both of the cases end up having brain tumors—case 1 was a rostral forebrain (rhinencephalon) meningioma, and case 2 was a medial temporal lobe glioma. Case 1 might be assumed to have genetic or idiopathic epilepsy (based solely on age, breed, and lack of interictal deficits), whereas case 2 would likely be assumed to have a form of structural brain disease. Treatment options are similar; however, the prognosis is quite different based on the location and type of brain tumor. Now, instead of giving case 2 (the older Boston Terrier) a brain tumor, give it a cerebrovascular accident (stroke). Obviously, some elements of treatment would be the same (medically); however, the long-term prognosis is significantly different (i.e., improved), which is why it is so important to not leap to conclusions of etiology based solely on the age of onset of seizures. What is more helpful is whether or not any other neurological deficits have progressively developed over time. Even without diagnostics—time will tell. The brain tumor in the case of the 4-year-old lab will eventually "declare" itself through the progression of other signs

of brain dysfunction, unrelated to seizures (i.e., behavior changes, blindness or circling). However, we should always assume the best until proven otherwise.

From the above examples, we can infer the primary objective should be to make a diagnosis of a specific etiology (what is the suspected cause). If the clinician can do this, no further classification is necessary at this time. This may occur when historical information is enough to determine the cause, such as exposure to a toxin, followed by acute onset seizures or head trauma. Without diagnostics, the clinician is limited to watching for the development of other neurological deficits over time (i.e., progression of disease), regardless of response to anticonvulsant medication. A syndromic classification (based on accumulated characteristics of the epilepsy without a defined etiology) may change which medications are used. For example, cats with focal seizures characterized by oroalimentary automatisms may respond to prednisone as a treatment if the cause of their epilepsy is *limbic encephalitis* (Pakozdy *et al.,* 2014; Glantschnigg-Eisl *et al.,* 2023). Feline Limbic Encephalitis might be one of the closest syndromic diagnoses that can be made in veterinary medicine (excluding the specific genetically known cases—such as benign familial juvenile epilepsy of Lagotto Romagnolo Dogs). Another example is a young purebred dog who has been diagnosed with one of the many forms of encephalitis. In this "syndrome," prednisone and other immunomodulators, may be part of the treatment protocol along with anticonvulsant medications. If a syndromic classification is not possible, the treatment of the seizures would be based on the seizure type, and the prognosis (prior to diagnostic testing) would be based on several factors, including the age of onset, presence of interictal deficits, and, most importantly, *progression of clinical signs related to brain dysfunction* over time. Lack of progression of clinical signs would be commonly observed in the case of a *static disease* such as a cerebrovascular accident, whereas progression of brain dysfunction would be expected in the case where a patient has a brain tumor, encephalitis, degenerative disease, and other growing or changing conditions. This is a fundamental and core concept that will hopefully prevent the unnecessary and premature euthanasia of animals who have recently suffered from a stroke—do not assume all old patients with recent onset of seizures (or vestibular disease—but that is another topic...) have a brain tumor. For veterinary medicine, it is the closest we can come to a syndromic classification for the majority of our patients (Table 3.7).

THE APPROACH TO CLASSIFICATION

An approach to classification is outlined in Table 3.6. Proposed classification schemes have weighted heavily on those used for human medicine, in particular that of the 2001 ILAE report (Engel, 2001; Mariani, 2013; Podell, 2013). Here, we may depart a little from the proposed standard. Much of the data used in the approach to the classification of epilepsy in humans is irrelevant. However, we should acknowledge that as our understanding of the pathophysiology of epileptic seizures advances, current and new diagnostic modalities become more commonplace, and as treatments become more refined, veterinary medicine will gradually gravitate to a similar classification approach. However, what we define as a *syndromic* classification will be less refined as long as our diagnostics are invasive (and expensive). The goal of this diagnostic scheme is to provide the clinician with information, which may help direct diagnostic tests, modes of therapy, and prognosis. We must consider that the underlying classification of seizures may vary in degree of detail, which is dependent on the observation of the event and, in many specific cases, recognized EEG abnormalities, which are used to define a particular type of seizure (i.e., the EEG waveforms characteristic of an *absence* seizure—Figure 3.1). Although broadly based on human classification schemes, the aim is to provide a contextual similarity between seizures in order to facilitate communication among clinicians, researchers, and the teaching environment.

Table 3.6 Proposed diagnostic scheme for veterinary patients with seizures.

Step 1: Determine if the described event is an epileptic seizure or a non-epileptic, episodic, or paroxysmal event.
Step 2: Describe the epileptic seizure event with as much detail as possible. Phenomenological description of epileptic seizure: using ictal semiology from the Glossary of Veterinary Descriptive Terminology for Ictal Semiology (Appendix 1 and Tables 3.4 and 3.5). Example: focal, left forelimb automatism consisting of abduction with secondary tonic–clonic generalization. Example: postural atonic collapse, absence, generalized seizure.
Step 3: Determine the seizure type (Table 3.5). Examples: generalized tonic–clonic, focal, and unknown.
Step 4: Localize the lesion (if possible). Example: right forebrain. However, the "brain" is sufficient for practicality (i.e., the localization at this time does not change treatment options).
Step 5: Classification of epileptic syndrome (may not always be possible) from Table 3.7. This may help direct treatment and diagnostic plan, as well as prognosticate. Especially useful if step 3 is not possible.
Step 6: Determination of underlying etiology utilizing diagnostic testing. May provide "peace of mind" or refine treatment options (see Chapter 5). Tier I, II, or III for an evidentiary basis.

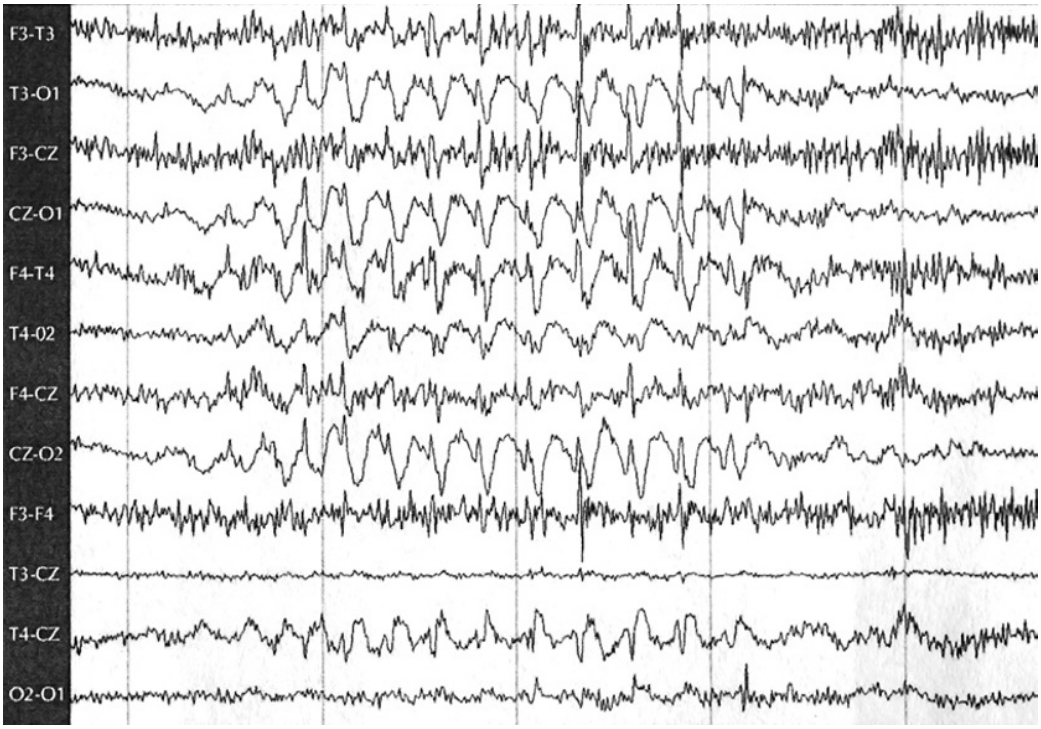


FIGURE 3.1 Ictal EEG of a dog with absence seizures showing a 2 s run of 4 Hz spike-and-wave complexes during the absence episode. Reproduced with permission from Poma et al. (2010)/Springer Nature.

Step 1 is to determine if the described events are truly epileptic seizures as opposed to a non-epileptic, episodic, paroxysmal movement disorder or other possible cause (Table 3.2).

Step 2 begins the diagnostic process and consists of a phenomenological description of the seizures using terms from the Glossary of Veterinary Descriptive Terminology for Ictal Semiology (Appendix 1). The onset and progression of the ictal events as well as the length of time of each stage (if applicable) should be included. The clinician should be as detailed as possible

(e.g., "fly-biting" or "lip-smacking" would be very detailed descriptions of the event, as opposed to "focal"). A suspected etiology or mechanism is not proposed or included in the description. This portion of the diagnostic algorithm is based on pet owner observations as described to the clinician or ideally through examination of video of an episode(s). The clinician may identify certain descriptors as being associated with epileptic seizures (e.g., laterally recumbent, paddling, foaming at the mouth, and urinating) and others that may be more suggestive of a "seizure-like event," such as neck pain, syncope, or myasthenia gravis.

Step 3 is categorizing the epileptic seizure type(s) the patient experiences relative to a list of accepted *epileptic seizure types,* but I would also include the potential category of "unknown" (Table 3.5). Is the seizure generalized, focal, or unknown, and within either category (if applicable), what subcategory would the seizure fall into (i.e., generalized tonic–clonic, focal with cognition, myoclonic, etc., see Table 3.4)? If a specific brain localization can be defined (e.g., sudden hemiparesis or asymmetric, involuntary muscle movement—referring to a specific cerebral hemisphere), it should be included along with any provoking events or stimuli. The use of the terms *status epilepticus* and *cluster* should be limited to and interpreted as descriptive extensions of any particular seizure type relative to the length of time of the seizure (status epilepticus) or the number of epileptic seizures in a period of time (cluster) relative to the individual (e.g., one patient may have a cluster of seizures in a day and another may have a cluster in a month). Status epilepticus is characterized by unremitting epileptic seizures not separated by a return to normalcy. A cluster of epileptic seizures would be considered to be an increased number of seizures within a given time period exceeding the average incidence of seizures over a longer time period *for the individual*.

Step 4 is to attempt to localize the lesion. Once you have determined the patient is having seizures, you have localized to the *brain*. However, in order to exercise your neurological localization skills, it is incumbent that the clinician (especially the neurologist or soon-to-be neurologist) attempt a more specific localization if possible. No degree of "myelominutia" should be frowned upon. However, it must be stressed at this time that this step will not influence diagnostic testing choices, treatment options, or prognosis, as long as you have determined it is not a *provoked* or *reactive* seizure. Epileptic seizures are always localized to the prosencephalon (i.e., forebrain), although the actual origin within the brain is debatable.

Step 5 is an attempt to classify an epileptic syndrome from the list of epileptic syndrome types (Table 3.7). This is perhaps the most important element and where veterinary medicine takes a bit of a turn relative to human medicine. Numerous *specific epileptic syndromes* have been classified in human medicine. The veterinary departure from this point is essentially related to a lack of diagnostic testing, in particular EEG (Nabbout *et al*., 2023). The clinician should recognize this is a *presumptive* classification based on the evidence at the time of examination and may change with diagnostic testing or historical account (i.e., progression or lack of progression of brain dysfunction over time). Because life and death decisions for a pet are often made based on the presumption (i.e., an old dog or cat with new-onset seizures = brain tumor), it is recommended that the "best-case scenario" should always be the first choice until proven otherwise. For example, an elderly patient (older than 7 years) with a new onset of generalized seizures may have an underlying etiology for the cause of epileptic seizures (*structural*). The substrate for the seizure could range from the potentially excellent prognosis of a cerebrovascular accident (stroke) to a more guarded or grave prognosis in the case of a primary brain tumor, where treatment options may be more limited. Even within the category of brain tumors, an easily accessible, slow-growing forebrain meningioma or multilobular tumor of bone (MLO) has a significantly different prognosis and treatment options compared to a deep, rapidly growing glioma or ventricular

Table 3.7 Syndromic (functional) classification of seizures.

- **Idiopathic (proven genetic[a], suspected genetic[b], or unknown[c])**
  - Formerly referred to as *primary* epilepsy
  - Generally, seizures start between 1 and 6 years of age (range a few months to 10 years)
  - Generally, a normal interictal neurological exam
  - Disease progression over time = static (i.e., no development of other neurological deficits)
- **Reactive** (metabolic or intoxication)
  - Seizures secondary to a systemic disorder or toxin
  - Generally, patients are "sick" (history or blood work suggestive of a cause)
  - Generally, if the cause is removed, the seizures stop
  - Disease progression over time = variable depending on the degree of sickness
- **Structural** A known or suspected primary damage or disorder of the brain
  - *Static*: Disease does not progress over time. Examples: congenital malformation, head trauma, cerebrovascular accident (i.e., stroke), etc.
  - *Progressive*: Disease progresses over time, demonstrated by the development of clinical signs attributed to brain dysfunction independent of the seizures (e.g., blindness, balance problems, behavioral changes, etc.). Examples: neoplasia, encephalitis, degenerative disease, etc.
- **Unknown** The cause is unknown and might be genetic, metabolic/reactive, or structural
  - Typically, enough data is not available to classify (but may present itself over time)
  - No cause can be found in a patient who is classified as either metabolic/reactive or structural, and the clinical course does not behave in an expected manner

[a] A demonstrated pedigree showing multiple either direct or indirect modes of inheritance or confirmed genetic testing.
[b] A strong suspicion of a genetic basis.
[c] Often a diagnosis by exclusion.

tumor. Not knowing what the definitive cause of the epileptic seizure is, *one should always assume the best*, most positive, and optimistic outcome until proven otherwise either through diagnostic testing or by monitoring for the progression of disease (new signs related to brain dysfunction) over time. The majority of your pet owners will appreciate a more positive outlook. The clinician should always remember *progression of seizures* (worsening in either frequency or intensity) is not necessarily a sign of *progressive brain disease* (see Chapter 6). Certain syndromes would be more realistic assumptions depending on factors present at the time of evaluation, such as a young dog of a breed known to have a strong genetic predisposition to genetic epilepsy (Table 3.8).

Step 6 is the presumed or determined underlying etiology for the epileptic seizures through diagnostic testing. Few *specific* epileptic syndromes exist in veterinary medicine, in contrast to human medicine. One syndrome is Lafora disease. Any older patient presenting with myoclonic seizures, hypnic jerks (i.e., sleep startles), or seizures induced by photo stimulation should be suspected of having Lafora disease (von Klopmann *et al.,* 2021). However, the majority of cases will not be able to be classified into a specific disease syndrome, especially if diagnostic testing is not performed. Therefore, a final element would be the presumed or determined etiology (through diagnostic testing) of the epileptic seizure. This may be the easiest approach to take with the majority of patients, especially since the information determined will have the most influence on therapeutic recommendations and prognosis. Answering the question "what is the cause?" will have the greatest impact on the patient and its caretakers. The aspects of step 6 are based on

Table 3.8 Breeds of dogs with proven or highly suspected genetic link to epilepsy.[a]

Australian Shepherd (Weissl *et al.,* 2012)
Beagle (Bielfelt *et al*., 1971; Ekenstedt *et al.,* 2011)
Belgian Shepherd (Famula *et al*., 1997; Berendt *et al*., 2008; Seppälä *et al.,* 2012; Belanger *et al.,* 2022)
Bernese Mountain Dog (Kathmann *et al*., 1999)
Border Collie (Hülsmeyer *et al*., 2010)
Border Terrier (Kloene *et al.,* 2008)[b]
Dachshund (Holliday *et al*., 1970)
Dalmatian (Licht *et al*., 2002)
English Springer Spaniel (Patterson *et al*., 2005; Ekenstedt *et al.,* 2011)
Finnish Spitz (Viitmaa *et al*., 2006, 2013)
German Shepherd (Alsatian) (Falco *et al*., 1974)
Golden Retriever (Srenk *et al*., 1994)
Greater Swiss Mountain Dog (Ekenstedt *et al.,* 2011; Ostermann *et al.,* 2022)
Irish Wolfhound (Casal *et al*., 2006; Ekenstedt *et al.,* 2011)
Italian Spinone (De Risio *et al.,* 2015b)
Keeshond (Wallace, 1975; Hall & Wallace, 1996)
Labrador Retriever (Heynold *et al*., 1997; Jaggy *et al.,* 1998)
Lagotto Romagnolo (Jokinen *et al*., 2007, 2015; Seppälä *et al.,* 2011)
Petit Basset Griffon Vendeen (Gulløv *et al.,* 2011; Deschain *et al.,* 2021)
Shetland Sheepdog (Morita *et al*., 2002; Sakurai *et al.,* 2013)
Standard Poodle (Licht *et al*., 2007)
Vizsla (Patterson *et al*., 2003; Ekenstedt *et al.,* 2011)

[a] Associated breeds with known storage disease disorders are excluded from the list.
[b] It has been suggested the epilepsy described in this breed may be mistaken for Paroxysmal Dyskinesia.

operational significance from a practical point of view. If diagnostic testing can be undertaken, a more complete and specific diagnosis will be possible. However, if diagnostic testing is not possible, treatment options and prognosis can still be *presumed*. For example, consider an older patient with a new onset of epileptic seizures. Options include a conservative approach *or* a diagnostic approach. If the pet's owners elect a conservative approach, you may start anti-seizure medications and watch to see if new clinical signs develop with time. Antiepileptic drugs may affect seizure frequency and intensity, but they will not affect encephalitis or a brain tumor. If a sufficient amount of time has passed to exclude the possibility of a growing or changing problem (i.e., encephalitis, brain tumor), the clinician would *presume* the patient has some sort of structural, *static* disease such as a vascular accident or other nonprogressive disorder. The amount of time to make the determination is variable with a suggested time frame of 1–3 years based on the literature; however, practically speaking, in the author's experience, manifestations of progressive structural disease will usually *declare themselves* within 6–10 months of presentation (De Risio *et al.,* 2015a). If new clinical signs develop over time, empirical response to steroids may help narrow the cause ("diagnosis by treatment"). Response to steroids (i.e., temporary resolution of interictal deficits) in the face of an otherwise progressive disorder would suggest an inflammatory etiology such as neoplasia or encephalitis (infectious or autoimmune). Lack of response to steroids in the face of a progressive disorder (i.e., not inflammatory) would suggest degenerative disease (emphasis on *suggest*).



FIGURE 3.2 (a–c) Various images from video recordings of feline patients exhibiting orofacial automatisms (see Videos 8, 16–18). Feline Complex Partial Cluster Seizures with Orofacial Involvement (FEPSO) is associated with limbic encephalitis resulting from antibodies directed at leucine-rich glioma inactivated 1 protein. Similar in semiology to (d–f) of humans with limbic encephalitis. (d) Huo, Tiantian et al. (2022)/ Wolters Kluwer Health, Inc./CC BY 4.0. (e) David S. Younger (2022)/Scientific Research Publishing/CC BY 4.0. (f) Permission to use from Creative Commons By 4.0 (https://creativecommons.org/licenses/by/4.0/). Uribe-San-Martín, R., Ciampi, E., Santibañez, R., Irani, S. R., Márquez, A., Cruz, J. P., Soler, B., Miranda, M. C., Henríquez, M., & Cárcamo, C. (2020). LGI1-antibody-associated epilepsy was successfully treated in the outpatient setting. *Journal of Neuroimmunology*, *345*, 577268.

When presented with a case in the exam room, being able to at least initially place the patient in a syndromic classification may help determine which diagnostic tests to perform, which therapy to start (if any), and what the possible prognosis might be. It may seem academic to strive toward better seizure classification, after all, just the recognition of a seizure is enough to get you through the appointment. However, we may be able to refine our diagnosis based ultimately on a *specific* syndromic classification, where specific patterns of clinical signs direct us toward a specific disease entity. Also, it's ok to nerd out a little—keep it fresh! Being able to recognize similarities between veterinary and human seizure semiology may help us with treatment, based on syndromic classification alone (Figure 3.2).

PHENOMENOLOGICAL SEIZURE TYPES

It is important to be able to classify a seizure based on a general category or "type" from the point that when a syndromic diagnosis cannot be made or a specific etiology is not or cannot be identified (through diagnostic testing), therapeutic decisions may be made based on the identified

seizure type. Prognosis and suspected etiology may also be strengthened with a defined seizure type. In general, the identification of a seizure type is only beneficial for certain specific reasons:

- Using the phenomenological description to determine if the patient is having an epileptic seizure as opposed to a "seizure-like" event (see Appendix 1).
- Monitoring the effectiveness of a medication. Although there is no direct correlation between the physical manifestations of a seizure and the degree of abnormal electrical activity in the brain, monitoring the *intensity* and/or *frequency* of epileptic seizures may help to determine if a trial medication is working. This becomes especially important if we consider the longer and more intense epileptic seizures are, the more likely they are to cause physical damage to the patient or the brain, worsening seizures through kindling or development of a mirror focus.
- Suggesting progression. It is very important to remember *progression of seizures does not necessarily imply the progression of disease* (i.e., seizures can cause seizures). However, when monitoring trends and patterns, if one recognizes progression, a heightened state of alertness or "worry" for that particular patient may contribute to earlier modification of treatment or diagnostic testing recommendations by the clinician or choices by the pet owner.
- Providing clues to what part of the brain the seizure may be originating from. This is important if surgical resection of epileptic tissue as a therapy is considered (Hasegawa, 2016). The sophistication of "brain mapping" in veterinary patients compared to human patients is lacking primarily for practical reasons (see Chapter 10).

The underlying pathophysiology, or cause, of the seizures is generally regarded as more important when considering therapeutic options as opposed to the clinical manifestations or neuroanatomical origination of the epileptic seizures. This differentiation is dependent on the recognition that certain medical or surgical options are more beneficial for different types of seizures or etiologies. Ultimately, complete cessation of the epileptic seizures and achieving a balance between acceptable quality of life and seizure frequency, intensity, and side effects of the therapeutic options are the goals. As our understanding of the pathophysiology of epilepsy and the application of medications known to be more beneficial in treating certain seizure types compared to others is elucidated, the importance of discovering the pathophysiological mechanism increases (see Chapter 6). Elucidating the benefits of one anti-seizure medication over another, specific to the epileptic seizure type being treated, is an area of veterinary medicine that will undoubtedly expand as our knowledge of the neurolocalization, neural networks involved, and pathophysiology of epilepsy improves. Much of the research in these areas has been performed in animal models and applied to humans; however, from a practical point of view, applying advanced and sophisticated diagnostic methods to veterinary patients (such as video EEG recordings and functional MRI) will continue to be a challenge. This should not inhibit the veterinary clinician from applying results from animal models (i.e., response to certain therapies) to our clinical patients.

As we discuss epileptic seizure types, we must remember generalizations will be made that may not be applicable to all cases. As stated before, the factors leading to epileptogenesis are multivariate. Epileptic seizures arising from a small, discrete area of the brain tend to manifest as focal seizures, whereas those originating from large, diffuse areas or which are quick to involve both hemispheres tend to be generalized. Focal seizures arising from certain areas of the brain may be more likely to generalize, whereas those in other areas will not generalize. These differences are related to the organization of neural networks and the interconnectivity of associated networks (see Chapter 2). For example, there is an increased potential for generalization with epileptic seizures arising from the associative areas of the brain (implied interconnectivity) and a decreased

chance for secondary generalization from epileptic seizures arising from the motor areas of the brain (those areas whose networks are more discrete and isolated from other regions) (Bancaud *et al*., 1974).

FOCAL SEIZURES

There is a general paucity of research directly related to the natural development and occurrence of canine and feline focal seizures. There is a significant amount of experimental data regarding focal seizures in dogs and cats, as they are a common platform and model used in the comparative study of epilepsy. Most humans are aware of what the term "convulsion" implies and can readily describe it, making the report of generalized seizures commonplace. On the other hand, the signs associated with a focal seizure may often be overlooked or misinterpreted (e.g., behavioral issues, gastrointestinal distress, and seeing a hot dog which triggers a nonconvulsive event). The diagnosis in humans is based on a classical description of the ictal event and verified with EEG recordings. The EEG is rarely used in a common everyday veterinary specialty practice, and even within academic institutions, the practical and functional use of this diagnostic tool is limited. However, in a research setting, the instrumentation used to record the electrical activity of the brain can be helpful in classifying certain epileptic seizure types. The EEG is beginning to be more commonly used in selected referral environments. Due to a general lack of EEG data, we will categorize canine and feline epileptic seizures as *focal*, based on factual observation and anthropomorphisms along with experimental induction of similar described events in animal models of human epilepsy. There is widespread acceptance of the comparative nature of seizures in humans and dogs (Colter, 1989; Podell *et al*., 1995; Berendt and Gram, 1999; Licht *et al*., 2002; Berendt *et al*., 2004). Three general categories of focal seizures are considered in human classification schemes. These are those originating in the neocortex (neocortical), those originating in the hippocampus or parahippocampal structures (*limbic*), and focal seizures, which secondarily generalize. The occurrence of focal seizures is common among dogs and cats. In a study of classification, it was reported that 65% of the canine patients experienced focal seizures (partial), with 68% of the group categorized as focal with cognition—awareness (simple, partial) and 27% as focal with dyscognition—unaware (complex, partial) (Berendt and Gram, 1999). Progression to secondary generalized seizures occurred in 85% of the dogs with focal (partial) seizures. The distribution of seizure types in dogs is similar to that of humans (Keränen *et al*., 1988; Hauser *et al*., 1993). As stated previously, focal seizures were formally referred to as *partial seizures* after the 1981 ILAE International Classification of Epileptic Seizures. Partial seizures were further distinguished as to whether or not consciousness was *not* impaired (i.e., simple partial seizure), consciousness *was* impaired (i.e., complex partial seizure), or the partial seizure evolved into secondary *generalized* seizures. At the time, it was recognized these seizures were formally referred to as *focal* or *local* seizures. The 2010 ILAE Commission on Classification and Terminology returned to the former term of *focal* seizures but at the same time recognized the need to distinguish between impairment of consciousness/awareness and "other dyscognitive features." Additionally, any other descriptive terms considered useful in evaluating patients, distinguishing epileptic seizures from non-epileptic events, aiding in the formation of differential diagnoses, and choosing appropriate therapies were recommended (Berg *et al*., 2010). The classification of the exact seizure type does not change the course of diagnosis or treatment. However, it may help provide clues to diagnosis or treatment based on the syndromes typically associated with the seizure type, alter the course of medications used to treat the epileptic seizures, identify the progression of seizures, and, in some cases, provide evidence and clues to what part of the brain might be affected (Lüders *et al*., 1993). We are beginning to recognize this with veterinary-specific syndromes—such as with oroalimentary automatisms associated

with limbic encephalitis in cats (Figure 3.2). In the face of drug—resistance in these cases, the clinician may reach for corticosteroids.

Admittedly, many of the so-called "focal" seizures dogs and cats exhibit may not warrant treatment if considered mild, nonprogressive, and infrequent (e.g., three drop attacks a year). The characterization of the event will, however, establish a baseline to compare future events or syndromes, which may develop. Focal seizures with cognition tend to only involve one cerebral hemisphere, whereas those with dyscognition usually have bilateral hemispheric involvement. There may be little value in providing a distinction between "dyscognitive" and normal cognition, as treatment would likely not vary, and current veterinary consensus statements note this determination in animals is purely subjective and therefore not constructive (Berendt *et al.,* 2015). However, all attempts should be made to provide as many descriptors of the ictal symptomology as possible because of the aforementioned benefits. Recognizing a state of dyscognition in an animal may be argued as impossible; however, there are clear distinctions between "responding to environmental cues" (e.g., calling the pet's name) and being in a state of "unresponsiveness." The value in the distinction may serve future benefits, as a response to certain medications associated with various epileptic seizure syndromes is more adequately categorized and reported. For example, in humans, certain anti-seizure medications are reported to be more effective when treating focal seizures as opposed to others (Rogawski and Löscher, 2004). Furthermore, the distinction between "aware" or "responsive" during an event may help in distinguishing between an epileptic seizure and a non-epileptic episodic paroxysmal event (De Risio *et al.,* 2015a).

The clinical signs associated with a focal seizure may be reflective of the origination of the seizure (the epileptogenic zone) or the site where the seizure propagated (the symptomatogenic zone). The symptomatogenic zone may be a significant distance from the origination of the seizure. We tend to assume postictal deficits are also reflective of where the epileptic seizure originated. Although they may have localizing significance, they do not always reflect the area of seizure origination but rather can be indicative of seizure propagation. Seizures beginning in the limbic system may propagate to neocortical areas, resulting in changing signs from those associated with behavior to primary motor, and conversely, neocortical seizures may propagate to the limbic center with an associated change from motor to behavior signs.

An association may be made between the categories of focal seizures recognized in humans and what we see in our veterinary patients. Focal seizures originating from the neocortex usually represent a discrete lesion near the area of the neocortex, which results in classic motor signs (*automatisms*) that pet owners are usually quick to recognize. These epileptic seizures are typically representative of the particular somatotopic portion of the motor cortex/sensory cortex they either originate from or propagate to. Motor signs are usually recognized as turning the head to one side, oscillatory movements of the head and/or trunk, flexing the body to one side, rhythmic contraction or flexion of a single and specific limb on one side of the body, tonic opening of the jaw, as well as other signs. They may also include commonly observed but *uncommonly* associated motor automatisms. Oroalimentary automatisms are often recognized in veterinary patients and include such signs as lip-smacking (chewing-gum fits), licking, bruxism (i.e., teeth grinding), and repetitive swallowing (see Videos 16–18). An astute owner may also recognize a condition where the countenance of the pet suggests an emotional state such as fear, confusion or anxiety (see Videos 11, 12, 23, and 24). *Hyperkinetic* motor signs usually affect one limb or one side of the body and are characterized by irregular, ballistic movements. Often, these movements are versive in nature, where one limb or side of the body, usually in conjunction with the head or trunk, undergoes a sustained and forced contraction resulting in a deviation from the midline. *Hypokinetic* signs, such as pelvic limb atonia and brief episodes of collapse, often occur with a state of "bewilderment." Vocal iterations may also be observed, characterized by grunting, howling, barking, whining, etc. Although classically we think of

seizures as being spontaneous and unprovoked, focal seizures may also be *triggered* through various cues in the environment. When this occurs, they are labeled as *interactive*. We may also refer to these as "reflex" seizures. This may include triggers such as lights, sounds, familiar faces, or emotional states (such as extreme excitement or anxiety). Triggers can be different for any dog or cat, but the key similarity is the recognition by a pet owner that a particular trigger exists, and avoiding the trigger lessens the incidence of seizures (see Videos 35 and 38) (Mandigers and Santifort, 2023).

Nonmotor signs frequently observed during a focal seizure can include nebulous or poorly characterized behaviors such as attention-seeking from the pet's owner, being "clingy," and restlessness (see Video 12). Many of the nonmotor descriptors dogs and cats experience may be assigned conjugate descriptions of human nonmotor semiology. A *sensory* seizure is a perceptual experience that is not caused by an appropriate stimulus from the external environment. These symptoms can be negative (lack of sensation) or positive (extra sensation). They are thought to originate from focal areas within the appropriate portion of the primary sensory cortex. An *elementary* sensory seizure is characterized by a single perception of one sensory modality, such as visual, gustatory, auditory, olfactory, somatosensory, etc. Examples of *elementary phenomena* include:

- Somatosensory: numbness, tingling, pain, shock, and a sense of movement or desire to move. For a dog or cat, this could be equivalent to face rubbing, whining or crying for no particular reason, anxiety due to a poorly understood sensation, licking a particular body part (possibly a negative sign or *asomatognosia*), tail chasing, flank sucking, hair clipping or chewing, and swaying, to name a few (see Videos 8, 29, 35, and 42). In humans, these are lateralized to the ipsilateral side.
- Visual: flashing or flickering lights, spots, and amaurosis. Humans may describe white or colored luminous spots or patterns (*phosphenes*). In dogs and cats, this may be what the patient is visualizing when we observe *fly-biting*, watching objects that are not present, and stargazing. Ictal visual symptoms are typically correlated with an epileptogenic lesion in the contralateral visual occipital lobe but not necessarily the visual cortex (Engel, 2013) (see Videos 7, 9, and 10).
- Olfactory: it is well recognized that dogs and cats "see with their noses." We must consider ictal symptoms reflective of olfactory epileptogenesis may manifest in our patients with signs such as anorexia (anosmia or a negative sign) and sniffing the air (a positive sign of a potential olfactory hallucination).
- Auditory: sounds may be "heard," such as ringing, buzzing, humming, etc., in which case they are positive symptoms (a *paracusis*). Humans also describe attenuated, muffled, or absence of sounds (*hypoacusis*). In dogs and cats, this may manifest as "looking around in confusion," running away, fear or confusion, and vocalization when there is no external stimulus to justify the behavior. The epileptogenic focus is thought to originate in the contralateral temporal lobe, although lateralized localization may be difficult without EEG (see Videos 10 and 36).
- Vertiginous symptoms: humans may complain of a sensation of vertigo or vague dizziness. Pets may exhibit a truncal sway, stumbling or falling, perceived ataxia, and hyperkinetic (overcorrection) or hypokinetic (bumping into objects when vision is present) movement. Humans may show nystagmus (slow phase towards the symptomatogenic zone). The epileptogenic focus is in the lateral temporal and parietal lobes (see Videos 14 and 28).
- Epigastric: humans will describe episodes characterized by abdominal discomfort, nausea, churning of the stomach, *butterflies* in the stomach, hunger, and abdominal pain. The manifestation of these signs in the dog and cat may be anorexia, vomiting, eating inappropriate objects

(grass, carpet, drywall), drooling, licking at the air, lip-smacking and potentially "gulping" (see Videos 7, 8, and 37).

- Cephalic: signs reflective of a "headache" typified by the animal placing its head and neck in a "neutral" position (in horizontal alignment with the spine—not up or down) and nose to the ground or signs commonly associated with cervical pain (looking out of the corner of the eyes—the "guilty" look, not shaking, and self-restriction of activity) (see Videos 25 and 26).

Autonomic events are signs reflective of the involvement of the autonomic nervous system, such as cardiovascular abnormalities, alterations in blood pressure, thermoregulation, piloerection, excessive lacrimation, urination, pupil changes, etc.

A dog (less likely to be testable in a cat) that is unresponsive to commands during a focal seizure may be classified as dyscognitive or possibly *dyspraxic*. Dyspraxia is the *inability* to perform learned movements spontaneously or on command despite having intact motor and sensory systems. In humans, an added component of adequate understanding and comprehension is also considered part of the definition. Humans will also describe complex visual *hallucinations*, which are ictal signs in and of themselves. During these *experiential* events, intricate and detailed scenes, including faces, voices, conversations, and other sensory modalities, are present. They may also describe simple *illusions*, where normal sensory experiences are altered. It is difficult to say if similar episodes occur in dogs and cats. Many of the observed, nebulous, and poorly described behaviors pets exhibit may be attributed to ictal sensory symptoms. However, weight must be given to evidence of the spontaneity of the events (the majority of the time) and stereotypy of the events prior to labeling them as epileptic seizures. *Affective* components of an experiential seizure may include feelings of fear, rage, aggression, anxiety, happiness, and depression. Certain descriptors are likely to be perceived in dogs and cats (anthropomorphically), whereas others might be implied (e.g., depression).

Historically, focal seizures were less commonly reported to be of genetic origin (idiopathic) (Colter, 1989; de Lahunta and Glass, 2009; Lorenz *et al*., 2011). This idea is based on the fact focal epileptic seizures are usually associated with a discrete abnormality in one hemisphere of the brain. The clinical implications of focal seizures would then be more suggestive of a *physical* disorder or damage to the brain, and as such, early diagnosis and treatment may be weighted more heavily. The view that generalized epileptic seizures are associated with genetic epilepsy and focal seizures are structural (i.e., symptomatic or cryptogenic) does not hold true and has been demonstrated in epidemiological studies (Poncelet, 2011). The incidence of focal seizures in veterinary patients has been underreported in the past. Many focal epileptic seizures were incorrectly classified as generalized epileptic seizures when, in fact, many were focal seizures with secondary generalization leading to overrepresentation of genetic (primary or idiopathic) epilepsy (Berendt and Gram, 1999). If the focal epileptic seizures are not progressive, do not interfere with quality of life, and are not debilitating, careful consideration must be given as to whether or not they should be treated.

Limbic seizures may look very similar, from a clinical standpoint, to focal seizures; however, due to a lack of EEG evidence in animals that would correlate the behavioral manifestations with the epileptogenic site, the use of the term is discouraged. These forms of focal seizures have a psychic component with or without automatisms. Seizures originating in the hippocampus will usually propagate within the limbic structures, whereas those originating within the neocortex often propagate to the hippocampus and associated limbic structures. Whether the seizures originated within the hippocampus or parahippocampal structures or within the neocortex, the ictal symptomology may look identical. Therefore, without supporting EEG evidence, a distinction should not be made. Many of the characteristic descriptors of the ictal symptomology expressed in people are not possible to recognize in animals. Descriptors such as *amnesia*, *dysmnesia* (sensations of distorted memory, feelings of

familiarity, or "strangeness"), cognitive disturbances (dreamlike states, disorders of the sensation of time or space, and sensations of "unreality"), and of course, *gelastic* symptoms (sudden, uncontrolled, unprovoked, and inappropriate laughter) will likely never be observed, recognized for what they are, or shown to exist in animals. In humans, a limbic seizure may consist of only a disorder or impairment of consciousness with or without automatisms. It is very common for people with limbic seizures to display an *arrest reaction* or motionless stare. These descriptors are often encountered in veterinary patients. Lesions in the mesial temporal areas may exhibit gustatory and olfactory symptoms. These taste (parageusia) and smell (parosmia) sensations are typically described as "disagreeable" (e.g., rancid, fetid, bitter, sour, metallic, etc.) in humans who experience them and have historically (although incorrectly) been thought to be associated with a higher incidence of neoplasms than other focal seizures (Engel, 2013). Perhaps the *anorexic*, elderly veterinary patient is exhibiting similar signs? Dogs and cats may exhibit signs referred to as oroalimentary (lip-smacking, hypersalivation, etc.) or olfactory (sniffing the air, sneezing, rubbing the muzzle on the ground, etc.). Autonomic signs may accompany limbic seizures, many of which are observed in dogs and cats, such as piloerection, pupil dilation, urination, and sexual symptomology such as pelvic thrusting (see Video 33). Fear (presumed by observers) is a common ictal *affective* symptom in dogs and cats. Humans may also experience *reactive* automatisms where simple tasks or activities may continue to be performed during the ictus. These activities are not stereotypical because the local environment at the time of the epileptic seizure triggers them. They may include continuation of handwriting (unintelligible) while staring off into space or a violent (and inappropriate) reaction to a perceived threat. A warning to not restrain humans experiencing a focal seizure may be applied to animals, as well as a precaution to restrain inappropriate violent reactions. Limbic seizures are more difficult to localize based on ictal symptomology alone, as postural or versive behaviors may be either *contraversive* (movement away from the lesion) or *ipsiversive* (movement toward the lesion). Owners of dogs and cats who observe focal seizures often describe a "confused" state in the pet following an epileptic seizure, a phenomenon commonly reported in people who experience the limbic form of focal seizures. If we make associations based on epidemiology between humans and dogs/cats regarding classification, we may extend this association to the presence of limbic seizures, where in humans, they are estimated to affect approximately 40% of people with epilepsy (Gastaut *et al*., 1975). They are associated with temporal lobe epilepsy, regarded as the most difficult to treat medically but are typically the most amenable to surgery, as is also turning out to be the case in veterinary medicine (Pakozdy *et al.,* 2014; Hasegawa *et al.,* 2021a; Glantschnigg-Eisl *et al.,* 2023).

The amygdala and hippocampus are the most common structures associated with limbic seizures. Lesions of these areas have been associated with aggression and focal seizures with dyscognition that can be experimentally produced through lesions of the amygdala (Caldwell and Little, 1980; Hasegawa *et al*., 2002). Electrical stimulation of the hippocampus in unanesthetized cats will create episodes of staring at a fixed object that is not present, lack of response to external stimuli, contralateral searching movement, and quick glances (Brodal, 1981). Examples of autonomic signs such as piloerection, salivation, and pupil dilation along with growling and hissing are created with stimulation of the hypothalamus and amygdala. These signs accompany affective behavior associated with fear and defensive reactions (Colter, 1989). An *arrest reaction* can be induced through electrical stimulation of the thalamus in unanesthetized cats. In these experiments, a complex defensive reaction and versive movements accompanied by circling were also observed. If stimulation were continued, a generalized seizure would ensue (Hunter and Jasper, 1949). The literature is filled with experimental research and animal models showing most forms of symptomology associated with limbic seizures described in humans. Toxin-induced episodes of abnormal behavior referred to as "psychomotor seizures" were documented in dogs who

suffered from bilateral destruction of the hippocampus or pyriform lobe after eating food that contained agenized flour (treated with nitrogen trichloride) (Campbell *et al*., 1951). The psychomotor signs were described as running around wildly, growling, barking, and being seemingly unaware and unresponsive to the animal's environment. At times, the affected dogs would stand in the corner, growling and barking with dilated pupils and piloerection (de Lahunta and Glass, 2009). In a cat with a chronic, kainic acid-induced, epileptogenic lesion of the left hippocampus, researchers showed a lateralized hyperreactivity. When the cat was approached from the left side, it assumed a "friendly" demeanor, rubbing up against the offered hand and purring. However, when the cat was approached from the right side (the contralateral side of the lesion), it responded by assuming a defensive posture, ears back, piloerection, hissing, and striking out against the offered hand (Engel, 2013). Although EEG documentation and patient descriptions of the ictal symptomology are not or will never (presumably) be possible, much experimental evidence exists to form a comparative relationship between limbic epileptic seizures in dogs and cats and in humans (see Videos 16–18).

Focal seizures, which secondarily generalize (develop into convulsions), are the most common seizure types in dogs and humans (Heynold *et al*., 1997; Berendt *et al*., 2004). Although they are common in humans with focal epilepsy, the convulsive aspect of the seizure tends to be infrequent and easily managed with anti-seizure medication (Engel, 2013). In dogs and cats, the generalized seizure can begin so rapidly the initial focal signs are often overlooked. In humans, the prognosis worsens if the secondary generalized seizures occur frequently. No correlation exists in canine or feline populations; however, considering the similarities between species, the generalization may be reasonably implied. The benefit of classification would not necessarily change the treatment; however, as surgical treatment options advance in dogs and cats, the ability to localize based on ictal symptomology along with EEG characteristics may make surgical treatments more successful, as they are in humans (see video 25). Furthermore, recognition of focal signs in veterinary patients, leading to earlier treatment (before secondary generalization), may lead to less pharmacoresistant cases, as is observed in humans.

GENERALIZED SEIZURES

The category of "generalized seizures" is labeled as it relates to the bilateral, diffuse, hemispheric involvement of the cerebral cortex. Following the 2017 ILAE classification scheme (Table 3.4), within the category of generalized seizures are subcategories labeled as:

Motor

- Tonic–clonic
- Tonic
- Clonic
- Myoclonic
- Myoclonic atonic
- Myoclonic tonic
- Atonic

Nonmotor (absence)

- Typical
- Atypical

- Myoclonic absence
- Eyelid myoclonia

Several of the categories above are not described among veterinary patients. This may be due to a lack of case examples, poor recognition of symptomology, or lack of existence of similar ictal symptomology. It's the author's belief, considering the many comparative features between human and animal models of epilepsy, that the syndromes are likely to exist among veterinary patients; however, they are poorly recognized due to a lack of diagnostic testing (particularly EEG) and accurate descriptive as well as video documentation of the ictal events. An awareness of the symptomology may help promote further identification in veterinary patients and, ultimately, treatment options.

Tonic–clonic generalized seizures, formally referred to as *grand mal*, are the most easily recognized seizures and those most people are familiar with. This form of epileptic seizure produces the classic *convulsion*; however, numerous forms of ictal symptomology exist, with each having the common characteristic of affecting both cerebral hemispheres in a diffuse pattern of epileptiform activity, arising within and rapidly spreading diffusely throughout the brain via bilaterally distributed networks. Animal experiments have demonstrated the tonic phase (stiffness) of the epileptic seizure is mediated through brainstem structures, while the clonic phase (alternating contraction/relaxation) originates from or requires the forebrain (McCown and Breese, 1991; Moraes *et al.*, 2005). Research also demonstrates that with many classic generalized tonic–clonic epileptic seizures, the more repetitive the seizures, the more likely the cortex is to be involved with epileptiform activity (Naritoku *et al.*, 1992). Although we tend to associate epileptic seizures with an abnormal brain, generalized seizures are commonly present not only in the genetic forms of epilepsy but also in the metabolic or reactive forms. Therefore, the condition has the ability to be present in the normal brain when it is in a particular state, which could trigger the events. Little information is known as to what exact mechanisms need to be present to create generalized seizures. In regard to the genetic forms of epilepsy, simple disorders of ion channels, imbalance of neurotransmitters, or disorders of neural connections may tip the scale of brain balance more toward the unregulated epileptiform activity of neural networks. When considering structural brain disease from an acquired form, the disturbance of brain function is considered to either be so widely distributed as to affect the entire cortex bilaterally or to originate in a solitary locus but spread so rapidly that a focal event is missed for the more obvious generalized seizure. Generalized tonic–clonic seizures are the most disturbing to our clients and have the greatest potential to cause the most physical harm through mechanisms triggered by sustained muscle contraction leading to hyperthermia and systemic acidosis. A *justified*, extreme emotional reaction is often reported by a pet owner when they see a generalized seizure. The notion that the pet is in pain or "suffering" often leads to premature euthanasia (see Videos 1–4).

Humans who suffer from epilepsy will often describe a prodrome occurring minutes to hours (and occasionally days) prior to an epileptic seizure. Dogs and cats likely experience similar phenomena; however, they may be difficult to detect. Prodromes are estimated to occur 1–24 h prior to the ictus (Berendt and Gram, 1999). An astute pet owner may notice a general sense of uneasiness, clinginess, anxiety, hiding behavior, or otherwise atypical activity. Prodromes are not seizures in the sense of the previously described aura; however, they are practically difficult to distinguish from one another without EEG recordings of the event. Recognition of the prodrome may allow early treatment intervention (see Chapter 6, Treatment Strategies).

A generalized seizure will classically have a sudden onset with no visible warning signs and follow a very stereotypical pattern for the particular patient. They can happen at any time of the day or night and may follow certain patterns (e.g., always in the early morning hours)

or have no distinguishable pattern at all. The very nature of the seizure activity is often very unpredictable; however, when patterns develop and are predictable, their recognition may help with treatment options (see Chapter 6). The tonic–clonic seizure is the most commonly recognized, and most people are familiar with the description as it is the most used manifestation of seizures in entertainment media. The seizures usually begin with a tonic phase (sustained muscle contraction) that may be precipitated by a versive movement (sustained, forced, truncal rotation, or lateral deviation from the midline). The tonic phase is often followed by a clonic phase (regularly repetitive myoclonus involving the same muscle group, usually with a frequency of 2–3 cycles/s). Myoclonus is an involuntary, sudden, brief contraction of a muscle or muscle group. There is usually a concomitant loss of consciousness, potential vocalization, clamping of the jaw, foaming at the mouth, an increase in blood pressure and heart rate, and apnea. The eyes may remain open or tightly closed. If the eyes are open, the pupils will usually be dilated. Apnea may lead to cyanosis, and if there is prolonged, sustained muscle contraction, the patient's temperature can rise to critical levels (104–108°F or greater). At this temperature, organ dysfunction and damage along with metabolic derangement of the brain can lead to death; however, this is uncommon. As the epileptic seizure progresses, the time between the tonic and clonic (paddling) phases usually reaches a crescendo and then starts to decrease in severity and intensity. The typical "convulsive" event will last from a few seconds to several minutes, although status epilepticus is also possible. As the motor symptoms start to abate, breathing usually begins, and often the animal will urinate and/or defecate. Most observers of the seizure will overestimate the time of the event. The initial postictal time period will last several minutes to hours. The patient may seem disoriented, stagger during recovery, go immediately into a deep sleep, or seem to have a ravenous appetite. They may pace or wander in a state of confusion, hide from their owner, or seek their attention. Occasionally, a second convulsive event will occur as part of a *cluster* of epileptic seizures. Usually, within a few minutes or hours of the ictus, the patient will recover with minimal to no symptoms. Rarely, the postictal time period will last days, requiring hospitalization for supportive care (see Video 4).

One of the most common questions owners of animals having epileptic seizures will ask is whether or not the patient is in pain. We can only assume the experience of a pet having epileptic seizures is similar to that of a human. People typically report a headache, fatigue, and a general feeling of being disconnected from the surrounding environment as if just suddenly waking from a deep sleep. They do not seem to "suffer," although occasionally, they may bite the sides or front of their tongue and the buccal surface of the inside of the mouth. It is estimated generalized seizures affect approximately 20% of veterinary patients with epilepsy (Berendt and Gram, 1999), and in another study, 73% of the population was affected by generalized epileptic seizures (Podell *et al*., 1995). This discrepancy may be due to the high incidence of focal seizures, which secondarily generalize and are mislabeled as generalized as opposed to the latter (Berendt and Gram, 1999).

Generalized Motor

Tonic generalized epileptic seizures are characterized by *sustained contractions* of axial flexor muscles, which can last from 5 to 20 s (longer than the typical myoclonic contractions). Autonomic signs may accompany them (hypersalivation, pupil dilation, piloerection, and hyperthermia). The interval between contraction and relaxation is rhythmic but not oscillatory (as in tremors). There is invariably a loss of consciousness. These seizures are thought to originate from brainstem structures, although cortically induced tonic seizures are also possible.

Clonic generalized epileptic seizures are characterized by *rapid contractions* at the rate of 1–5 cycles/s involving variable and often multiple groups of muscles either at one time or in series (i.e., "paddling"). The ictal symptomology tends to be very chaotic and difficult to describe.

They can be very violent and often are accompanied by a lack of consciousness and autonomic signs similar to tonic and tonic–clonic seizures (see Videos 2, 3, and 31).

Myoclonic generalized epileptic seizures may be mistaken for focal epileptic seizures. They are characterized by brief, sudden, myoclonic jerks of the head and forelimbs, which are often triggered by simple external sensory stimulation (such as sounds, flickering lights, or gusts of wind). The very short, sudden jerks appear as "shock-like" contractures that can vary in frequency and intensity. They may occur singly or in bursts and mainly affect the shoulders, neck muscles, and forelimbs. They are bilaterally symmetrical and synchronous. EEG recordings demonstrate bilateral synchronous poly-spike-and-wave discharges that do not tend to have a correlation with the erratic myoclonus (Gredal *et al*., 2003). Consciousness is usually not impaired, which is another potential cause of mischaracterization as a focal epileptic seizure. The maintenance of consciousness suggests the anatomic substrate, pathological process, or both are not identical to the other forms of generalized epileptic seizures. Myoclonic epilepsy is most commonly recognized in canine patients with Lafora disease (Davis *et al*., 1990; Webb *et al*., 2009). Lafora disease results from a genetic mutation affecting the NHLRC1 gene, leading to an abnormality in glycogen synthesis resulting in an insoluble form that gradually accumulates in the form of Lafora bodies (a "storage" disease) and leads to severe and rapid neurodegeneration. The same mutation that causes the disease in dogs is also found in humans (Ahonen *et al.,* 2018). The disease affects multiple breeds of dogs and has also been found in cats and other species (Flegel *et al.,* 2024). Clinical signs of spontaneous myoclonic epilepsy triggered by auditory and visual stimuli, which often progress to generalized tonic–clonic epileptic seizures, usually affect dogs between 6 and 13 years old and often progress to impaired vision, hearing, and mentation. It must be differentiated from the non-epileptic forms of myoclonus, which tend to be more sporadic and not stereotypical (see Videos 13, 16, 17, 23, 40, 43, and 45).

Myoclonic atonic generalized seizures are not described in the veterinary literature but likely exist and are simply not recognized. In humans, they are described as bilateral synchronous events where the myoclonic jerks will induce a sudden loss of muscle tone, characterized as "nodding" and occasional falling. During the events, the patient appears to lose awareness and may develop a *behavioral arrest*, have a "blank stare" or "dazed look," and then abruptly lose muscle tone of the head and neck postural muscles. Veterinary clinicians and owners of patients may observe these events but are unsure of their significance (see Videos 5, 6, 14, and 36).

Myoclonic tonic–clonic generalized seizures are a rare form of epileptic seizures described in very young children with a symptomatic etiology (encephalopathy, head trauma, asphyxia, etc.). The symptomology consists of a brief tonic or myoclonic onset trailed by behavioral arrest. The myoclonic event would be characteristically sudden and brief, and the tonic event would also be brief. The behavioral arrest is described as a "slight eye version," "dazed look," or gentle relaxation of body tone (Nordli *et al*., 2007). The entire event lasts less than 10 s and has a distinct EEG pattern that separates it from other juvenile epileptic syndromes. As with other poorly recognized forms of epileptic seizures, this symptomology likely exists among veterinary patients but is poorly recognized and therefore lacks documentation (see Video 15).

Atonic generalized epileptic seizures, or "drop attacks," are poorly understood in humans, and there are no comparative animal models of these types of seizures, although they are reported (Podell, 1996). They are described in humans as a sudden loss of tone affecting postural muscles, which when mild may only cause a head drop and when more severe may result in complete collapse. Following the collapse, the patient may be unconscious and flaccid for several minutes (Nordli, 2010). This rare form of seizure is common in human children diagnosed with Lennox-Gastaut syndrome. It is often successfully treated with vagal nerve stimulation or corpus callosotomy, both of which have been described in veterinary patients (see Chapter 10) (Bagley *et al*., 1995; Muñana *et al*., 2002; Asada *et al.,* 2021; Hasegawa *et al.,* 2021b) (see Videos 5, 6 and 41).

Generalized Nonmotor

Nonmotor (absence) generalized seizures are classified as *typical, atypical, myoclonic, and eyelid myoclonia*. These forms of seizures were previously referred to as *petit mal* (French for "small sickness") *seizures*. The *typical* form is most commonly associated with diffuse brain dysfunction from an inherited (genetic) basis as opposed to structural brain disease. Based on an experimental feline model of chronic epilepsy, it is thought the seizures are generated from an abnormal response of the neocortex to synchronization input from the thalamus and brainstem (Quesney *et al*., 1977). These epileptic seizures are most often characterized by a brief and sudden loss of consciousness. They may be described as having a motionless stare, which interrupts normal activity, and at times, the affected patient may then continue on with the previously initiated motor movement. There may be automatisms such as oroalimentary symptoms, clonic movements, and autonomic signs (piloerection, hypersalivation, pupillary dilation) (Loddenkemper *et al*., 2004). Absence seizures associated with myoclonic movements of the head and nose have been reported and well-documented in a young Chihuahua (Poma *et al*., 2010). During the events, the dog demonstrated an arrest moment described as "staring" along with head and nose twitching. Occasionally, the patient would have intermittent hind limb jerking. EEG abnormalities consisting of generalized, bilaterally, synchronous 4 Hz spike-and-wave complexes at the same time as the altered behavior (Figure 3.1). The dog responded favorably to phenobarbital. A syndrome of generalized myoclonic epilepsy with photosensitivity has also been reported in young Rhodesian Ridgeback dogs (Wielaender *et al.,* 2018). A genetic mutation of the DIRAS family GTPase 1 (DIRAS1) gene in the Rhodesian Ridgeback is responsible for the disorder and 38% of the studied cases progressed to generalized tonic–clonic seizures (Wielaender *et al.,* 2017). The dogs retained normal cognition throughout their lives. Seizure events are typically described as "shock-like," myoclonic twitches involving the thoracic limbs, head, ears, eyelids, cervical musculature, and shoulders, usually during or around times of sleep, although they can occur when awake and active. With these forms of seizures, the clonic symptoms are bilaterally symmetrical and often involve the eyes and muscles of the face and head. If the postural muscles are affected, the patient may have a *head nod* or fall. These can be mistaken for atonic generalized seizures (drop attacks). This typical form of absence seizure may be triggered by light stimulation and, in people, hyperventilation. This form of epilepsy has a high rate of remission in humans and is generally responsive to anti-seizure medication (see Video 12). The Rhodesian Ridgeback dogs were treated with a variety of anti-seizure drugs, with a reported most favorable response to levetiracetam and potassium bromide. Of essential importance is the reporting of EEG data which helps to categorize this condition into a *specific epileptic syndrome* (Wielaender *et al.,* 2017).

Atypical absence generalized epileptic seizures have more pronounced motor signs compared to *typical absence* seizures, usually indicate a structural brain disorder, and are less responsive to anti-seizure medications when compared to the typical form. They still maintain the "absence" or behavioral disturbance characterized by a "distant gaze." Chewing movements, lip-smacking, eye blinking, and automatisms may occur. They may start and end more gradually as opposed to the more typical sudden onset of signs with other seizure types. The EEG demonstrates a slow spike-and-wave pattern (<2.5 Hz), and the events are not triggered by light stimulation or hyperventilation.

Myoclonic absence generalized epileptic seizures are characterized by the continuation of simple motor movements while the patient is experiencing an altered level of consciousness and rhythmic, myoclonic jerks of the shoulders, arms, and/or legs (described often as a repetitive start and stopping motion or "ratchet-like" jerking of the body). The EEG shows a pattern distinct from that of *typical absence* with myoclonia, and these epileptic seizures are more resistant to medical therapy (see Videos 15 and 23).

Eyelid myoclonia is described as profound jerking of the eyelids immediately after they are closed in response to bright light. The condition does not occur in the dark (Striano *et al*., 2009). It begins in early childhood, and debate still continues as to whether or not it should be considered a distinct form of absence seizures (although with the most recent classification scheme, it is considered its own entity). In humans, its diagnosis is made when a collection of signs forms the clinical syndrome and is also known as *Jeavons syndrome*. Eyelid myoclonia, with and without absences, eye closure-induced seizures EEG paroxysms, and photosensitivity are described (Jeavons, 1977; Panayiotopoulos, 2005). Naturally occurring eyelid myoclonia has not been recognized (yet) in veterinary patients.

UNKNOWN OR UNCLASSIFIED "SEIZURES"

Unknown or *unclassified* seizures are episodes where there is insufficient evidence to classify the event as generalized, focal, or both. As we gain more information and evidence as to the anatomical substrate responsible for these types of seizures (including genetic analysis), we may eventually be able to classify them into existing categories or create new categories. Certain stereotypical behaviors may be mistaken for epileptic seizures. Classification may be helped with the use of ambulatory EEG; however, for this discussion, we are mainly focusing on the description of the event (with ictal semiology) and using that information to first decide if the event is a seizure and then determine if it is generalized or focal.

Certainly, it is well recognized that epileptiform activity may be triggered by circadian sleep–wake cycles, and numerous experimental animal models of seizures demonstrate the association between sleep patterns and epileptic activity, as well as less defined phenomena such as *paroxysmal microarousals* (Shouse *et al*., 1995; Crespel *et al*., 1998). However, there are "epileptic seizure-like events" that do not lend themselves to organized classification based on the current evidence. These include sleep-associated behaviors such as *hypnic jerks* (sleep startles or sleep jumps), "chasing rabbits," and rapid eye movement sleep behavior disorders (see Videos 28 and 32).

Stereotypic movement disorders not associated with sleep may be spontaneous and sporadic or elicited by a "trigger event" (usually a stressor of some type). Descriptions of movement disorders may include terms such as *spasms*, *jerks*, *twitches*, *tremors*, *convulsions*, *seizures*, and *fits*. If the goal is to provide treatment for the clinical signs, the approach should first concentrate on the classification of the movement disorder. Through classification, the clinician can then determine if the movement disorder is a clinically distinct entity from an epileptic seizure disorder or a true ictal symptom. Certain movement disorders can be fairly predictable and are often mistaken for epileptic seizures. *Tremors*, *tics*, and *twitches* are a broad category of involuntary movements, which can be associated with physiological disturbances of the brain, spinal cord, peripheral nerves, and muscles. Tremors in dogs and cats can be caused by a variety of conditions affecting the nervous system. A tremor is an involuntary, *approximately rhythmic*, oscillatory, or roughly sinusoidal movement of a body part. Tremors can be found in both normal and abnormal animals. It can be distinguished from pure *myoclonus*, which is a sudden contraction of muscles without necessarily a rhythmic, oscillatory, or sinusoidal nature (such as a tic or twitch or those observed in certain forms of epileptic seizures). However, there are forms of myoclonic clonus that can have a rhythmic characterization and therefore be included under the category of tremor. In the broadest sense of the definition of a movement disorder, tremor is a distinct subcomponent. Tremors can reflect specific brain dysfunction, such as the *intention tremor* commonly associated with cerebellar disease, as well as pain, simple muscle fatigue, or electrolyte abnormalities. They may be easily mistaken in certain cases for focal seizures as unilateral automatisms associated with discrete

pathology or dysfunction of the brain. When reported, they should not be discounted as *not* seizures but considered as a possible prelude to more recognizable seizure events. Often, the history of the symptomology helps distinguish unrelated tremorgenic syndromes or movement disorders from true epileptic seizure activity (see Videos 27, 30, 40 and 43).

Titubation is an example of a potentially confusing symptomology. Titubation is a shaking of the trunk and head while sitting or standing, commonly observed as forward and backward oscillations of the body. Tremors of cerebellar origin are referred to as *intention tremors*. These tremors are manifested when the animal initiates voluntary movement. They typically appear as the to-and-fro movements or oscillations of the head and neck, which become more severe as the animal begins to reach the goal (such as a food bowl). Intention tremors imply a lesion of the cerebrocerebellum, the more lateral areas of the cerebellar hemispheres, or the dentate nucleus. This is the area of the cerebellum primarily influencing the application of voluntary movement (Sanders, 2008; Raethjen and Deuschl, 2009).

Repetitive, intermittent head bobbing (vertical, horizontal, or rotational) is a poorly understood movement disorder that is often encountered in dogs, particularly young adult Boxer Dogs, English and French Bulldogs, Labrador Retrievers, and Doberman Pinschers. The condition has been identified in 24 pure breeds of dogs, and the majority present with clinical signs before 4 years of age (Shell *et al.,* 2015). This is a benign condition for which the underlying mechanism remains elusive. Among the possibilities for a cause of this disorder is a potentially heritable abnormality of the stretch mechanism affecting the neck musculature similar to the mechanism associated with canine orthostatic tremor (Garosi *et al*., 2005). As with other postural tremors, the tremors tend to subside if the head is supported (i.e., not supported by neck muscles). However, they may also be present (although often attenuated) when the patient's head is supported (such as on a pillow while lying down). The tremors tend to stop if the dog is distracted (e.g., calling the patient's name or offering a toy or food). Neurologic examination is characteristically normal, as are diagnostic tests (including brain imaging, EEG, and CSF examination). Other terms for this condition include "head bobber" and *postural repetitive myoclonus*. Within the Doberman Pinscher breed, the age of onset is typically less than 1–2 years, and all cases have been traced back to one common sire, suggesting a genetic origin (Wolf *et al*., 2011). Many forms of tremor in humans and animals are treated (sometimes successfully) with anti-seizure medication (e.g., zonisamide) (see Video 31).

Reflex seizures are those that are consistently triggered or evoked by a distinct and specific external stimulus or generated by specific actions of the patient. These types of seizures are classified by the symptomology expressed by the trigger. Therefore, they may be classified as *generalized* or *focal*; however, their etiological significance and the anatomical substrates that may be responsible for the events do not fit nicely in the general categories. Therefore, they can be classified as unknown. Although the identifier "reflex" tends to classify the category and likely promotes a certain sense of curiosity for the examiner. This neurologist finds them extremely fascinating. Numerous types of reflex seizures are documented in animal experimental models of epilepsy, including those induced through photic stimulation (flickering lights, light patterns, or bright lights) and auditory stimulation (sudden loud sounds, particular sounds, and music). These forms of reflex seizures are rarely reported as naturally occurring in animals; however, because of the more similar than distinct nature of epilepsies between species, we assume they likely exist in canine and feline patients but are unrecognized or simply underreported (Hennessy and Binnie, 2000; Zifkin and Kasteleijn-Nolst Trenité, 2000). Seizure-evoking stimuli such as defection and eating specific foods, for example, have also been reported in the human literature (Harbord and Mitchell, 2002; Mimura *et al.,* 2017). Auditory-evoked seizures, including specific musical sounds or ringtones, have been reported in the human literature (Desai *et al.,* 2023). Not surprisingly, similar episodes of reflex seizures (although less frequently reported) exist in the veterinary literature (seizures precipitated by

eating) (Brocal *et al.,* 2020). The author has experienced a single case that was highly suspicious for a musically induced focal seizure triggered by the sound of a "bar chime." Although an EEG was not performed, no inciting behavioral trigger could be identified, and the patient responded to anti-seizure medication. Sound-triggered seizures in cats are a recognized syndrome of reflex epilepsy (Feline Audiogenic Reflex Seizures), whereby high-pitched sounds trigger an epileptic seizure of which type is unpredictable (focal or generalized) (Lowrie *et al.,* 2016). Additionally, some of these animals experienced spontaneous myoclonic jerks and generalized tonic–clonic seizures. In 75% of the cases, eliminating the sounds prevented the seizures from occurring. A defect in the number of GABAergic neurons in the inferior colliculus has been identified as possibly playing a role in the propagation of audiogenic seizures in the genetically epilepsy-prone rat model (GEPR) (Ribak, 2017). Additionally, light-evoked focal seizures are occasionally encountered, with the patient often staring into space or at shiny and reflective objects. Reported stimuli of reflex seizures in humans are listed in Table 3.9. More reports in veterinary medicine are certainly to come forward with increased use of ambulatory EEG and awareness. In many instances, if possible, removing the stimulus is the "cure."

A case of somatosensory-evoked epilepsy has been reported in a cat (Boydell, 2010). *Rub epilepsy*, as it is referred to, was described as brief extensor rigidity of the left forelimb, immediately followed by extensor rigidity of all forelimbs, opisthotonos lasting 3–5 s, and a postictal period of general flaccidity lasting approximately 1 min. Shortly thereafter, the cat returned to normal. Rubbing by a person or licking the dorsum of the left forepaw by the cat 9–10 times could trigger the incident. The episodes decreased in frequency after treatment with phenobarbital. Recent descriptions of this type of epilepsy have been associated with somatosensory-evoked stimulation as opposed to a historical association with startle epilepsy. The author has observed this form of epilepsy in a dog and a cat (see Video 35 and 38).

Startle epilepsy, *human hyperekplexia*, or *startle disease* has been reported in dogs (Gill *et al*., 2011). This condition has also previously been reported in cattle (bovine congenital hypertonia), rodents, and humans (Charlier *et al*., 2008; Dreissen and Tijssen, 2012). A defect in glycinergic synaptic transmission is the cause of the condition. Mutations of the genes associated with the postsynaptic glycine receptor and the presynaptic glycine transporter are responsible. A sudden onset of hypertonia and exaggerated startle reflex may be elicited with either tactile or acoustic stimuli. Two Irish Wolfhound puppies out of a litter of seven were

Table 3.9 Stimuli associated with reflex seizures in humans.

- Auditory
- Complex thought—praxis (initiated by complicated movements or calculations)
- Eating/orogastric/cutlery
- Defecation
- Hot water/bathing (proprioceptive?)
- Movement associated
- Musicogenic (sound specific)
- Proprioceptive/positional
- Reading
- Startle stimuli
- Thinking (not necessarily complex thinking)
- Visual

Adapted from Wolf, Peter. 1994.

affected with an exaggerated startle reflex in response to handling. A homozygous microdeletion in the SLC6A5 gene of the glycine transporter (GlyT2) results in a frameshift causing loss of function of GlyT2. Genetic testing confirmed a recessive mode of inheritance (Gill *et al*., 2011). Startle epilepsy may look very similar to *canine paroxysmal movement disorder* (Lowrie and Garosi, 2016; Liatis and De Decker, 2023).

In the fringe zone of epilepsy exists a nebulous condition frequently reported but not entirely understood. *Idiopathic phenobarbital-responsive hypersialosis* is suspected to be a form of limbic epilepsy (Mawby *et al*., 1991; Chapman and Malik, 1992; Stonehewer *et al*., 2000). Reported cases often responded to primidone and phenytoin, as well (Kelly *et al*., 1979). This condition is characterized by idiopathic, bilateral enlargement of the salivary glands and periodic automatisms characterized by gulping, stretching the neck forward, teeth chattering, and retching. EEG recording in one dog demonstrated 20 μV, 25–30 Hz rapid, intermittent, spindle bursts on EEG in both cerebral hemispheres (Stonehewer *et al*., 2000). The EEG abnormalities did not appear to be muscle artifacts. Following treatment with phenobarbital at anti-seizure doses, mandibular salivary glands return to normal size, and the abnormal behavior stopped. If the phenobarbital was reduced, the clinical signs returned and again abated with subsequent increases in phenobarbital. All other potential causes of hypersialosis were eliminated. Response to phenobarbital is typically rapid, with a reduction in clinical signs (including a reduction in the size of the salivary glands) occurring within 48 h of starting therapy (Alcoverro *et al.,* 2014). Although a lack of response to phenobarbital does not exclude the disease (not all respond), additional factors should be considered (such as esophagitis or esophageal stricture) (Chae *et al.,* 2021). Additionally, because the disease is poorly understood, it's unclear if the "vomiting" associated with the disease is a manifestation of a pathology outside of the nervous system, such as sialadenosis or esophagitis, or a form of epilepsy (visceral epilepsy or reflex epilepsy).

EPILEPTIC SYNDROMES

A syndrome is a collection of clinical signs or symptoms that, when considered together, constitute a distinctive disorder based on a specific lesion or other causes. By itself, a syndrome is not a disease entity. A condition having a specific pathological cause (underlying substrate) is a disease. We tend to think the disease may be associated with epileptic seizures, and seizures themselves are not a disease, but rather they are an indication of brain dysfunction. The ILAE has redefined epilepsy as a "disease" as opposed to a "disorder" (Fisher *et al.,* 2014). This redefinition was an attempt to bring forward the importance of epilepsy and its impact on patients, clinicians, and society. Therefore, in this pure sense, "epilepsy" may be referred to as a *disease*; however, *seizures* would still be a disorder (like a limp). If an epileptic syndrome can be empirically identified or implied through history and symptomology, the lack of a distinct pathological cause (i.e., the cause) of the epileptic seizures via diagnostic testing (whether due to inability to perform tests or normal test results) will still allow the clinician to provide insights into the prognosis and management of the seizures. Therefore, in essence, we can look at an *epileptic syndrome* from two separate perspectives, both of which can be very helpful. If we can box the patient into one of these groups, we gain prognosticative and treatment power.

1. A Functional Syndrome: a practical and useful description based on current evidence.

    a. Idiopathic / Genetic / Suspected Genetic
        i. Age of onset (1–6 years-ish)
        ii. Neurological exam = normal
        iii. No interictal deficits

iv. Blood work = normal
v. Imaging (MRI) = normal
vi. CSF = normal
vii. EEG = consistent with epileptogenic discharges

b. Metabolic / Reactive / Provoked
i. Any age
ii. History of incidence (ingestion, exposure, etc.)
iii. Neurological exam = normal or abnormal
iv. Interictal deficits = normal or abnormal
v. Blood work = often abnormal
vi. Imaging (MRI) = normal to bilaterally symmetrical changes
vii. Imaging (ultrasound) = may be abnormal
viii. CSF—normal

c. Structural
i. Age of onset = tend to be older, or <6 months and >6 years
ii. Neurological exam = abnormal (usually)
iii. Interictal deficits = generally yes
iv. Blood work = usually normal
v. Imaging (MRI) = abnormal (usually)
vi. CSF = may be abnormal

d. Unknown
i. Age of onset = any
ii. Neurological exam = normal or abnormal
iii. No interictal deficits = present or not present
iv. Blood work = normal
v. Imaging (MRI) = usually normal
vi. CSF = usually normal

2. An Operational Syndrome: A clear concise, detailed definition of the disease which applies to the patient (Table 3.11)
a. Canine epileptic syndromes
b. Feline epileptic syndromes

Identifying a syndrome may help to narrow down a diagnostic plan, thereby avoiding unnecessary or risky tests (those requiring anesthesia) and focusing on those tests that will have the greatest diagnostic yield with the lowest risk to the patient and cost to the pet owner (such as genetic testing for a suspected disease prior to or in lieu of MRI). Furthermore, the clinician may be aided in providing information as to the probability of more seizures occurring and preparing pet owners for possible future implications associated with the brain dysfunction causing the seizures. In the case of Juvenile Myoclonic Seizures of Rhodesian Ridgebacks, for example, the client may be helped by knowing the disease is not terminal. By knowing what to watch for and understanding the progression of certain diseases over time, the pet owner may elect to perform diagnostic testing at an earlier date before clinical signs associated with the underlying disease process are irreversible. Classifying a patient with a *functional* epileptic syndrome does not imply a cause or a common etiology, as opposed to an *operational* syndrome which does. Early diagnosis usually leads to more successful and more complete treatment. Understanding progression aids in intervention. Classifying an epileptic syndrome may also help researchers investigate specific genetic etiologies of epileptic seizures and the collation of data leading to better predictability in regard to prognosis, treatment, and outcome, as well as the development of diagnostic modalities, which may aid in earlier or more complete identification

of the underlying pathology. Finally, knowing what a specific disease is may help pet owners with expectations regarding management and lifestyle.

An epileptic seizure has a specific neural origin. Although all epileptic seizures are a manifestation of brain dysfunction, the underlying cause of the seizure may not be in the brain (i.e., metabolic, provoked, or reactive seizures); therefore, not all epileptic seizures are defined as *epilepsy* (Podell *et al*., 1995). Epilepsy is a chronic condition of the brain where the principal cause leads to the persistent tendency of the brain to generate epileptic seizures (Fisher *et al*., 2005). If the disorder leading to the seizures resides in the brain, the patient has epilepsy. If the cause of the epileptic seizures resides outside of the brain, the patient does not have epilepsy. For example, seizures secondary to a brain tumor would be characterized as epilepsy; however, a patient with seizures secondary to a toxin or liver disease would not have epilepsy because removal of the toxin or treatment of the underlying condition typically would eliminate the seizures. This statement is a generalization, of course, as in many patients the neural circuitry, which forms an epileptogenic site, may be persistent even though the underlying disorder is eliminated. In those cases, the cause of seizures resides outside of the brain; however, the seizures themselves changed the brain tissue to the point where it evolved into an epileptogenic focus in and of itself. We may also classify reactive, metabolic, or provoked seizures as an epileptic syndrome, but understand this is primarily to aid clinicians and pet owners with decision-making and communication based on classification.

In veterinary medicine, a functional syndromic classification takes into consideration several factors, of which the importance of the individual factor must be considered (see Table 3.10). Some of the factors will weigh heavily on the classification, whereas others have a less convincing influence. Heavily weighted factors include the age of onset of the first seizure, the presence of interictal neurological deficits, the time since the first seizure, the progression of clinical signs not associated with the epileptic seizures, the presence of other animals or humans having epileptic seizures in the household, and certain historical information (such as exposure to toxins, free-range or roaming pets, history of trauma, vaccination status, etc.). Other factors are considered to be less significant but still may aid in the consideration of a syndrome and include the type of epileptic seizure (typically focal or generalized), the time of day the seizure occurs, the interictal time between the first and second seizures, the size of the patient, the breed, and the breed status (purebred or mixed). Other factors such as sex, alteration status (neutered males or spayed females), lunar cycles, season of onset, physical activity, days of the week, or holidays have been shown to *not* be influencers on epileptic seizures (Farnbach, 1984; Podell *et al*., 1995).

Whether we are aware of it or not, most of the time, we will classify clinical signs into syndromic groups. It's the essence of the diagnostic puzzle. Some pieces of the puzzle we are handed only fit certain disease patterns, while other pieces could fit into multiple puzzles. Syndromic classification (functional) of seizures in veterinary medicine has traditionally followed that used in human medicine as defined by the ILAE. Previous classification schemes based on etiology have been abandoned primarily due to the fact the terms *idiopathic*, *symptomatic*, and *cryptogenic* had become associated with "good" or "bad" outcomes (Berg and Scheffer, 2011). Patients previously placed in the category of *primary epilepsy* were suspected to have a genetic cause or no underlying cause of the seizures, which could be found in the dog or cat. Often, this placement was strengthened by a young patient between 1 and 6 years old when the first seizure occurred (although a few months up to 7.5 years are also "accepted"). This category is now replaced by *idiopathic*. This implies an underlying inherited basis of *essential* epilepsy as opposed to using the term "idiopathic" to mean "unknown cause." "Essential" epilepsy means "epilepsy in and of itself" or for no other underlying reason. However, included within the category of idiopathic are

Table 3.10 Factors associated with a functional syndromic diagnosis.

- **Strong consideration**
  - Age of onset of the first seizure
  - Presence of interictal neurological deficits
  - Time since the first seizure
  - Progression of clinical signs not associated with seizures
  - Certain historical information (see text)
- **Moderate consideration**
  - Type of epileptic seizure
  - Time of day or night of the seizure
  - Interictal time between the first and second seizures
  - Size of the patient (< or >15 kg)
  - Purebred or mixed
  - Specific breed
- **No consideration**
  - Sex
  - Alteration status
  - Lunar cycles
  - Season of onset
  - Physical activity
  - Days of the week
  - Holidays

those patients with a known genetic cause (through specific testing or known lineage) and those patients with a suspected genetic cause (based on breed association). Patients having epileptic seizures secondary to a known or presumed disorder of the brain were characterized as *symptomatic* and later categorized as structural. Finally, patients who were presumed to be symptomatic, where no underlying cause could be found, were labeled as *cryptogenic* (of obscure or uncertain origin). This category is replaced with *unknown*. The category of *unknown* may also be applied (technically) to the young patient who would fit in the *genetic* category but for whom there is no pedigree analysis proving a genetic link to the particular breed or the affected pet is not a recognized breed known to have epileptic seizures (Table 3.8). Because true *genetic* epilepsy is rare in cats and likely just not identified to the degree of dogs, young cats for which no underlying cause of seizures can be identified would also be placed in the *unknown* category. The ILAE and the IVETF consider the classification scheme to be a "work in progress." The eventual goal is to develop a rational, scientifically justified approach for a true classification of etiologies based on scientific knowledge of how they are related. One of the primary limitations when attempting to model a veterinary classification scheme after a human scheme is the absence of electroclinical data, functional advanced imaging, and historical background based on observation (in veterinary medicine) as opposed to self-reflection (as in human medicine). For example, human patients can report their first seizure in many instances, whereas veterinary patients must be *observed* and then *reported*. Reporting may also be influenced by an owner's unwillingness to take a patient in to be examined

or uncertainty about what they observed. Finally, many patients with a single seizure may never have had the event observed (Podell *et al*., 1995). In taking a more practical approach to compensate for the lack of diagnostic data, incomplete history, and lack of discrete (operational) epileptic syndromes (and in no way implying we should not strive to achieve these objectives), the current ILAE scheme of etiological classification may be modified slightly in order to help the veterinary clinician achieve the goals of classification. Remember, the *goals* of classification are to aid in choosing diagnostic testing and treatment choices and provide insight into the prognosis. Although the category of *reactive/metabolic/provoked* is eliminated from the IVETF classification scheme (because they are not technically epilepsy), it is probably a good idea to keep the general classification in your memory, if only as an aid to explaining the possible causes of seizures to pet owners (see Chapter 4). The current classification scheme of *idiopathic*, *metabolic/reactive*, *structural*, and *unknown* is proposed and intended to serve as a foundation for continued updating as scientific knowledge advances. To aid the clinician in a functional, syndromic classification, modifiers particular to the observational nuances of veterinary medicine can be applied (e.g., static vs. progressive disease).

Finally, as we advance in our understanding and diagnostic testing, we continue to identify true *operational syndromes* of epilepsy within veterinary medicine (in the sense the term "epileptic syndrome" is used in human medicine). A syndrome is a group or cluster of features, including seizure type and diagnostic results, such as EEG and imaging, that tend to occur together (Scheffer *et al.,* 2017). Although the list in veterinary medicine is short—it is growing (Table 3.11).

Strong influences when considering a functional syndromic classification tend to be backed by epidemiological studies or are based on practical considerations. They include:

- Age of onset of the first seizure:
  - 1–6 years (0.5–7.5) tends to be *idiopathic, genetic,* or presumed genetic.
  - <1 year and >7 years tend to have an identifiable cause, either *structural* or *metabolic/reactive/provoked*.
  - There is no relation between the age of onset and the chance of *reactive* seizure (i.e., toxin exposure or ingestion).
- Presence of interictal neurological deficits (is the patient *abnormal* between seizures?):
  - If yes, then *most* likely to be *structural*
  - If no, then *most* likely to be *metabolic/reactive/provoked* or *genetic*
- Time interval from the first seizure to clinical examination without any signs of progression (i.e., growing or changing problems will show up sooner):
  - >6 months more likely to be *genetic*
  - <6 months more likely to be *structural*
- Progression of clinical signs of brain dysfunction (e.g., blindness, behavioral changes, proprioceptive deficits, etc.) not associated with seizures (i.e., growing or changing problems will eventually affect other areas of the brain):
  - If yes, they tend to be *structural*.
  - If no, they tend to be *genetic* or *metabolic/reactive*.

Table 3.11 Epilepsy syndromes (operational) identified in veterinary medicine.

- **Canine**
  - Lafora disease (multiple breeds—classic presentation of myoclonic epilepsy)
  - Juvenile Myoclonic Seizures of Rhodesian Ridgebacks
  - Benign Familial Juvenile Epilepsy in Lagotto Romagnolo Dogs (LGI2)
  - Idiopathic Epilepsy of Finnish Spitz Dogs
  - Remitting Focal Epilepsy (LGI2) any breed
  - Neonatal Encephalopathy of Standard Poodles
  - Focal Epilepsy of Belgian Shepherds (ADAM23)
  - Generalized Absence with Myoclonic Jerks of Chihuahua
  - Focal Onset with Generalization of Cavalier King Charles Spaniels
  - Neuronal Ceroid Lipofuscinosis—Progressive Myoclonic Epilepsy
  - Mesial Temporal Lobe Epilepsy
  - Vestibular Epilepsy
  - Episodic Head Tremor Syndrome (Head Bobbers) Focal Onset with Secondary Generalization
  - Phenobarbital Responsive Sialadenosis
- **Feline**
  - Feline Audiogenic Reflex Seizures
  - Familial Spontaneous Epilepsy of cats
  - Feline Temporal Lobe Epilepsy (FEPSO, Limbic encephalitis, LGI1, malformation, hippocampal sclerosis/necrosis, etc.)

- Certain pertinent historical information:
  - Presence of other animals or humans in the household having epileptic seizures would indicate *metabolic/reactive/provoked* but weighed more heavily toward an environmental cause or nutritional.
  - Vaccination status: poorly vaccinated or unvaccinated and related to a young age may suggest *structural* (i.e., inflammatory).
  - Free-roaming and young may be more suggestive of *reactive/* or *structural trauma*.
  - Exposure to potential toxins, contaminated water, and compost or having nearby neighbors (i.e., toxins) may suggest *metabolic/reactive/provoked*.
  - History of head trauma may suggest *structural*.
  - History of epileptic seizures in the linage may suggest *genetic*.
  - Travel history.

In the above considerations, of significant importance are the age of onset of the first seizure, the presence of interictal neurological deficits, the time from the first reported seizure to the initial examination, and the progression of clinical signs not related to the seizures.

Dogs and cats having their first seizure between the ages of 1 and 6 are more likely to have the *genetic* form of epilepsy (in the case of dogs and *unknown* in the case of cats). The immature brain is prone to seizures as the developing brain contains generally less inhibitory influence (GABA receptor activity) and more excitatory influence (glutamate receptor activity) (Coates and Bergman, 2005). The young, developing brain is also more susceptible to seizure-induced brain injury as, during this time, cell proliferation, cell migration, and dendritic connections are ongoing. Damage to these developing processes is more likely to lead to permanent dysfunction (Sanchez and Jensen, 2001; Holmes *et al*., 2012). Young dogs and cats are more likely to develop *metabolic/reactive/provoked* seizures as exploration of the environment and "trying new things" make toxin exposure more of a concern. Middle-aged and older dogs and cats are more likely to develop *metabolic/reactive/provoked* causes secondary to systemic disease, and older patients are more likely to develop *structural* disease (particularly neoplasia and vascular accidents such as stroke or hemorrhage).

Interictal neurological deficits are clinical signs of brain dysfunction that are not related to the seizure(s) or the postictal time period, where deficits may be present for several hours to days, simply reflective of recent cerebral derangement. If a neurological deficit persists, it would indicate either:

- Brain damage/dysfunction from epileptic seizures(s).
- Brain dysfunction from any anti-seizure medications, usually evident by nonspecific changes (e.g., sedation, ataxia, lethargy, and cognitive changes).
- Brain damage/dysfunction from the underlying cause of the epileptic seizures (e.g., tumor, encephalitis, stroke, etc.) often manifests as asymmetrical changes such as unilateral blindness, hemiparesis, circling, head turn, etc.

The time from the first reported seizure to the initial examination may be used to help define the underlying etiology. In the case of a *structural* cause where the problem is growing or changing (i.e., progressive), there will be a definitive "window" whereby eventually other signs of brain dysfunction will become evident or enough time will have passed to convince the clinician there is no underlying problem, growing or causing changes in the brain. If, for example, a patient has a 2-year history of seizures without the development of any other neurological deficits, one could be fairly certain the cause of the epileptic seizures was not progressive. Dogs with *genetic* (primary or idiopathic) epilepsy are reported to have a significantly longer time period between the first observed epileptic seizure and the first complaint to a veterinarian when compared to those with *structural* (secondary) causes (Podell *et al*., 1995).

The presence or progression of clinical signs of brain dysfunction not related to epileptic seizures would be expected where a condition was growing or changing in the brain. This would be expected to occur in cases of encephalitis, neoplasia, degenerative disease, and thromboembolic disease (i.e., multiple stroke events). Although neurological dysfunction may worsen in the case of *metabolic/reactive/provoked* seizures, the clinical signs tend to wax and wane relative to the degree of metabolic derangement (see Chapter 4, Figure 4.4).

Moderate influencers when considering a syndromic classification may be considered to be conditions that when met are *somewhat* suggestive of a particular syndromic classification. They include:

- The type of epileptic seizure:
  - *Focal* seizures are more *suggestive* of a *structural* etiology (Engel, 2013).
  - Certain seizure types may be specifically associated with a particular disease (e.g., myoclonic seizures and Lafora disease, orofacial automatisms and temporal lobe epilepsy) (Webb *et al*., 2009, Pakozdy *et al*., 2023).

- Time of day of the first seizure (Podell *et al*., 1995):
  - Midnight to 8 a.m. more likely to be *structural* (secondary)
  - 8 a.m. to midnight is more likely to be *genetic* (primary)
  - For *metabolic/reactive/provoked*, no correlation between the time of day and the first seizure
- Interictal time between the first and second seizures (Podell *et al*., 1995):
  - *Less than 4 weeks more likely to be structural (secondary) or metabolic/reactive*
  - *Greater than 4 weeks more likely to be genetic (idiopathic/primary)*
  - *Less than* 4 weeks unlikely to be *genetic* (*idiopathic/primary*)
- Size of the patient (Podell *et al*., 1995):
  - *Greater than 15 kg more likely to have idiopathic, genetic (primary) cause*
  - *Le*ss than 15 kg more likely to have *structural* (secondary) cause
- Purebred or mixed-breed association:
  - *Dogs* with *idiopathic*, *genetic* (primary) epilepsy are more likely to be purebred (Podell *et al*., 1995).
- Breed association (Farnbach, 1984):
  - *Certain* breeds of dogs are known or highly suspected to have genetic causes of epilepsy (Table 3.8). Age of onset and typical seizure type may be breed specific (Hülsmeyer *et al.,* 2015)

Within the category of moderate influences are certain conditions that, if met, might be more suggestive of a specific syndromic categorization. However, while there is distinct evidence to support many of the conditions, they should be a consideration only and not an absolute. Not all patients with focal epileptic seizures have structural disease of the brain; however, it is well recognized focal epileptic seizures originate within neural networks limited to one cerebral hemisphere and may be discretely localized to an area or be widely dispersed. Therefore, the manifestation of a discrete lesion tends to be focal seizures but can also be generalized.

An increase in synchronized brain activity occurs during slow-wave sleep (Malow, 2007). The suprachiasmatic nucleus (SCN) located between the base of the third ventricle and the optic chiasm in the anterior hypothalamus has several interconnected pathways between multiple relay centers of the brain (i.e., thalamus, pineal body, limbic system) and receives input from the geniculohypothalamic tract, the retinohypothalamic tract, the raphe and paraventricular nuclei, and the pretectal hypothalamic pathways. It is thought to play a major role as a "master pacemaker" through its spontaneous generation of a nearly 24 h pattern of activity (Loddenkemper *et al*., 2011). It controls the timing of the sleep–wake cycle and REM sleep and promotes arousal. Its oscillations are reset through light-activated retinal ganglion cells, which then project to the SCN via the retinohypothalamic tract. The hormone melatonin, produced by the pineal gland, also has an indirect effect on resetting the oscillations of the SCN. Like most neurons in the brain, spontaneous activity is inherent and occurs even when removed from the local environment *in vitro*. Interictal spike activity is preferentially activated during night sleep as opposed to daytime napping forms of sleep in all categories of epilepsy, which would naturally drive neurons toward depolarization and synchronization (Malow, 2007). This explains why most seizures *tend* to occur during night sleep. An imbalance between inhibitory (GABA) and excitatory (glutamine) neurotransmitters also contributes to increased synchronization during sleep. GABA-mediated, tonic inhibition is decreased during sleep and even more

so with sleep deprivation (Dell'Aquila and Soti, 2022). A paradoxical relationship exists between sleep and seizures. Seizures tend to occur during sleep and also increase with sleep deprivation. The presence of a structural lesion is suspected to be an additional factor, which might have a summative effect with the natural, inherent cortical synchronization, leading to an even greater tendency to depolarize during sleeping hours. There is no predictable aspect in regard to the time of day of seizure activity with *metabolic/reactive/provoked* seizures, as those animals are more likely to have random and more unpredictable seizures. Dogs with the *genetic* form of epilepsy are more likely to have seizures between 8 a.m. and midnight (Podell *et al.*, 1995).

A patient with a *metabolic/reactive/provoked* form of epileptic seizures (remember, not *technically* epilepsy) would have an increased frequency between the first and second seizures, as the *cause* of the seizures is the precipitating element in an otherwise normal brain. As long as the cause is present (i.e., toxin), the seizures will occur. Dogs with structural causes of epilepsy also have an increased chance of having a second seizure within 4 weeks of the first. The presence of an underlying structural abnormality similar to the presence of a toxin or other pathological reason could push the brain toward the theoretical seizure threshold. Those dogs with the idiopathic (incl. genetic or presumed genetic) forms of epilepsy are more likely to have an interval greater than four weeks between the first and second seizures. The increased interval between the first and second seizures is suspected to be due to the notion that different influencers of seizure activity would be more variably present during the patient's life, leading to a less predictable, sporadic, and greater interval between seizures (Farnbach, 1984; Engel, 2013).

The size of the patient in regard to dogs may have some predictive value in classification based on a syndromic diagnosis (although be cautious with this one). Dogs less than 15 kg are more likely to have structural causes of epileptic seizures (Podell *et al.*, 1995). This may be due to a predisposition of toy breeds to be born with hydrocephalus along with development or congenital abnormalities in the brain, including birth-related cerebral hypoxia (Thomas, 2010). Common canine breeds associated with the condition include Yorkshire Terrier, English Bulldog, Maltese, Lhasa Apso, Chihuahua, Toy Poodle, Boston Terrier, Pug, Pekinese, and Cairn Terrier. Congenital hydrocephalus is uncommon in cats; however, such as dogs, the acquired form of hydrocephalus, usually due to infection/inflammation of the brain or neoplasia, can occur. The clinician should be careful not to classify all young animals as having the idiopathic or genetic form of epilepsy, as there is always the potential for congenital malformation, neonatal encephalitis, and neoplasia (although not considered common). Encephalitis and neoplasia would be progressive disorders over time; however, a congenital malformation leading to the development of epileptic seizures may be static *or* progressive. These patients may be mistakenly classified as having idiopathic or genetic epilepsy without proper diagnostics (i.e., advanced imaging). Statistically, larger dogs (>15 kg) are significantly more likely to have the idiopathic form of epilepsy (Farnbach, 1984; Podell *et al.*, 1995). There is no reported size correlation regarding cats, and in general, epidemiologic data regarding epileptic seizures in cats is scarce.

Purebred dogs are reported to be more prone to epileptic seizures. Golden Retrievers and Labrador Retrievers were reported to be more likely to have the genetic form of epilepsy. Yorkshire Terriers and Poodles are more commonly associated with a structural cause of epilepsy (Podell *et al.*, 1995). Caution should be taken when considering this grouping as reported numbers are low and certainly not reflective of a more broad-based canine population. Regional demographics, breed prevalence, and socioeconomic status are likely to greatly influence the epidemiological data regarding purebred and mixed-breed association with seizures; however, it is well recognized the genetic form of epilepsy would be more common among purebred dogs as numerous breeds have either been well-documented as having a genetic cause of epilepsy or

associated with a significantly increased incidence of *presumptive* genetic epilepsy within their breed (Table 3.8). As far as a genetic form of epilepsy in cats, the only known incidence is in a research colony maintained in Japan, with Familial Spontaneous Epilepsy (Yu *et al.,* 2018). These cats have a form of epilepsy similar to the Familial Mesial Temporal Lobe Epilepsy of Humans (Kuwabara *et al.,* 2010). Seizures are generally infrequent (occurring 1–2 times/year) and consist of either spontaneous, focal (limbic) seizures with or without secondary generalization and vestibular stimulation or tonic–clonic seizures. A common finding on MRI and histopathological examination is hippocampal necrosis (although not specific to this form of epilepsy). Of interesting note is the report of *subclinical* (and clinical) seizure activity as monitored by chronic video—intracranial EEG in the regions of the unilateral hippocampus and amygdala (Hasegawa *et al.,* 2014).

Little to no consideration should be given to factors such as sex, lunar cycles, season of onset, physical activity, day of the week of seizures, or holiday-associated seizures unless a specific pattern is recognized. For example, stress or excitement may lower the seizure threshold, and seizures that tend to occur in stressful situations (e.g., trips to the groomer, dog park, holiday gatherings, etc.) should not be dismissed as these patterns may help in management strategies (see Chapter 6). Seizure precipitating factors should be noted if they exist; if not, just for the simple option of trying to avoid the provocative behavior or activity. Alteration status (spay or neuter) has been implied to correlate with seizure activity. It was commonly thought *intact* males were more "excitable" and neutering males could lead to better seizure control; however, there is no evidence to say altered or unaltered animals fit into any particular syndromic classification (Packer *et al.,* 2016; Van Meervenne *et al.,* 2019*)*. A possible consideration of this general rule would be *catamenial* epilepsy. In humans, catamenial epilepsy is a recognized syndrome where seizures tend to occur more readily during a single or certain phase of the menstrual cycle (Herzog *et al*., 1997). It is suspected an increased number of dendritic spines on hippocampal pyramidal neurons and neurons in the prefrontal cortex leads to an increase in neuronal activity (Morrison *et al*., 2006). Dendritic spines on hippocampal neurons will increase in number in response to estrogen and progesterone levels (Reddy, 2004). In animal and human models of epilepsy, *estrogen* is known to be a *proconvulsant* neurosteroid typically resulting in a higher frequency of seizures in the days preceding ovulation when large increases in estrogen are present (Herzog *et al*., 1997). Conversely, *progesterone* enhances GABA-mediated *inhibition* of neuronal excitability, acting as an anticonvulsant. An increase in seizure activity during the premenstrual time period may be due to a sudden withdrawal of progesterone similar to the withdrawal seizures associated with rapid cessation of benzodiazepines or barbiturates (Reddy, 2009). Of course, with most things related to the brain ... it is not that simple, as estrogen is also thought to have *anti-seizure* activity through the enhancement of secondary neurochemicals, which can also have agonistic influences on the $GABA_A$/benzodiazepine receptors (Osborne and Frye, 2009). There has been no demonstration of an increase in seizures in pregnant dogs (Heynold *et al*., 1997).

SUMMARY

When considering a presumptive syndromic diagnosis, it is important to critically review all aspects of history, signalment, and response to previous therapies. Pattern recognition is as important as recognizing circumstances, which tend to (generally) increase either the frequency or intensity of seizures and may provide useful information to the clinician. That same information can be helpful to the pet owner. However, one of the primary roles of the veterinary caregiver will be to help the pet owner distinguish between important and relevant details from those that only serve to add to the confusion.

Ideally, identifying the underlying substrate (at a gross level) responsible for the epileptic seizures should be the clinician's primary goal. The two benefits of this are:

1. The "peace of mind" *knowledge* may be provided to the pet owner. For example, the prognosis associated with epileptic seizures secondary to a stroke is significantly different from that secondary to a brain tumor. Knowing this may help an owner cope better with their pet's epileptic seizure disorder and pursue clinical control.
2. The ability to focus treatment more specifically on a particular brain disease or dysfunction. For example, treatment options and recommendations for encephalitis are significantly different than those for any idiopathic or genetic form of epilepsy. This knowledge may lead to more complete and successful treatment of the condition by more specific and early targeted treatment of the cause.

A *disease* of the brain would be a specific substrate or disorder responsible for epileptic seizures. A *syndrome* is a collection of clinical signs, which helps in identifying the underlying cause of a disorder. Disease identification is the most important aspect and the end goal of a diagnostic algorithm. However, when the identification of a disease substrate is not possible, being able to classify the epileptic condition within a functional *syndrome* (idiopathic, metabolic/reactive/provoked, or structural—progressive or static) will allow the clinician and the pet owner to consider important aspects of management and prognosis from this form of a syndromic perspective.

Because most epileptic conditions have multifactorial features, which may be present in both *idiopathic* and *structural* causes of epilepsy, the old classification system of *idiopathic* or *symptomatic* is no longer used in human medicine. Epileptic seizure *types* are classified as *generalized*, *focal*, and *unknown* (see Video 33). Within each category are more specific subcategories based on the phenomenology and symptomology of the epileptic seizure event. *Syndromic* etiologies are classified as *idiopathic/genetic*, *metabolic/reactive/provoked*, *structural*, and *unknown*. We may also gain useful information in being able to determine if a condition is *static* or *progressive* as a modifier applied to the syndrome of *structural* epilepsy (e.g., either structural—*static* or structural—*progressive*). In general, we consider the age-related or genetic forms of epilepsy, which do not demonstrate progression, to be benign; the reactive, metabolic, or provoked causes of seizures to be limited to the underlying disease process (and therefore not true epilepsy); and the structural causes to be more pharmacologically resistant to therapy and, in the case where *progressive* brain dysfunction is present, a more guarded prognosis. These unnatural divisions are necessary in order to begin the diagnostic and management process but should not be looked at as all-inclusive. They are artificial distinctions to a multifactorial condition and, therefore, possess an inherent, built-in flaw or bias. However, as long as we consider them to be more of a "guiding principle," of which they will continue to be modified and developed, they will serve a functional and beneficial purpose.

In trying to keep a common comparative aspect between species, the classification schemes utilized in human medicine and veterinary medicine should be as similar as practically possible in order to promote an understanding of scientific discourse, communication, research, and teaching. Furthermore, a guiding model utilizing a common classification scheme will aid the clinician in the treatment and management of epileptic seizure disorders.

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Client Communication CHAPTER 4

KEY TAKEAWAYS

Understanding basic models of communications can help you connect with pet owners.

Helpful narratives to get you started—explaining epilepsy and medications.

Description of a seizure diary and how to use it.

QUICK JUMP

Seizure diary—page 125

Epilepsy disease progression curve—page 128

Introduction	119	Examination and Discussion	127
Communication Models and Styles	120	Anti-seizure Medications	129
Exam Introduction and History	124	Summary	134
Seizure Diary	125		

Myelominutia: Dressing smart actually makes you smarter (enclothed cognition)—it's a real thing—page 124

INTRODUCTION

Like many disciplines, medicine and surgery rely on excellent communication to be effective. Veterinarians and pediatricians cannot communicate directly with their patients. This means going *through* the pet owner or person who is responsible for the medical decisions regarding the patient. The impact, we as veterinarians have, is composed of and dependent on many factors. These factors include compassion, intelligence, curiosity, friendliness, empathy, understanding, and, above all, a strong desire to help. The result of a successful interaction with clients (strong impact) is a client who understands the medical condition, is energized to help their pet, is willing to consider diagnostic and treatment options, and follows instructions (compliance). The client must *perceive* these elements. If you do not demonstrate to them in the brief 15–30 min exam/initial consultation, you risk losing the client, noncompliance, and ultimately failing to help a pet. The client must believe you *want* to help and are excited to be the patient's advocate. Proper communication, which is clear, concise, logical, and compassionate, is a prerequisite for a successful client—veterinarian

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interaction. Poor communication is correlated with a higher risk of treatment noncompliance (Zolnierek-Haskard and Dimatteo, 2009). With regard to epileptic seizures, this can be the difference between life and death for the patient, usually in the form of ignorance-based euthanasia or a lack of "hope." This chapter is not meant to be a treatise on communication. It is intended to help "coach" practitioners on effective communication tools they can apply in everyday practice. These tools are developed through practical application and experience.

The ultimate goals should be to build trust, be supportive, define the problem, develop a plan, and above all help the client understand the disease process. Medical communication is more of an art than a science, and as Sir William Osler said, "The practice of medicine is an *art* based on *science*" (Silverman *et al*., 2003). This subject usually creates a yawn fest when discussed, but if we really look deeply, effective communication is the most powerful tool we possess. After all, if you cannot disseminate your knowledge, what good is it to the patient? Good communicators turn a *good interaction* into a *great experience*.

COMMUNICATION MODELS AND STYLES

Numerous studies have been carried out looking at various aspects of the patient-physician communication relationship. Fortunately, as veterinarians, we can gain valuable information from these studies, and there actually is a strong correlation on most counts between these studies and the *client–veterinarian* relationship (Shaw *et al*., 2006). Three general models of communications have been created based on criteria such as (modified for veterinary interactions):

- Who sets the agenda for the appointment, the veterinarian, the client, or a combination of both?
- How much importance is placed on the client's values? The veterinarian either assumes the client's values are the same, the veterinarian tries to understand the client's values, or the veterinarian ignores the client's values.
- What is the functional role of the veterinarian (i.e., guardian, advisor, or consultant)?

Based on these criteria, the three models created cover a broad spectrum of the client-veterinarian relationship and include (1) a paternalistic relationship, (2) a relationship-centered model, and (3) a consumerism model (Figure 4.1). Certainly, a balanced approach in the form of a relationship-centered model will be a *partnership* between the client and the veterinarian. Relating to the patient–physician relationship, this model leads to the best outcomes regarding patient (client) satisfaction, physician (veterinarian) satisfaction, better patient health outcome, and fewer malpractice suits against physicians (Shaw *et al*., 2006). Communication *styles* have also been identified which parallel the communication models (Table 4.1). In this regard, a style weighted heavily on science, diagnosis, treatment, and prognosis, which has little concern for the client's needs or lifestyle, is more *paternalistic*. A style whereby the information the client receives is based on the questions the client asks, the consideration of diagnostics or treatment is based on the client's lifestyle, and follow-up is initiated by the client is based more on *consumerism*. Finally, a blend of the two styles is based on *bidirectional* communication and a long-term relationship, consisting of a reciprocal exchange of information, which is *relationship-centered*. Of course, many other elements are factored in, which may include gender (both client and veterinarian), socioeconomic status of the client, educational level of the client, ethnicity, language skills, attitude toward pets, and personality, to name a few (Figure 4.2). Finding the right communication style changes with each interaction and over time with the same client. Being able to identify which will work best in each situation and adapting to change are the hallmarks of a good communicator. For example, senior clients *tend* to want a more paternalistic approach to the care of their pet. A parent trying to wrangle toddlers in the exam room may appreciate a paternalistic approach on one day and on another (potentially with less distraction), may want a more bidirectional approach focusing on the pet, as opposed to the kids. Millennials, who tend to put off having children of their own,

Paternalistic

- The veterinarian sets the agenda of the appointment.
- The veterinarian assumes the client's values are identical to the veterinarian's.
- The veterinarian takes on the role of a *guardian.*

Relationship–Centered

- The agenda is *negotiated* between the veterinarian and client as a partnership.
- The veterinarian considers the clients values and tries to strike a balance between the client's values and their own.
- The veterinarian takes on the role of an *advisor* or *counselor*.

Consumerism

- The client sets the agenda for the appointment.
- The veterinarian does not explore the client's values.
- The veterinarian takes on the role of *technical advisor*.

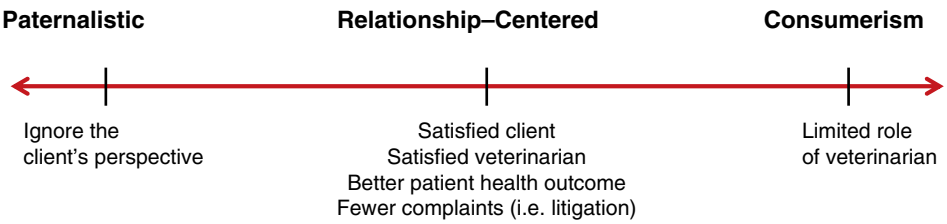


FIGURE 4.1 A simple diagram showing three different communication models. The advantages and disadvantages of each are outlined. Finding a balance between a natural communication style, the personality of the client, and the needs of the patient will allow the veterinarian to adjust their communication style to the individual situation.

Table 4.1 Communication Patterns.

Biomedical (paternalism)
Focus on medical problem, diagnosis, treatment, and prognosis. The veterinarian directs and instructs the client on what to do with little regard to how it might impact the client's lifestyle. Unidirectional communication. The client *depends* on the veterinarian.
Biomedical–lifestyle/social (relationship centered)
A balance is achieved with a mutually collaborative exchange of information.
Clients are informed and empowered to play an active role in the care of their pets.
A relationship is created involving long-term follow-up and *bidirectional* communication.
Consumerist (consumerism)
The client asks the questions.
Biomedical content given by the veterinarian is in response to the client's questions.
Focus on the client's needs, work schedule, interpersonal
relationships, and stress in caring for the patient.

will focus a similar amount of energy on the needs of their pets—but at the same can be fairly concerned about cost. People in their 50s and 60s tend to be at their peak financially. Clients who have been *burned* by veterinarians (whether true or simply perceived) will tend to dominate the interaction and take on a more consumerist approach based wholly on a lack of trust. Different cultural backgrounds will influence the amount of "trust" a client puts in the veterinarian. And of course, a client with any type of medical background may appreciate a conversation that is more

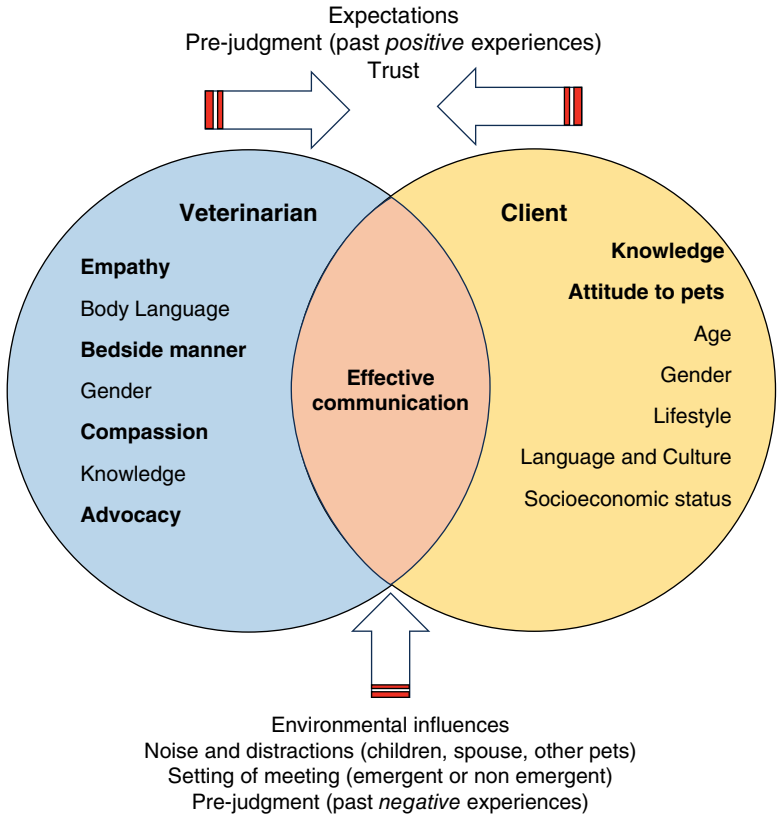


FIGURE 4.2 A representative diagram of communication in terms of sender, receiver, and context. Many factors will influence the message and feedback in a bidirectional manner. Certain factors create a barrier to split effective communication, while others help bring two parties together in effective communication. Some individual elements carry more weight than others to the *receiver* of the information (bolded), regardless of who is doing the receiving. For example, a client may be more willing or able to receive the message if the veterinarian has a good bedside manner and demonstrates a desire for advocacy as opposed to their knowledge on a particular subject. A veterinarian may care less about socioeconomic status compared to the desire of the client to help their pet.

on their level and weighted toward science but still considering their lifestyle. Hitting this moving target with every client interaction takes concentration and attention to detail, which will naturally spill over into the way a caregiver manages a case.

Natural-born communicators are not common, and this aspect of veterinary medicine receives a cursory mention at best in most medical training programs. However, there is a trend in teaching institutions to offer more classes in communications (as well as ethics, law, and other humanities). By following a few suggestions, even the most introverted veterinarian can excel at communication. Let's also not forget the value of confidence in your topic. Medicine in general is not a good place to *fake it till you make it*. A good start usually begins the moment you enter the exam room. The goals of successful medical communications would be:

- Establish trust and rapport
- Create confidence (if not in knowledge at least in the desire to help—advocacy)
- Disseminate information in a clear and concise manner

Success in these three areas will ultimately lead to an understanding of the dysfunction, disease, or disease process, by the pet owner, allowing them to make the best decisions for their pet with the guidance of the veterinarian. Attaining these goals ultimately leads to higher client satisfaction, fewer complaints, and above all better compliance. The message you are trying to send may easily be *lost in translation* and, even if delivered, may not necessarily be received (i.e., comprehended). The client will nod as if they understand but typically have a blank far-off gaze signaling "I have no idea what you are talking about." In your attempt to explain a clinical condition (a biomedical style), you lose the attention of your audience, or their *perception* of what you are trying to communicate is different from what your intention is. Often, the vocabulary we choose can be too "cerebral," but at the same time, it is necessary to choose words that do not dumb down the problem (or your education). A client who understands the problem is more likely to trust the medical provider and spend their money on the pet. Here's a common example:

> *In an attempt to provide all of the possible management options to a client (give them the choices), their perception is you (the veterinarian) may not follow your own recommendations, for your own pet. In routine practice, we may offer a client several different options and then allow them to choose which is best for their situation. This is a great example of a biomedical and lifestyle/social balance. Choosing a management plan often boils down to a conservative approach or a diagnostic approach. The tone of your voice, body language, and overall demeanor may give the client a perception you are leaning one way or another. If you are lucky, they will mention this. "So, you're saying I should do nothing?" would be a common response when in actuality, you are saying they have options. If you focus on one particular aspect or do not include all of the options, the client may feel as if their choices are limited or worse you do not care to help them. Most people do not expect to be presented with different options. Options are an element of customer service. Your ability to provide options may set you apart from others. Clients tend to give more weight to the option you offer first (pro tip—if you offer diagnostics first, they will tend to choose this option).*

Effective communication requires two parties to understand what the other is trying to infer through spoken words, visual cues, or even body language and facial expression. Occasionally, nodding, eye contact, an open stance, and hand gestures are also very effective means of body communication. If a client is not interested in diagnostics and as the veterinarian all you talk about are *diagnostics* and no other options (a conservative or empirical approach), their perception may be you are either not listening or do not understand what they are trying to communicate. The veterinarian has to listen to the client's words; interpret inflections, body language, and countenance; but at the same time remember the client may not be aware of all of the options. This process is a two-way street. The veterinarian has to listen to the client, and the client has to listen to the veterinarian. They may not *want* to listen to you. In those situations, you may do more listening than you want, but there will be opportunities to inject your opinion (last of which is the discharge report). If the client dominates the conversation and is setting the agenda, you can enthusiastically interrupt in an attempt to steer the conversation back on course. You have to be careful to do it in a way that does not disrespect the client, make them feel ignorant, talk down to them, or give the perception they are not doing the best thing for their pet. An especially tricky aspect is making sure the client does not feel as though you are trying to rush the appointment. Most of all, at the end of the day, we must try to avoid making the client feel *guilty* for not doing what you, the veterinarian would do, or make them feel *crazy* for wanting to do something they perceive you would not to do.

One of the most important elements of successful communication is having the receiver engaged in what the communicator is trying to say. This simply means the person listening should be interested in what is being said. The clinician has the advantage, as the person they are speaking to *wants* to hear your opinion. After all, they sought you out. Use this to your advantage and capitalize on it by being engaged and interested in the client's story. You may have heard it a hundred

times before, but to the client and their pet, it is the first time and it is the most important. Try to anticipate the client's state of mind before you speak with them. They may be scared, sleep-deprived, emotionally drained, eager for answers and help, or even angry. They are usually not apathetic (although, occasionally a disgruntled teen might be sitting next to them). They may be under high emotional and financial stress. Remember, epileptic seizures can be very scary to pet owners. They often experience the feelings and thoughts their pet is dying at the time of the seizure, only to experience this over and over again. Try to be compassionate, empathetic, patient, and understanding. To the client in the room, you represent hope. Stay positive. Pet owners appreciate optimism without false hope. When in doubt, always consider the most positive outcome. For instance, for a geriatric patient with a new-onset of epileptic seizures, think vascular accident (stroke) before brain tumor (until proven otherwise). For some specific situations, we will look at each element of the client–veterinarian interaction with regard to the epileptic seizure scenario.

EXAM INTRODUCTION AND HISTORY

Make sure you are dressed for the part. A clinician should be dressed business casual. While a white coat is not necessary to perform great medicine, research has shown *wearing* a white coat improves selective attention through what is referred to as "enclothed cognition." Essentially, if you wear a white coat, *you will be* smarter (Adam and Galinsky, 2012). We all certainly wish it were that easy. However, in addition to improved attention to a task, it is well-established physicians with a good bedside manner have better patient compliance. A white coat connotes authority and professionalism for some individuals, but for others, it may mean arrogance and intimidation (Person and Finch, 2008). Certainly, many elements are combined to create effective verbal and *non-verbal* communication. External demeanor, internal frame of mind, and medical caregiver's appearance were emphasized by Hippocrates (460–370 BCE):

> *The physician ought also to be confidential, very chaste, sober, not a winebibber, and he out to be fastidious in everything, for this is what the profession demands. He ought to have an appearance and approach that is distinguished. Everything ought to be in moderation, for these things are advantageous, so it is said. Be solicitous in your approach to the patient, not with head thrown back (arrogantly) or hesitantly with lowered glance, but with head inclined slightly as the art demands.*
>
> *He ought to hold his head humbly and evenly; his hair should not be too much smoothed down, nor his beard curled like that of a degenerate youth. Gravity signifies breadth of experience. He should approach the patient with moderate steps, not noisily, gazing calmly at the sick bed. He should endure peacefully the insults of the patients since those suffering from melancholic or frenetic ailments are likely to hurl evil words at the physician.*
>
> (*Carmichael and Ratzan, 1991*)

Hippocrates' words, written over 2500 years ago, still resonate today. While our patients may not hurl evil words at us, their owners might. We should look with empathy toward their situation. We should also always consider the demeanor of a sick, painful, or mentally inappropriate patient and do our best to attend to their needs with as little stress and as much compassion as possible. Studies in human medicine have shown empathy affects clinical outcomes in a *positive* manner (now, there's a surprise); however, many medical care providers are incapable of expressing empathy (although they think they are) (Berg *et al.*, 2011). Caregivers who have a good bedside manner are perceived to be smarter by the human patient and are less likely to be sued for malpractice (Spice, 2003). A good bedside manner is also well correlated with increased patient satisfaction (obviously a human study) and health outcomes (Roter *et al.*, 2006).

Before entering the exam room, read through the history (if possible). You do not have to know the specifics but try to have a general idea of when seizures started and potentially which diagnostics have been performed in the past, relating to the seizures. You will ask more specific

questions later regarding seizure type, frequency, postictal time, interictal deficits, etc. (see Chapter 5 on diagnostics). Walk into the exam room with confidence, not trepidation or confusion. Be composed as opposed to rushed or *frantic*. Greet the client by the first name and introduce yourself by your first name. They probably know you are a doctor and it is certainly OK to introduce yourself formally as "Hello, I'm Dr. _____"; however, a more casual introduction is more likely to set a congenial tone and foster multidirectional communication. Try to avoid the use of the terms "sir," "madam," or "ma'am" unless you are getting a speeding ticket, in the military, or addressing a head of state. Set the tone of your voice as one of confidence. Greet the patient but do not reach out to touch a dog or wait to let it sniff your hand. That gesture alone can be a bit threatening to a dog in an unusual environment. Let the dog approach you. You should speak to it but you don't have to be best friends. It's a working balance between being neutral to a suspicious dog or cat but at the same time sending a message to the pet owner that you "like" their pet. Allow the dog or cat to wander around the room. While you are talking to the client and getting the history, observe the patient in the unfamiliar environment. Having a dog bed in the exam room can help, as it gives the patient something to focus on and maybe even take a nap while you speak to the pet owner. Listen attentively to the client. Try to avoid typing or staring at a screen while the client is speaking and certainly, do not turn your back to the client. Writing or taking notes or history is well accepted in the client–veterinarian interaction, but try to sprinkle in eye contact, head nods, and verbal agreement.

SEIZURE DIARY

Any account of epileptic seizure activity can be helpful. However, when presented with a jumbled list of written out dates and descriptions of the seizure event, the sheer volume of information can be challenging and time-consuming to evaluate. What we are really after is a *general* idea of the frequency and intensity of the seizures. From this information, we can look for specific patterns, reactions to the environment, or changes secondary to medication alterations. If presented with a list, it can be helpful to transcribe the information into a linear *timeline* format. This can be very simple or very involved. Helping clients understand the value of this style of record-keeping will keep them involved in the process of managing an epileptic patient and will provide the clinician with valuable information, which may help in management or strategic decisions (Figure 4.3). This chart provides a general overview of seizure activity and can help to correlate changes in seizure frequency or intensity with environmental influences (stressors), medication changes, comorbidities, and other illnesses. Recognition of patterns may help with the implementation of new or altering current medication and management strategies (see Chapter 6). Here is an example:

A patient with suspected genetic epilepsy typically has 15–20 seizures a year. They are generalized and considered brief (lasting less than 30 s with a 1–2 min postictal time period and rapid recovery). Prior to starting chronic therapy (a prophylactic strategy), the patient was having two to three seizures a month. This patient is considered well-controlled, and the owners of the dog are happy. The patient tolerates the medications well and has not experienced any side effects. The owners started to notice an increase in the frequency of the episodes, which tend to happen intermittently at various times of the year. By looking at the linear calendar, they realize the increased activity tends to happen around family gatherings happening at the household (graduations, holidays, birthdays, etc.). Rather than changing the prophylactic medication, potentially resulting in a negative side effect or increased financial burden, the pet owners have two options to consider:

- Avoid the stressor. Have gatherings at another family member's house or place the dog in an environment during the gathering, where he is not "stressed."
- Try a *bridge* medication strategy. Use a temporary add-on anti-seizure medication to *bridge* the time when the pet would be under additional stress, without altering the otherwise working prophylactic medication (e.g., start clorazepate 1–2 days before the stressor and continue for 1–2 days after the stressor has gone).

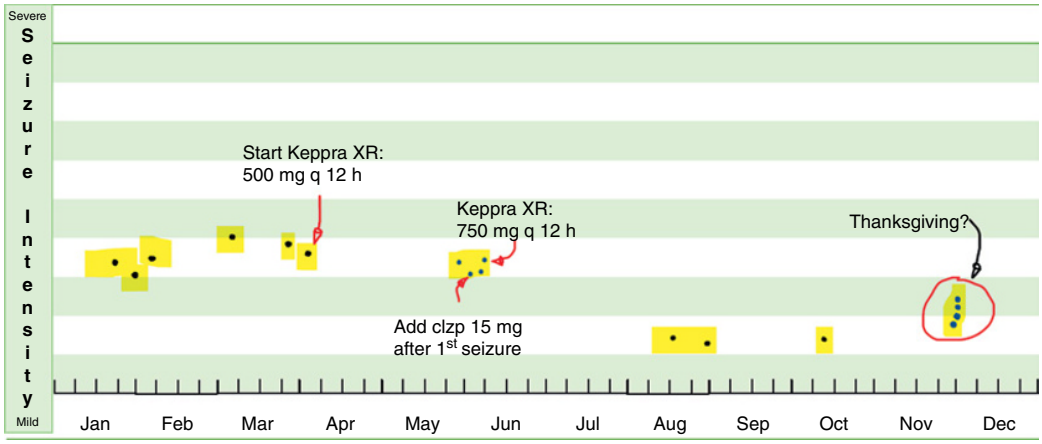


FIGURE 4.3 Viewing the seizure history in a more pictorial manner allows easier identification of patterns. Analyzing patterns from a "sky view" as opposed to a list or even a month-by-month calendar is easier. The seizure log may provide predictive information and aid in medication changes. For example, adding clorazepate after the first seizure of a group of predicted clustered events and using it for a few days prevented further cluster events. Increasing Keppra XR from 500 mg every 12 h to 750 mg every 12 h resulted in better seizure control and fewer seizures when they did occur. Finally, adding in clorazepate as an extra booster for control a few days before guests arrive for the holidays may help prevent "excitement"-induced seizure activity.

Avoiding the stressor would be ideal; however, some stressors are difficult to avoid (e.g., trips to the vet, groomer, etc.). In those cases where the stressor cannot be avoided, adding on a medication such as clorazepate for a few doses prior to the stressor and a few doses once the stressful event is over may help suppress seizure activity for the short amount of time where the seizure threshold is lowered. In the case of a gathering, the pet owner could start dosing the bridge medication the day before the event, continue the day of the event, and then stop 1 day after the event. Each circumstance will vary; however, the general concept is the same; the pet owner identified a pattern by keeping a seizure diary, which was easy to evaluate. Elements that can be added to the diary plot include:

- Date
- Time
- Intensity of seizure
- Medication changes
- Trips to vet, groomer, etc.
- Vacations
- Business trips
- Dates when a family member comes or goes
- Illness
- Other medications
- Changes in food
- Integrative medicine (e.g., acupuncture)

Many other possible elements exist. Let the client use their imagination. If they think the seizures are related to cycles of the moon, this gives them a chance to prove it (although this example has been discounted in the literature) (Benbadis *et al*., 2004; Browand-Stainback *et al*., 2011). A "blank" seizure log can be found in Appendix 2 and on the companion website.

EXAMINATION AND DISCUSSION

Throughout the exam, narrate to the owner what you are doing. Most pet owners are a little surprised and chuckle a bit when they see reflexes being tested. They often need subtle reminders the veterinary patient has nearly identical physiological processes as that of a human. Describe what you are testing and why. For example:

> *When we flip over the paw, we are sending a signal to the brain through the nerves and the spinal cord. The correct response, which is to flip back the paw, allows us to check the integrity of some of the most basic functions of the nervous system. It's like making a phone call to the brain and waiting to see if we get a response.*

Pet owners are interested in this most of the time, and it's a nice tool to help engage them in the process as opposed to awkward silence as you carry out the exam. You may be surprised when they start to suggest previous clinical signs, they were unaware of such as "oh yeah, she has been scuffing her toes on walks for the last six months." If possible, try to examine the patient on the floor. A padded rubber floor mat/cushion can be helpful for most neurological patients who might have trouble standing and will save your knees as well. Getting down to the patient's level can help to relieve stress and tension in the patient as opposed to standing on a slippery exam table. If you do use an exam table for cats and small dogs, place a *silicone-baking mat* on the table to provide traction for the patient. A pet owner will appreciate these small attentions to their pet's comfort, which helps to build trust.

After the exam comes the explanation of the clinical findings. Your epilepsy narrative should be fairly straightforward and will not change much from patient to patient. Analogy improves cognition of unfamiliar concepts by allowing a person to compare the unknown to a more elemental and familiar example. Simple explanations (use some poetic license) and analogies are useful in each element as in the following narrative:

NARRATIVE

From your description, it really sounds like Milo is having epileptic seizures. Seizures are not really a disease but rather a "sign" of brain dysfunction. Much like a limp is a sign of a hurt leg. The limp is not the disease. A seizure is the brain's way of "limping" and showing us there may be a problem. Neurons in the brain generally *want* to be active. They tend to spontaneously fire. Neurons are the *gas* of the brain. They make the brain go, which results in any particular action or behavior. Neurons are kept in check by the extracellular environment and glial cells. Glial cells are the *brakes* of the brain. They keep neurons quiet. So essentially, the brain is like a car at a stoplight with the gas and the brakes on at the same time. It is ready to go at a moment's notice by either applying more gas or taking away the brakes. A seizure is uncontrolled brain activity. It may start with a single neuron firing uncontrollably, which then triggers surrounding neurons to fire. As more and more neurons are recruited, waves of electrical activity spread out from the seizure focus. It's kind of like when in a stadium, at a sports event, one group of fans starts chanting and before you know it, the entire stadium is recruited into the chant. It spreads out from a small area to envelop the entire stadium. The stadium is the brain, and the fans are individual neurons.

There are four large categories as to why a patient might have epileptic seizures. The first is the *idiopathic* or *genetic* form of epilepsy. It usually shows up between the ages of 1 and 6. A hallmark of this form of epilepsy is the patients' have a normal neurological exam and stay normal in the long term.

There are no easy diagnostic tests to confirm idiopathic epilepsy; rather, it is a diagnosis we make by *excluding* the other causes of epilepsy or when we have a really strong suspicion based on breed or genetics. The next category is the *metabolic* causes of seizures (for simplicity we will ignore the technical fact this category is not true epilepsy . . .). With these problems, the patient is usually sick, and the seizures are secondary to the metabolic derangement or sickness. These patients typically appear ill and may have a history of vomiting, diarrhea, or poor appetite. These patients could be of any age. Most metabolic disease is diagnosed with routine blood work; however, we occasionally employ specialized tests such as bile acids to evaluate liver function, insulin/glucose ratios, and abdominal ultrasound. Similar to metabolic causes, *reactive* or *provoked* causes of seizures are seizures secondary to a toxin, although rapid discontinuation of certain drugs can also cause reactive seizures. Most owners know if their pet is *getting into things* such as slug bait or chocolate. Other possible toxins such as lead are less common these days; however, be aware of pets drinking out of ponds, fountains, or stagnant water or getting their water from a shallow well near agricultural land (i.e., excessive nitrates). Seizures *usually* abate once the toxin exposure has stopped or the metabolic condition has been corrected, however, reactive seizures can alter the environment of the brain to the point where an epileptic focus is created and seizures continue even after the toxin is removed, although this is uncommon.

The next category is structural brain disease. In this category, there is something physically wrong with the brain. This category can be further subdivided into *static disease* and *progressive disease*. With a static disease, the problem responsible for the generation of brain damage (which results in an epileptic seizure) has come and gone, but it has left seizures in its wake. A good example would be a stroke, hemorrhage (bleeding), or head trauma. With static disease, we do not expect *new clinical signs* of brain dysfunction to develop over time. The disease is *static*. With a progressive disease process, epileptic seizures may be the first sign of brain dysfunction; however, new clinical signs related to *brain dysfunction* will eventually show up over time. This may include blindness, balance problems, or behavior changes. Finally, we have the *unknown* category. These are patients who might be too old to fit into the genetic epilepsy category but do not show any signs of progression, and/or despite all testing carried out, an underlying cause cannot be identified. A degenerative condition would most likely fit into this category, although unidentified vascular accidents, cerebral malformation, and inflammation not detected on cerebrospinal fluid (CSF) analysis could also fit into this category. If we look at a graph of how each of these categories will behave over time, we can get an idea of what to expect [*at this point you can draw a disease progression curve*] (Figure 4.4). With an idiopathic, genetic condition or static structural disease, we would not expect any clinical signs to

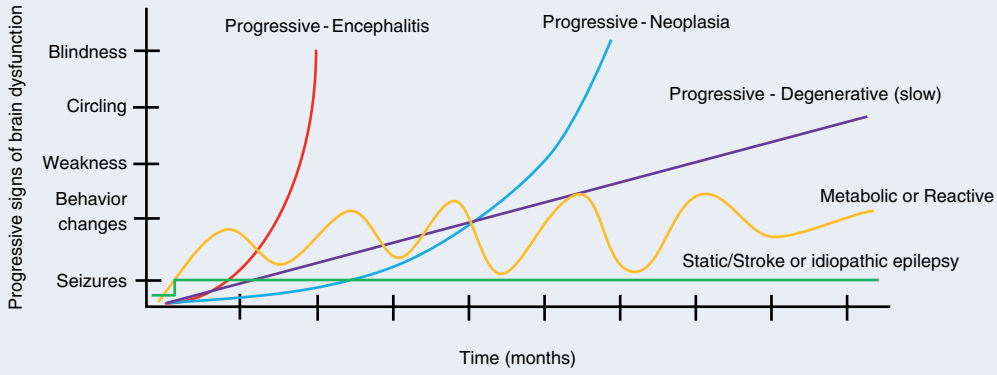


FIGURE 4.4 An example of a simple disease progression curve can help clients understand what to watch for. It is important to emphasize they are watching for other signs of brain dysfunction, which develop independently of seizures. *A progressive* disease gets worse with time. The time it takes to get worse depends on what the problem is and where it is in the brain. *Metabolic* and *reactive* causes of brain dysfunction vary depending on the sickness or exposure (i.e., toxin). *Degenerative* disease is slow and steady. Finally, with *static* disease, such as idiopathic, genetic epilepsy or stroke, you only see seizures and any secondary deficits related to an injury (i.e., in the case of vascular accident) over time.

develop over time. With a progressive problem, we would expect to see other signs of brain dysfunction over a period of time. This *window of opportunity* tends to be between 2 and 8 months depending on what the disease is. For most forms of infectious encephalitis, it is fairly quick. However, with slow-growing brain tumors, such as a meningioma, certain autoimmune forms of encephalitis, and degenerative disease, the development of other signs of brain dysfunction tends to take months. The longer you go without seeing the development of new clinical signs, related to brain dysfunction, the less likely they are to show up and the more convinced you will be the problem is either genetic epilepsy or static structural disease.

There are two basic pathways we can take. One would be to take a *conservative approach*, where we use medications to try to stop the seizures along with time to watch for the development of any new signs of brain dysfunction. With a conservative approach, you are watching for other signs of brain dysfunction. Knowing what to watch for will allow you to identify a progressive problem earlier. We use anti-seizure medications to try and stop the seizures. The medications will not prevent or slow down the development of other signs of brain dysfunction. They will only help to make the quality of life for your pet and you better.

The other option is a *diagnostic approach*. With a diagnostic approach, we use tests to try and figure out the cause of the seizures. The tests will only give us two benefits—either the *peace of mind* everything is OK or the ability to treat differently when we know what the problem is or is not. For example, if you can't sleep at night, worried that your elderly pet might have a brain tumor or the information might help make quality of life decisions easier, finding out what the problem is would be a very reasonable option. If, on the other hand, knowing what the problem is might provide us with other treatment options, for example, treating encephalitis or more targeted treatment for a brain tumor (such as surgery), then the diagnostic tests will provide us with a diagnosis, from which various treatment options may be offered, each with their own prognosis, advantages, and disadvantages. With a diagnostic approach, we usually start with the tests that have the greatest diagnostic yield, with the lowest cost and the lowest risk to the patient. This may include blood work, urinalysis, fecal exam, etc., and then we follow the diagnostic pathway. If blood work is suggestive of a metabolic disease, other tests such as abdominal ultrasound or radiographs might be warranted. However, if the basic testing is considered normal, we move on to tests requiring anesthesia and greater expense, such as an MRI and CSF analysis. The MRI and CSF analysis tend to be the highest diagnostic yielding tests. However, we want to make sure an underlying etiology, which could have been identified with less expensive tests and, more importantly, not *requiring anesthesia*, is not missed. So, at this point, either option would be reasonable. As a clinician, I tend to recommend the diagnostic approach as it gives me the best information to provide you with the most options regarding treatment and prognosis. However, if, for any reason, doing diagnostics does not fit with what you want to do right now, we can still help you with the conservative approach.

Once the explanation of seizures is complete, some clients may have additional questions creating an opportunity to expand on the explanation. Being able to classify the type of epilepsy as a syndrome, will also help the clinician to choose the best diagnostic options and medical treatments for the patient (see Chapter 3).

Often pet owners will ask more questions and occasionally ask you what you would do if the patient were your own pet. I answer this freely but qualify my answer to let the client know no matter what I would do they should not feel "bad" for not wanting or being able to do something I would do and conversely not feel "crazy" for doing something I would not want to do if it were my own pet. Their wants and desires for their pet may be completely different from yours. My goal is to provide them with reasonable *options* and *recommendations*. Then I will try to help them as much as possible to achieve their desired goals within the specific framework they set forth.

ANTI-SEIZURE MEDICATIONS

Many factors are considered when choosing an anti-seizure medication. The client should have a clear understanding regarding *how* and *why* we choose certain drugs and drug strategies. If the client has a clear understanding of the process and a basic knowledge of the medications, they are

more likely to comply with medication dosages and strategies. A poorly informed client will more likely question the methods and may decide on their own to change medication dose or scheduling because of a lack of knowledge or lack of perceived advocacy on the veterinarian's part. As veterinary practitioners, we must always remember in order to get to our patients, we have to go through the pet's caregiver. Compliance buys us time to try different medications and strategies. If the client understands this, they are more likely to give medications time to work and will understand why a single medication trial is often not the end point.

To that end, any means of communication, which strengthens our ability to send a clear message and is interpreted correctly by the pet owner, will go a long way toward better understanding and compliance. Using a whiteboard in the exam room along with a written summary of what you discussed (usually a form or "boilerplate" document tailored to the patient) is a powerful tool that allows clients a visual to put with your words (Figure 4.5). Studies have shown a higher retention rate and up to 85% better recall rate when pictographs and written communications are provided over verbal communication alone (Houts *et al.*, 2006). An outline of why dogs and cats have seizures followed by conservative or diagnostic options along with a treatment plan is generally regarded as "going the extra mile" in helping clients understand. These explanations do not need to take 45 min (although they certainly can). Identifying your strengths with a client will give them the confidence they need to entrust the care of their pet to a complete stranger (Figure 4.6). Don't forget to follow up with a written summary of your explanation.

Analogy is a powerful communication tool. It allows a complicated or poorly understood topic (such as anti-seizure medications) to be explained on a level playing field with an individual who may not have the same degree of understanding regarding a particular subject. Analogy is one of the most powerful tools used to improve cognition and comprehension. We all use analogies every day almost without thought. Coming up with clear analogies regarding complicated subjects can greatly improve your ability to communicate.



FIGURE 4.5 Using a whiteboard and other visual aids will greatly enhance communication/reception and provide a substrate that will encourage clients to pay attention to what you are saying. Visual aids create a more engaging conversation and also help the client and *clinician* keep track of complex disease pathways, diagnostics, and treatment options.

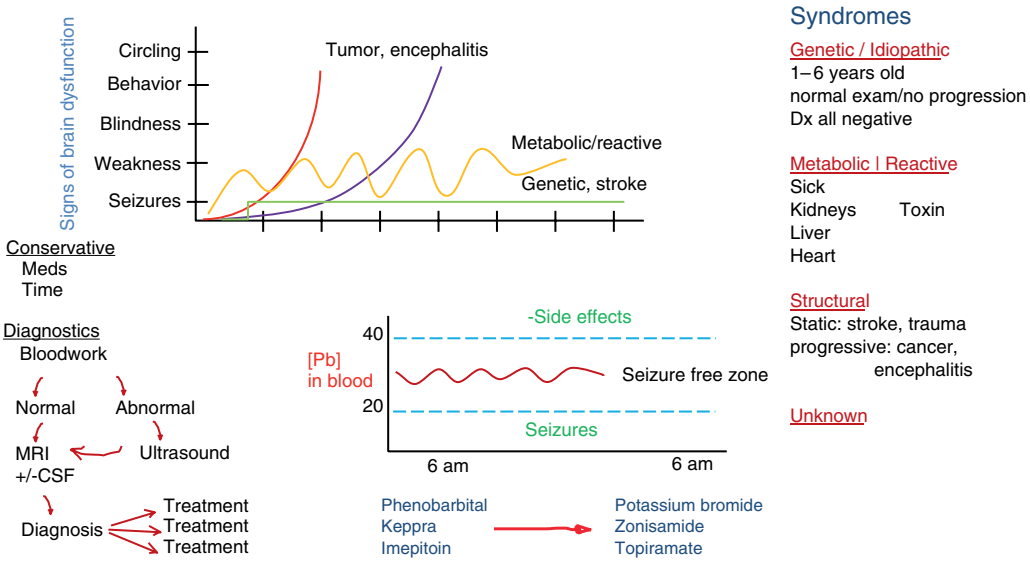


FIGURE 4.6 Example of a whiteboard diagram used during a *typical* seizure talk. Simple graphs and lists augment verbal communication to allow for better attention, comprehension, retention, and recall. The information is also repeated in the written discharges so the client can focus on the veterinarian instead of taking notes and has reference material to take home and explain to other family members. Many clients will take pictures of the board and applaud your efforts in explaining complex medical and surgical topics. Pro tip . . . have plenty of different color markers available and take your time.

As an example, imagine you are trying to explain what types of anti-seizure medications there are and why some would be used in certain situations as opposed to others.

NARRATIVE

The ultimate goal of any anti-seizure drug is to prevent or reduce the frequency and intensity of epileptic seizures with no or as few side effects as possible. Some anti-seizure medications have very broad-spectrum activity. They act to suppress all neuronal activity without much specificity as to which groups of neurons are abnormal. Other anti-seizure medications are more specific and targeted. Imagine the example of a ballroom filled with people listening to a speaker (similar to the stadium analogy earlier). The ballroom is the brain; the individual people are the neurons. One person in a far corner starts to chant, and before you know it, the whole room is chanting in synchrony. If you were to apply a broad-spectrum crowd (i.e., neuron) control (or broad-spectrum anti-seizure medication), it would be like shutting the lights off in the ballroom. All at once, the crowd (brain) would shut down. Even though the problem started with one disruptive individual (i.e., neuron) in the far corner of the room, the entire brain was affected by the method of "control" (i.e., shutting off the lights). That's how a drug like phenobarbital or potassium bromide works. They are both considered *broad spectrum*. Apply a more specific crowd control mechanism that would take care of the corrupt individual (neuron) without affecting the rest of the room (brain) would be to call security as soon as the abnormal firing individual started to get out of control. The person would be quietly escorted out of the room or asked to take their seat. The abnormal activity ceased at the onset, and the rest of the room was unaffected. That is how newer, more specific anti-seizure medications such as zonisamide and levetiracetam work. They *target* abnormal neurons with less effect on *normal* neurons; therefore, the side effects tend to be more mild or not even present.

NARRATIVE

Most anti-seizure medications are very well tolerated; however, like all medications, there is a chance for the individual to develop a negative side effect to any particular medication. The side effects tend to be mild and manageable; however, as a pet owner, you need to be able to recognize them. There is no single, perfect dose or drug used to treat all types of seizures. Each patient will be different. Finding the right dose of medication or combinations of medications is like cooking a gourmet meal; we start with a recipe but season to taste for the individual. The anti-seizure medication(s) is (are) tailored to the individual. Choosing an anti-seizure medication to stop epilepsy is like choosing an antibiotic to stop an infection when you do not know what the bacteria are. You pick the one having the greatest chance of working with the fewest side effects and wait to see if it works. Unlike an infection, however, where bacteria can be grown in culture and tested against an antibiotic to see if the antibiotic kills it, we cannot practically *test* anti-seizure medications in a clinical situation (note that technically, an electroencephalograph (EEG) may be used to indirectly detect if a medication is working through the suppression of previously documented epileptiform activity, such as pHFOs, interictal paroxysmal discharges, etc.—nerd alert!). We choose the medication we think might work best, usually using our experience and comfort level and also considering the concerns of the owner. Many pet owners are against using certain medications, which have the possibility of more severe side effects or are unable to follow dose guidelines (e.g., every 8 h dosing). We choose a typical starting dose that is known to be effective with the majority of the population, and we *watch/wait* to see if it works. We have to give the medication enough time to build up in the pet's system. This can be anywhere from a few days for medications such as zonisamide, levetiracetam, and imepitoin, to a few weeks for phenobarbital, or a few months for potassium bromide. If the seizures continue after the medication has reached saturation or a *steady state* in the blood, then we gradually increase the dose until we either achieve acceptable seizure reduction or we get a side effect that is not acceptable. With some of the "safer" medications, we simply increase to effect, to side effect, or to a point where we know more of the same will not help. Usually, this is double the starting dose. It would be like continuing to use an antibiotic with an infection that was not sensitive to. More of the same ineffective drug will not be any more beneficial.

Most people will understand these simple analogies, and while they may seem very elementary, they do allow a complex topic such as the physiology of epilepsy to be distilled down to an easy-to-understand explanation. Remember you are allowed "poetic license" with analogy. Also, be careful of your word choices. Words we use commonly everyday such as "vascular," "synchronous," and even "neurons," for example, might as well be a foreign language to those without a medical background. Consider "blood vessels," "firing at the same time," and "brain cells." You get the idea. The more we become fluent in a subject, the more likely we are to forget how complicated it might be to an individual who is not as versed in the topic. Analogy helps to bridge this gap. As you continue to discuss anti-seizure medications, it is important to prepare the owner for the possible complications, which may be encountered in using these drugs.

Using the whiteboard to draw out a *dose–response* curve can help clients understand this concept (Figure 4.7). Being able to link a picture to the spoken word is a powerful tool for communication and understanding. Remember, a client who understands the problem is more likely to comply with your instructions. A brief discussion on anti-seizure medication strategies (see Chapter 6) can also be approached if time allows. This helps the client to understand we have various tools and methods to use those tools. They are less likely to think we are haphazardly picking medications and changing doses without a *plan*.

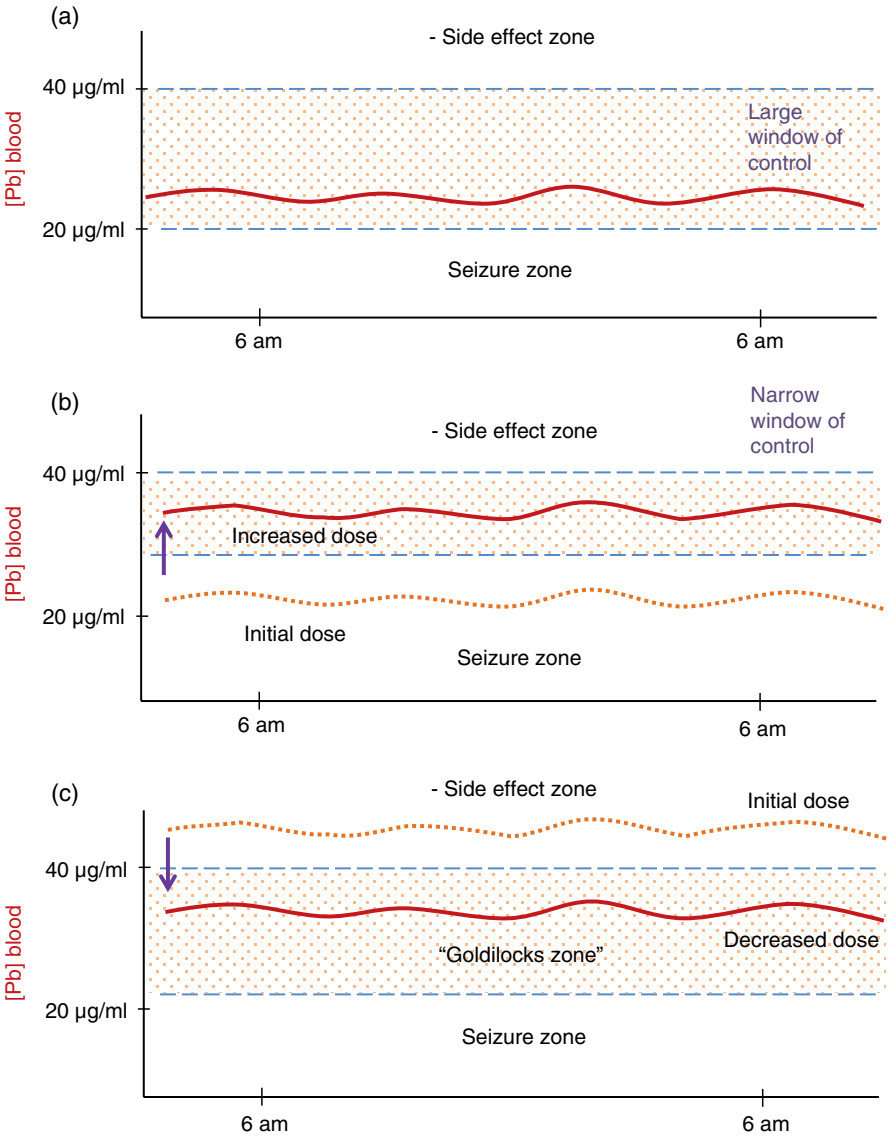


FIGURE 4.7 A discussion with clients about drug levels. In (a), the effective control window (*Goldilocks zone*—just the right amount) for phenobarbital for this particular patient is wide and falls in the reference range for the drug. A low dose (i.e., low serum drug level) gives good seizure control with no side effects. There is no reason to increase the dose. In (b), the *actual* control window for the particular patient is narrow. The initial dose was too low (dashed line). The patient continued to have seizures. The dose was increased and the seizures stopped because the drug level was now in the control window. In (c), the dose is too high (dashed line), causing negative side effects. The dose needs to be lowered and the patient watched for reduction of side effects with continued seizure control. This simple explanation can make a pet owner aware of the nuances of therapeutic drug monitoring and adjusting a medication dose to effect or side effect.

Following the explanations of the exam and a discussion on seizures and anti-seizure medication, the client will usually decide at that moment or take a few days to discuss with family members their preferences as to a conservative approach or a diagnostic approach. This may also include a referral to a specialist. Most will be prepared to follow your recommendations for anti-seizure medication at that time.

SUMMARY

Discussing epileptic seizures is no different from any other medical disease or disorder. However, clients tend to be on a higher level of alert status. They may be emotionally fatigued, physically sleep deprived (from pets having seizures in the night), financially strained, and most of all feeling confused and helpless. As a veterinarian, you have the potential to make much of their grief go away. Simply knowing someone is on their side, interested, compassionate and caring, empathetic, and optimistic will help make them feel at ease. This will give you time to help the pet. Effective communication begins with an audience interested in the message. You have already achieved that aspect as they have sought out your advice and expertise. Developing your own communication style and comfort takes time. To some, it may be easier than to others. Acknowledging you need to develop a relationship with the client, which is mutually beneficial, is a great start. Being able to effectively communicate the message then relies on a basic understanding of the disease you are discussing, using tools such as analogy and metaphor to improve cognition, as well as applying visual feedback to reinforce key concepts and enhance recall and adherence to complicated subjects. The development of trust comes with time. You cannot force trust; however, it will develop naturally if you genuinely care. Your clients will see this. It always amazes me to see a client who at the beginning of the exam is upset about their pet's condition, is an emotional wreck, or worse "turned off," uncaring, skeptical, unresponsive, and rude do a complete 180° turn around by the end of the exam. To see them become "convinced" you are trying to help reinforce why we do what we do every day. At the end of the exam, they may ask to take a photo of your whiteboard or even ask (jokingly of course) if you could be their own doctor. Making that connection is ultimately not about fulfilling our own egoic needs but knowing we were able to get to the pet by getting through the pet owner.

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Diagnosis

CHAPTER 5

KEY TAKEAWAYS

Diagnostic protocols help with consistency of treatment and understanding of disease processes, allowing for better communication and expectations.

Know which diagnostics to apply (or not apply) to the patient based on syndromic classification.

The electroencephalogram (EEG) is a powerful but underutilized diagnostic test. We should do more EEGs.

QUICK JUMP

IVETF MRI diagnostic testing recommendations page 165

IVETF criteria for diagnosis of idiopathic epilepsy Table 5.1

Underlying etiology Tables 5.3, 5.4, and 5.5

Storage diseases Table 5.7

Toxins Table 5.8

MRI characteristics of parenchymal hemorrhage Table 5.10

Introduction 135
History 137
Physical and Neurological Exam 146
Minimal Database 148
Additional Non-invasive Tests 150
Advanced Diagnostics (Invasive or Requiring Anesthesia) 157
Research and Future Diagnostic Modalities 177
Functional Neuroimaging 178
Epilepsy Biomarkers 186

Myelominutia: Magnetic resonance *elastography* allows clinicians to "palpate" the brain.

INTRODUCTION

The International Veterinary Epilepsy Task Force (IVETF) has made recommendations for the diagnostic approach to epilepsy in dogs (De Risio *et al*., 2015) (see Table 5.1). The consensus report takes into consideration numerous factors and results of investigative studies to provide evidence-based criteria regarding which diagnostic tests to perform and when. Regarding cats, we can take

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Companion website: www.wiley.com/go/sanders/seizures2e

Table 5.1 Criteria for the diagnosis of idiopathic epilepsy in dogs

Criterion	Tier I	Tier II	Tier III
Age of onset >6 months <6 years	●	●	●
Normal interictal exam	●	●	●
Normal bloodwork and urinalysis	●	●	●
Normal bile acids (fasting and fed)		●	●
Normal MRI[a]		●	●
Normal CSF analysis		●	●
EEG abnormalities[b]			●

Adapted from De Risio *et al*., 2015.

[a] If abnormalities are detected on magnetic resonance imaging (MRI) or cerebral spinal fluid (CSF) which may be consistent with postictal changes—consider repeat diagnostics after a 16-week seizure-free interval (or 6 weeks for repeat CSF).

[b] Ictal or inter-ictal EEG abnormalities characterized and associated with seizure disorders in human medicine.

a similar if not parallel approach to diagnostic testing. Although there are nuances to the approach in cats, for the most part, the bulk of the recommendations will hold true.

Regardless of the underlying etiology of seizures, the diagnostic approach is straightforward and typically very consistent. The goal is to identify the cause of the epileptic seizures (either through definition or exclusion). The benefits of diagnostic testing can be distilled into two primary reasons to perform any diagnostic test:

1. The results of the test will provide *peace of mind*.
2. The results of the test will change a treatment approach or modify a decision-making process.

In the first case, a pet owner may just want to make sure (i.e., verify) for peace of mind they are assuming the cause of the epileptic seizures is the presumptive diagnosis (e.g., a young dog with a long history of seizures presumed to have idiopathic epilepsy). The benefit of the information may help an owner accept why a pet may not be responding to therapy or allow the owner to rest assured they are doing everything possible to treat a particular case. For example, a 2-year-old Border Collie has a history of epileptic seizures starting 8 months ago with no signs of progression but having inadequate seizure control despite trying several medications. This particular owner may just want to make sure they are doing everything possible. As long as the benefits of the test outweigh the costs and risks (anesthesia), the diagnostic approach is reasonable.

In a second case, the results of the tests may change the treatment options. For example, a 12-year-old cat with a recent onset of seizures. Determining if a meningioma is present may help decide if surgery is a reasonable treatment option. Another example might be a pet with encephalitis. In this case, while treating the seizures is essential, specific treatment targeting the underlying cause of the encephalitis (meningoencephalomyelitis of unknown origin [MUO], or infectious disease) may also help the patient. This may be especially pertinent if the breed of the dog is commonly associated with MUO or the presenting clinical signs are suggestive of limbic encephalitis, whereby a corticosteroid trial may be in order.

Finally, a diagnosis of idiopathic epilepsy is a diagnosis *by exclusion*. Because there are no commercially available diagnostic tests or biomarkers to determine if seizures are genetic or not (unless highly suspicious based on breed), the diagnosis is presumptively made either through the demonstration of no other underlying cause or through a demonstrated history of chronic epilepsy without the development of any other progressive signs (generally accepted time course is 1–3 years). For the genetic determination, the patient may belong to a breed known to have a high

incidence of epilepsy (>2% of breed's population affected) (see Table 3.8), come from a line with a demonstrated inheritance of epilepsy (strongly suspected from genealogical analysis), or a significant number of individuals within the lineage who have had epilepsy (suspected to be idiopathic). The diagnostic approach is aimed at answering two fundamental questions:

1. Are the described episodes epileptic/reactive seizures or another form of paroxysmal event (see Table 3.2)?
2. What is the underlying cause of the seizures (etiology)?

Along the way, additional questions can be answered to help fill in the blanks such as:

- Is there an underlying cause, which may be treated specifically to help control or eliminate the seizures (e.g., encephalitis or brain tumor)?
- What are the frequency, intensity, and type of epileptic seizures? Is there a trigger or stressor? This may affect treatment decisions.
- Does the patient fall into a specific epileptic syndrome (see Table 3.11)?

The process begins with a thorough and accurate history which may be helped tremendously by the pet caretaker filling out an epilepsy questionnaire prior to the appointment (see Appendix 2 and companion website). The logical approach is built on basic steps:

- Chief complaint—Why is the patient here?
- Time course—Is the problem static, progressive, or improving?
- Physical exam—Presence of comorbidities or other disease. Is the problem even in the nervous system?
- Neurological exam—Neuroanatomical localization. What part of the nervous system is affected?
- Create a list of *differentials*. What could cause this problem?
- Create a list of *diagnostic tests*. What tests will help rule in or rule out the differentials?
- Provide treatment options.
- Prognosticate the realistic outcome based on treatment options and the condition of the pet.

Common causes of epileptic seizures based on the age of the patient may help direct the clinician as to what diagnostic tests to choose (Table 5.2). Following the above logical steps will allow the clinician to treat the seizures more effectively, determine if other treatment options are available, form a baseline from which to evaluate the success or failure of treatment, and give the best advice to the pet owner. The start of the diagnostic process begins with a thorough history. Remember, anti-seizure medications (technically, corticosteroids could be considered anti-seizure medications) will not affect any diagnostics tests other than possibly EEG or CSF in the case of steroids.

HISTORY

An accurate and thorough history is an essential starting point. Even if a client does not want to pursue diagnostics, there are certain historical elements, which may alter treatment and prognosis. Particular questions include:

- When did the seizures start? How long have they been going on?
- How old is the pet?

Table 5.2 Typical underlying etiology of seizures based on age of onset.

0–6 months—*neonatal and juvenile*
Developmental
Metabolic/reactive/provoked
Trauma (including hypoxia)
Structural (hydrocephalus, neoplasia, etc.)
Nutritional
Inflammatory
Toxic
Degenerative
6 months–7 years—*adult*
Idiopathic (genetic or suspected genetic)
Metabolic/reactive/provoked
Toxic
Trauma
Inflammatory
Structural
7 years and older—*geriatric*
Structural
Metabolic
Inflammatory

- Is the pet altered? If not, is it in heat or pregnant?
- Is the pet fully vaccinated?
- Any history of head trauma?
- How often (or how many) do the seizures occur?
- How long do they last? How long is the postictal state?
- How long until your pet is normal again after a seizure?
- Is the pet normal in between the seizures (i.e., are there any interictal deficits such as changes in gait, behavior, mentation, sight, habits, appetite, or weight)?
- How do they appear immediately after the event? Normal? Dazed? Confused?
- What do the seizures look like? Do you have a video?
- When do the seizures occur? Always at the same time or at random? Around feeding, exercise, sleep, or excitement?
- Is there anything that triggers the seizures?
- Does the pet let you know a seizure is going to happen (e.g., any strange behavior such as hiding, trembling, or clinginess)?
- Do they ever occur in clusters?
- Can you get their attention during an event, make them "snap out of it"? Do they seem aware?
- If on medications for seizures, which have worked and which have not?

- Any familial history of seizures or other pets or other members of the household (i.e., humans) that are also having seizures?
- Any previous illness or surgery?
- Is there any history of trauma?
- Any current medications? Which ones? How long?
- Vaccination status?
- Travel history?
- Exposure to toxins? Ask about exposure to water sources, livestock, agricultural property, old house (i.e., lead), dead animals, compost, trash, human medications, or recreational drugs.
- Does the pet roam? Are they indoors or out? Are they supervised?
- What is the current diet? Has there been a recent diet change? Many pet owners will have video of the seizure or *seizure event* on a cell phone, tablet, or laptop. This can be very helpful in trying to determine if the patient is actually having a seizure or a *seizure-like* event.

Conditions that may look like a seizure include:

- Syncope or heart problems resulting in *fainting*
- Vestibular disease
- Severe muscle weakness (myasthenia gravis)
- Neck pain (see Videos 25 and 26)
- Tremors and other involuntary movement disorders
- Behavioral abnormalities
- Gastrointestinal disorder
- Periodic weakness or collapse (e.g., "Scotty Cramp")
- Narcolepsy/cataplexy (see Video 34)
- Parasomnias
- Paroxysmal Dyskinesia and other movement disorders

Finally, obtain a list of current medications. Include previous medications used to treat seizures, their doses, why they were stopped, which ones seemed to make a difference, and any side effects the pet may have experienced from the medications. Also ask if any "natural" remedies have been tried, such as herbal medicine, acupuncture, homeopathic, naturopathic, and Ayurvedic medicine or any other possible treatments.

A seizure questionnaire, filled in by the client prior to the initial examination can be very helpful. A sample questionnaire provided by the IVETF is provided in Appendix 2 and on the companion website.

SEIZURE LOG

If an owner keeps a seizure log of their pet, a quick scan may reveal a change in seizure pattern. Seizure logs should contain information such as time of seizure (day or hour), intensity of the seizure, current medications at the time of the seizure, therapeutic drug levels, changes to medications, and any particular stressors or triggers, which may have occurred prior to the onset of the seizure. For an example of a seizure log, see Figure 4.3. A blank seizure log can be found in

Appendix 2 and on the companion website. A seizure log can be as detailed as an owner wants but it is important to be able to recognize patterns. A list may provide detailed information about the actual seizure but can be difficult to interpret over time. Plotting the information in a linear format allows for easier pattern recognition.

AURA OR PRODROME

If the pet owner recognizes a change in the behavior or mannerisms of the pet, this may indicate an *aura* or *prodrome*. Recognition of these events may allow for earlier treatment intervention. Generally speaking, the longer the aura or prodrome prior to the epileptic seizure, the greater the chance of intervention and the less debilitating the seizure may be due to early intervention. The *pulse* medication strategy may be employed if the event is recognized early on (see Chapter 6). However, careful consideration must be given as to which medication to use in order to intervene. If the aura or prodrome occurs within 1 h of the epileptic seizure, a long-acting benzodiazepine, such as clorazepate or clonazepam, may be given. It will take approximately 20–60 min to be absorbed and reach the brain. If the aura or prodrome occurs in less than 60 min (they often are only a few seconds), the veterinarian will choose a rapid-acting benzodiazepine, given in a manner to afford quick entrance into the central nervous system. Rectal diazepam and intranasal or oral lorazepam or midazolam may help in these cases to circumvent a "predicted" epileptic seizure. Well-defined auras or prodromes, which are followed by seizures with a distinct *behavioral* component, are recognized to be pathognomonic of a diagnosis of focal seizure in humans (Engel, 2013).

THE ICTUS

A video of the episode in question is ideal. A description of the typical seizure event may provide information, which helps the clinician with lesion localization. For example, recognizing a lateralizing stereotypic movement during the seizure, such as movement of a single limb or hemi-tonicity, may suggest a certain area of the brain is either the epileptogenic focus or the region of the brain the seizure has propagated to (i.e., the symptomatic zone). However, this information can only be considered and should not be used to diagnose a specific condition. The description of the seizure may also impart some information as to which medication might be better suited for the seizure type. Choosing a medication that might be more beneficial for treating various types of seizures is common in human practice. In veterinary medicine, we are a little more limited as we rarely have all of the clinical data necessary to choose medications, which are considered more beneficial for certain seizure types. For example, the first drug of choice for treating absence seizures as opposed to temporal lobe epilepsy (TLE) in human medicine may be quite different. Lack of data, such as electroencephalogram (EEG) information, should not prevent the veterinary community from trying medications that are clinically recognized to work better for certain seizure types in human medicine. Some of our restrictions (e.g., economic euthanasia and disposition of drugs), however, may prevent experimentation with these medications and their novel uses.

Generalized seizures were previously recognized to be the most common epileptic seizure types veterinary patients experienced (Heynold *et al.*, 1997). We now recognize focal seizures are the most common type of seizure occurring in dogs with secondary generalized seizures being a common sequela (Licht *et al.*, 2002). Generalized seizures, with their classic tonic–clonic, tonic, or clonic phase, are more recognized as *true seizures* or convulsions by the people who witness them and are therefore more commonly reported (Berendt and Gram, 1999; Berendt and Dam, 2003). A careful description of the seizures and the events leading up to the seizures may trigger memories of other, previously unrecognized behavior, which in hindsight, could be interpreted as focal seizure activity. This may warrant more aggressive seizure control in patients where the concern by the owner is not indicative of the true seizure frequency. The earlier the seizures are treated, generally, the more beneficial the outcome (Koh *et al.*, 1999; Freitag and Tuxhorn, 2005).

THE POSTICTAL PERIOD

A detailed description of the postictal period can be helpful in numerous aspects. Determining which medications to use for the *bridge* medication strategy (see Chapter 6) will depend on how quickly the patient recovers from the seizure and when and how the patient can take bridge medications (oral vs. intranasal or rectal and long-acting or short-acting medications). For instance, if a patient recovers quickly from the ictus and suffers no postictal symptomology, it may be advised not to treat the specific seizure with a bridge medication. However, if the patient has a protracted postictal state that often leads to another seizure minutes to hours later, a temporary bridge medication may be used to try to prevent a cluster event from occurring (i.e., a "cluster buster"). Focal neurological deficits, which are observed in the postictal time period, may be helpful in lesion localization (e.g., circling, weakness, or other lateralizing signs). Changes in the behavior or patterns of the postictal state may alert the pet caregiver to possible progression. Management decisions may change based on the behavior of the pet in the postictal state. Aggression is commonly reported, and knowledge of this may prevent possible injuries to pet owners or others who come into contact with the pet in a postictal state. Protecting the pet from drowning, falling down stairs, off decks, or from other elevated places can reduce visits to the emergency room. Many pets are blind for minutes to hours after a seizure. Recognizing this may also help prevent injury by placing the pet in a safe, calm environment where they can recover minimizing the risk to themselves and others. The identification and recognition of patterns are very important to help successfully manage the patient who has epileptic seizures.

Pattern recognition allows owners to be proactive in asking about possible medication changes, strategy changes, and management of the seizures. Lifestyle changes may be considered in order to lessen the chance of a patient having a seizure induced by a stressor or trigger event. Simple lifestyle changes such as avoiding the situation that triggers a seizure or knowing, for example, a patient always has clusters of seizures for 24 h following the first event, may allow a pet owner to "pretreat" for these seizures in anticipation they are going to occur, of course, with demonstrated historical observation (ideally a seizure diary).

The frequency of seizures should be as accurately determined as possible. In many cases, the pet is not under constant observation. Certain *clues* may be available, which suggest a seizure has occurred. Atypical urination or defecation in the house, torn bedding, dried saliva on the chest or muzzle, scleral hemorrhage, oral lesions (such as a bitten tongue), or abrasions on the side of the face may be indicators a seizure has occurred. An accurate determination of the frequency of seizures, as well as the intensity, may identify changing patterns and help to determine when to begin medical management or change management techniques and strategies. Warn owners about the potential for other pets in the house to either attack the animal having a seizure or become frightened/frantic or hide.

PROGRESSION OF CLINICAL SIGNS

Seizures are not a disease, epilepsy is. Seizures are only a sign of brain dysfunction, much like a "limp" is only a sign of a leg dysfunction—not a disease itself. An increase in either the frequency or intensity of seizures may signal worsening of the underlying disease condition; however, progression of seizures does not always imply progression of disease. On the other hand, the addition of other signs of brain dysfunction does imply the progression of the disease. Seizures may become more frequent or more intense through kindling, long-term potentiation, sleep deprivation, or inefficacy of medications. If new clinical signs develop over time, progression may be implied (see Figure 4.4). Conversely, the lack of development of new clinical signs related to brain dysfunction would suggest a static disease, such as genetic forms of epilepsy, brain trauma, or stroke. The longer the patient goes without showing progressive dysfunction of the brain, the

more likely they are to have static disease. If new signs of *brain dysfunction* are developing, they may be related to:

- Progression of the underlying problem (e.g., brain tumor growing or encephalitis worsening)
- A direct result of the seizures (brain trauma) or unrecognized seizures
- An effect of the medication
- The development of a separate problem either intra or extracranial

Relating the development of new clinical signs to the proximity of medication changes or seizures may help differentiate from the progression of the underlying disease. It is important to also remember postictal deficits may persist for several days (up to a week, possibly) after a seizure. Therefore, be careful with prognostication in the immediate postictal time period. Blindness following a seizure does not necessarily imply disease progression.

A chronic history of epileptic seizures may allow the clinician to classify the patient into an epileptic syndrome (see Chapter 3) without diagnostic tests. When a client chooses a *conservative* approach over a *diagnostic* approach, the clinician can gather important and relevant information regarding the syndromic classification, based on the development of additional signs of brain dysfunction (a progressive problem) or the lack of development of new signs (a static condition). The "window of opportunity" of progressive disease, which is the time one would expect additional signs of brain dysfunction to show up, is generally less than 8 months in the author's experience, however, the literature suggests 1–3 years (Pákozdy *et al*., 2008; Hülsmeyer *et al*., 2010; Fredsø, *et al*., 2014). For example, a growing or changing problem in the brain, such as a brain tumor or encephalitis would be expected to result in progressive signs of brain dysfunction within months of the onset of seizures. Of course, this is a generalization. It is thought certain "benign" brain tumors (i.e., meningioma, especially in cats) may grow for months or years before the development of seizures and many more months before the development of other signs of brain dysfunction, which may explain how they can get so big without causing significant problems (often just epileptic seizures). On the other hand, when presented with a 5-year-old Labrador Retriever who has been having epileptic seizures since it was 2 years old, it is most assuredly a diagnosis of idiopathic/genetic or unknown epilepsy (i.e., not progressive).

A change in the nature of chronic seizures may indicate the development of a new disease. Since seizures are only a sign of brain dysfunction and many disorders or diseases may result in brain dysfunction, it is possible two disease conditions may be occurring at the same time. Do not take for granted a change in seizure frequency or intensity related to idiopathic epilepsy, especially in an older patient. For example, a 10-year-old cat has an 8-year history of relatively well-controlled epilepsy. The patient presents with a sudden increase in the intensity and frequency of the seizures. The change could be the result of a natural progression of the disease, tolerance to medications, or the development of another problem that *also has seizures as a sign of that disease* (i.e., meningioma or a metabolic/reactive cause). The etiology of a seizure disorder can be generalized based on the age of presentation; however, all possible causes must be considered (Tables 5.3, 5.4, and 5.5). One cautious note regarding head trauma; if a dog or cat starts having seizures after falling off a piece of furniture (e.g., sofa, cat tree, etc.), consider the fall may be a consequence of the seizure and not the cause.

ANTI-SEIZURE MEDICATION HISTORY

Our selection of anti-seizure medications is limited to veterinary patients. There are only a few "tools in the toolbox"; therefore, it is essential to know what experience, if any, the patient has had with anti-seizure medications. If negative side effects prevent the continued use of a medication, it should be *failed* and removed from the management array (i.e., the toolbox). Knowing which

Table 5.3 Typical underlying etiology of seizures in young dogs and cats (up to 1 year old).

Developmental
Hydrocephalus
Lissencephaly, porencephaly, hydranencephaly, polymicrogyria
Caudal occipital malformation syndrome (COMS)
Intracranial arachnoid cyst
Dandy–Walker syndrome
Other—any malformation of the brain is possible
Metabolic
Electrolyte abnormality (hypoglycemia, hypocalcemia)
Hepatic encephalopathy (portosystemic shunt—microvascular dysplasia)
Renal encephalopathy
Parasitic disease
Trauma
Hypoxia
Structural trauma to the brain (bite, crush, parasitic migration, etc.)
Nutritional
Thiamine deficiency
Inflammatory
Infectious (viral, fungal, bacterial, protozoal, rickettsial, parasitic)
Noninfectious
Breed-specific encephalitis (meningitis of unknown etiology)
GME, other autoimmune (Pug, Maltese, Yorkshire Terrier)
Genetic
Demonstrated (Beagle, Belgian Tervuren, Keeshond, British Alsatian, Labrador Retriever, Golden Retriever, Collie, Poodle, Dachshund, Vizsla, and others—see Table 3.8)
Suspected (any breed)
Toxin
Heavy metals (lead, mercury, thallium)
Pesticides (organophosphates, pyrethrins, carbamates)
Slug bait (metaldehyde)
Rodenticides (bromethalin, rotenone, zinc phosphate, strychnine)
Drugs (ivermectin if P-glycoprotein deficient), illicit drugs, prescription drugs
Poisonous plants
Mycotoxins
Antifreeze
Disinfectants (hexachlorophene)
Methylxanthines (caffeine, theobromine—chocolate)
Toads (*Bufo* ssp.)
Degenerative
Storage disease (lysosomal, ceroid lipofuscinosis, glycogen, Lafora disease)
Multisystemic neuronal degeneration
Spongiform encephalopathy (leukodystrophy)
Subacute necrotizing encephalomyelopathy
Neoplasia
Intracranial
Extracranial

Table 5.4 Typical underlying etiology of seizures in dogs and cats (1–6 years old).

Metabolic
Electrolyte abnormality (hypoglycemia, hypocalcemia)
Hepatic encephalopathy (portosystemic shunt—microvascular dysplasia)
Renal encephalopathy
Endocrinopathy—secondary electrolyte abnormalities or hypoglycemia (thyroid disease, adrenal, insulinoma, leiomyoma, etc.)
Parasitic disease
Trauma
Structural trauma to the brain (bite, crush, parasitic migration, etc.)
Nutritional
Thiamine deficiency (diet change poor or incomplete diet)
Inflammatory
Infectious (viral, fungal, bacterial, protozoal, rickettsial, parasitic)
Noninfectious
Breed-specific encephalitis (meningitis of unknown etiology)
GME, other autoimmune (Pug, Maltese, Yorkshire Terrier)
Genetic
Many breeds show strong evidence for a heritable basis (see Table 3.8)
Suspected (any breed)
Uncommon in cats
Toxin (less likely with age)
Heavy metals (lead, mercury, thallium)
Pesticides (organophosphates, pyrethrins, carbamates)
Slug bait (metaldehyde)
Rodenticides (bromethalin, rotenone, zinc phosphate, strychnine)
Drugs (ivermectin if P-glycoprotein deficient), illicit drugs, prescription drugs
Poisonous plants
Mycotoxins
Antifreeze
Disinfectants (hexachlorophene)
Methylxanthines (caffeine, theobromine—chocolate)
Toads (*Bufo* ssp.)
Degenerative
Certain storage diseases may have a late onset
Lafora disease (typically before 2 years)
Ceroid lipofuscinosis (typically 1–2 years; range, 1–10 years)
Fucosidosis (4 months to 2 years)
Neoplasia
Intracranial
Extracranial
Vascular
Stroke
Hemorrhage

Table 5.5 Typical underlying etiology of seizures in dogs and cats (6 years and older).

Metabolic
Electrolyte abnormality (hypoglycemia, hypocalcemia)
Hepatic encephalopathy (acquired liver disease)
Renal encephalopathy
Cardiac disease (secondary to hypoxia)
Endocrinopathy—secondary electrolyte abnormalities or hypoglycemia (thyroid disease, adrenal, insulinoma, leiomyoma, etc.)
Parasitic disease (highly unlikely)
Trauma
Structural trauma to the brain (bite, crush, parasitic migration, etc.)
Nutritional
Thiamine deficiency (diet change, poor or incomplete diet)
Inflammatory
Infectious (viral, fungal, bacterial, protozoal, rickettsial, parasitic)
Noninfectious
Breed-specific encephalitis (meningitis of unknown etiology)
GME, other autoimmune (Pug, Maltese, Yorkshire Terrier)
Genetic
Late-onset idiopathic/genetic is suspected to occur (range, 0.5–7.5 years)
Toxin (less likely with age)
Heavy metals (lead, mercury, thallium)
Pesticides (organophosphates, pyrethrins, carbamates)
Slug bait (metaldehyde)
Rodenticides (bromethalin, rotenone, zinc phosphate, strychnine)
Drugs (ivermectin if P-glycoprotein deficient), illicit drugs, prescription drugs
Poisonous plants
Mycotoxins
Antifreeze
Disinfectants (hexachlorophene)
Methylxanthines (caffeine, theobromine—chocolate)
Toads (*Bufo* ssp.)
Degenerative
Cognitive dysfunction
Age-related neuronal degeneration/dysfunction (dx: by exclusion)
Storage disease (e.g., Lafora disease)
Neoplasia
Intracranial
Extracranial
Vascular
Stroke
Hemorrhage

medication(s) the patient has failed is made easier by following the rule: "treat to effect or to side effect." If a medication is failed, there is no need to revisit it. A common mistake in treatment is the *premature* failure of a drug, either due to perceived ineffectiveness (usually at subtherapeutic doses) or intolerance of often *temporary* side effects (leading to pseudo-drug resistance). If the clinician is going to fail a medication, they need to be certain it will not be revisited in the future. Avoiding the "see-saw" effect of medicating is best done through the use of one medication at a time. There is no way to predict which medication may work or not, which medication may create intolerable side effects, or which medication(s) may be a complete success. Choosing an anti-seizure medication is like picking an antibiotic when you do not know what the source of the infection is (see Chapters 4 and 6). You hope to choose a drug with broad-spectrum activity and minimal side effects. Knowing which medications, the patient has been on in the past, why they are not on them now, or what side effects they experienced may help piece together a more appropriate management plan. For example, if I suggest phenobarbital to a client and they mention intolerable side effects such as sedation, polydipsia, and polyphagia, I will then ask when those side effects occurred. Since the side effects of phenobarbital often resolve within a few weeks of beginning treatment, it may be a medication that can be revisited, if in fact the medication was discontinued prematurely. Specific questions that should be answered include:

- A complete list of any medications tried, the maximum doses, the length of time on each medication, and any combination with other medications.
- Any negative side effects associated with a particular medication or combination of medications.
- Any benefits of any medication or combination of medications. This should include reduced frequency or intensity of seizures, as well as reduction of side effects.
- If any drug was discontinued, why was it discontinued?
- Any other modalities used to treat epilepsy (integrative medicine, diet changes, etc.).

Question the owner about lifestyle. Are they able to monitor the pet? Are they able to give a medication every 12 h? What about every 8 h? Knowing a little about the client's lifestyle may help the clinician formulate a therapy plan. For example, a person who works 8–10 h a day may not be able to dose levetiracetam every 8 h to their toy poodle. In this situation, zonisamide might be a better choice simply because of the dose schedule. As veterinarians, we often run into the economic realities of diagnosis and treatment of disease. A client's financial ability to diagnose or treat the condition may warrant which medication is considered, how aggressive to be with medication choices, and which diagnostic tests have the best cost/benefit ratio. Oftentimes, anti-seizure medications are discontinued prematurely due to perceived toxic side effects, worry, or suspicion of potential toxic effects. The veterinarian needs to be a source of empathy, as well as factual knowledge regarding the use of anti-seizure medications, progression of disease, treatment, and prognosis. Many side effects will resolve spontaneously with time or slight alterations in dose while still maintaining adequate seizure control.

PHYSICAL AND NEUROLOGICAL EXAM

If history is the foundation for the building of a differential list, an accurate physical and neurological exam culminating in a neuroanatomical localization is the framework. For those who struggle with neurology and neuroanatomical localization, fear not, for when presented with a complaint of epileptic seizures, half the battle is over. Epileptic seizures are always a sign of *brain* dysfunction. Your localization is done. As mentioned before, seizures are not a disease but a *sign* of disease, much like a limp is a sign of dysfunction of a limb (note: very important to remember). A history of seizures only gives a beginning, but fortunately, the puzzle we piece together when presented with a patient having seizures is very similar no matter how many

times you solve it. This may lead to complacency. One of the fundamental tenants of the physical and neurological exam is to approach every case as if it will be the most unique and unusual workup you have ever seen. This allows the clinician to look at the case with *eyes wide open*. If you approach the case in a systematic and logical way, much like pilots use a checklist prior to a flight (no matter how routine a flight is), you will miss less and see more. As my mentor used to say, "you are only as good as your differential list." All clinicians should also be aware the more you look at the problem and the greater number of eyes on the problem, the more likely you will see the problem. Finally, the individualistic approach to the patient as opposed to what epidemiologic studies say allows for discovery and focusing your attention on the patient as opposed to the disease. Seizures may be stopped only 1% of the time. But what if this patient is the 1 out of 100?

Often, the physical and neurological exams are combined to create less stress for the patient. Approach animals directly and safely. If beneficial, use the pet owner to help calm the patient or stand behind you as you perform the exam, in order to get the patient to look straight ahead. We all have our preferences as to how to perform an accurate, stress-free, and safe physical exam. In patients who might be leery of a stranger, try to establish trust by starting at the tail end, scratching the base of the tail, and use a calm but firm voice to tell the patient "You're fine," over and over again. As the patient gets comfortable with your presence and begins to realize the exam is not a life-or-death threat, they will usually relax. You can then move forward. Essential components of the physical exam should include:

- General appearance, weight, mentation, and symmetry
- Hair coat
- Abdominal palpation
- Long bone, joint, and muscle palpation. Palpate for pain, range of motion, and effusion
- Femoral pulse palpation
- Checking for differential cyanosis (prepuce or vulva)
- Lymph node palpation
- Ears
- Rectal exam
- Heart and lung auscultation, ideally with concurrent palpation of femoral pulses
- Upper airway auscultation
- Oral exam and mucus membranes

A good, thorough physical exam may identify comorbidities or possible metabolic causes of epileptic seizures, such as an abdominal mass, cardiac disease, or suspicion of endocrine disease. The clinician may discover differential cyanosis, jaundice, signs of anemia, bleeding disorders, abdominal masses, heart murmurs, thoracic disease, and indications of endocrine disease.

The neurological exam is also very systematic and logical. If the clinician is unfamiliar with the neurological exam, following a defined checklist is helpful (see Appendix 2). The neurological exam itself is often interwoven with the physical exam. In performing the neurological exam, the clinician is looking for neurological deficits. Any deficits, that are noted, should be considered relative to when the last seizure occurred. It is not unusual for a deficit to be present several days after a seizure. Persistent deficits could be due to a consequence of any medications (e.g., sedation or ataxia), the result of permanent brain damage from severe seizures (i.e., status epilepticus or cluster events), or because of the underlying cause of the seizures. A neurological deficit does not indicate progression and has little etiological significance, unless persistent and progressive. In

cases where deficits are persistent and/or progressive, there should be a suggestion of diffuse structural or metabolic causes for the epileptic seizures. The clinician would automatically localize to the brain simply because epileptic seizures occurred. It is certainly possible to be even more exact in the localization; however, it does not add to the differential list or diagnostic testing choices. Serial neurological examinations should be performed days or weeks apart if the clinician is attempting to distinguish between ictal, postictal, and interictal deficits. The presence of subtle weakness, ataxia, lethargy, or dullness could also be due to side effects of antiepileptic drugs (especially phenobarbital and potassium bromide). Oftentimes, with a slight (e.g., 10–25%) reduction in medications (assuming seizures are well controlled), the deficits will resolve. The neurological exam should include the following:

- Assess mentation. Is the patient behaving normally for the environment?
- Assess gait. Try to observe the patient as they freely move around the exam room (if possible). Is the patient weak? Do they have any ataxia? Are they limiting their own movement (self-restriction = pain)? Are they stiff or lame? Do they circle in the room? Are the circles tight or wide?
- Assess posture. Is there a head tilt, head turn, torticollis, lordosis, opisthotonus, neck neutral or dropped head, kyphosis, or scoliosis?
- Assess movement disorders. Tremors, tics or twitches, or head bobbing.
- Perform a cranial nerve exam and note any deficits.
- Check proprioception. A proprioceptive deficit is not a localizing sign; it only tells you a problem exists in the nervous system, not where that problem is. For example, an older patient with recent onset seizures could have a proprioceptive deficit from a herniated disk in the spine as opposed to definitively due to brain dysfunction.
- Check reflexes. Reflex changes if related to epileptic seizures, may suggest multifocal disease (encephalitis) or comorbidities.
- Perform a fundic exam. Ruptured retinal capillaries may suggest hypertension/stroke, while gold medallion lesions, other changes to the fundus, or anterior uveitis may be reflective of systemic disease or infection/inflammation.

Performing the neurological and physical exam in a logical, stepwise, and stereotypical manner (following a checklist if necessary—see Appendix 2) is an essential step to creating an accurate differential list. From this list, further testing can be proposed.

MINIMAL DATABASE

A minimal database is a collection of initial and essential diagnostics tests. The results of the tests will rule out the obvious metabolic causes of epileptic seizures (e.g., electrolyte abnormalities), show indications of other possible tests to run (e.g., fasting and fed bile acids, lead, etc.), provide a baseline for determining which anti-seizure medication to use, evaluate anti-seizure medication side effects (i.e., liver/kidney values), and help to prepare for possible anesthesia. A recommended minimal database should be evaluated with adjustments based on suspicion of disease, age of the patient, and history (Table 5.6). In general, it should consist of a complete blood count (CBC) and biochemical profile with thyroid evaluation (T4, Free T4, and TSH). A urinalysis is also recommended. Blood pressure should be measured if the patient tolerates it. A fecal exam should be included in pets younger than 1-year-old or those that roam and are otherwise at a higher risk of exposure to environmental parasites. A three-view thoracic, radiographic metastasis check is recommended in any patient older than 6 years as a screening test for metastasis, especially if

Table 5.6 Minimal database and additional testing considerations.

CBC
Biochemical profile:
Sodium, Potassium, Chloride, Calcium, Phosphate
Alanine Aminotransferase[a], Alkaline Phosphatase[a], Total Bilirubin, Fasting Bile Acids or Ammonia
Creatinine, Albumin, Glucose[a] Cholesterol, Triglycerides, Total Protein
Urinalysis (incl. sediment cytology)
Additional Tests (based on suspicion or necessity)
Fasting (12 h) and Post Prandial (2 h) Bile Acids / or Fasting Ammonia
Abdominal Ultrasound
Thyroid (T4, Free T4 and TSH)
Fructosamine, Glucose Response Curve and or Glucose:Insulin
Creatine Kinase / Lactate (if muscle disease suspected)[a]
Serology/PRC for regionally specific infectious agents
B_{12} if Cobalamin malabsorption is suspected
Ionized Calcium
Specific tests for toxins or toxicological screening
Specific tests for inborn errors of metabolism (oligosaccharides, glycosaminoglycans, purines, pyrimidines, quantification of amino acids, and organic acids) in serum, CSF or urine

[a] May be abnormal following an epileptic seizure.

advanced testing requiring anesthesia is contemplated. Additional diagnostics may be advised based on physical exam and history (e.g., echocardiogram, electrocardiogram, abdominal ultrasound, fasting and fed bile acids, multidrug resistance 1 mutation, etc.).

COMPLETE BLOOD COUNT (CBC)

Results of a CBC, which may be abnormal in epileptic patients, include:

- Anemia (e.g., lead toxicity)
- Polycythemia
- Leukocytosis
- Leukopenia
- Nucleated red blood cells (i.e., lead toxicity)
- Thrombocytopenia
- Ideally, a white cell differential should be included with the CBC. A manual platelet count is necessary if the results indicate thrombocytosis.

BIOCHEMICAL PROFILE

Results of a biochemical profile, which may be abnormal in epileptic patients or suggestive of a metabolic disturbance, include:

- Hypo or hyperglycemia (e.g., vascular disease secondary to diabetes and insulinoma).
- Elevated Blood Urea Nitrogen (BUN) (intestinal bleeding indicating more serious coagulopathy)

- Azotemia (renal encephalopathy)
- Electrolyte abnormalities (e.g., calcium, potassium, and sodium)
- Severe acid–base abnormalities
- Elevations of hepatic enzymes and bilirubin (hepatic encephalopathy)
- Hypo or hyperthyroidism

URINALYSIS

There are no abnormalities of a urinalysis, which would be pathognomonic for a seizure disorder. However, urine may be collected for metabolic screening of storage diseases, which could result in a seizure disorder. Identification of specific organisms in the urine such as *Aspergillus* may prompt further testing (i.e., serology) (Dallman *et al*., 1992). Additionally, as part of the minimal database, a urinalysis may be helpful in further classification of comorbidities either related to the underlying disease process or the accumulation of disease in geriatric or otherwise metabolically deranged patients. It can also provide a baseline to be used for future evaluation of certain anti-seizure drugs (e.g., topiramate).

FECAL ANALYSIS

A fecal analysis should be performed in all young (<1 year) patients who present with a complaint of seizures. A heavy parasite burden could be an underlying cause of epileptic seizures, particularly *coccidiosis*. While modern antiparasitic preventatives are generally very effective, young animals, in particular, may be more susceptible. Be wary of histories where a young animal is exposed to farmland, unsanitary conditions, or poor husbandry.

ADDITIONAL NON-INVASIVE TESTS

SPECIAL BLOOD AND URINE TESTS

Blood lead determination should be tested in any animal suspected of having exposure to lead or where there are areas of historically high incidence of lead poisoning. This is due to chronic exposure and often seizures are the only presenting clinical sign. Any patient with known exposure to lead should have blood lead levels tested. An acute onset of seizures usually combined with a history of known ingestion, exposure, or an acute history of vomiting, diarrhea, or unexplainable hypersalivation, excitability, obtundation/lethargy, hyperthermia, bradycardia, or tachycardia is highly suspect for a toxicity cause of seizures. Any other affected pets or humans in the household should be suspicious of an environmental toxin. The identification of specific neurotoxins through hematological examination is nearly impossible unless the specific toxin is known and an assay for the toxin is available (e.g., marijuana). Be wary of human testing labs and "normal" ranges for toxins. These normal values may still be in the toxicity range for pets. The author evaluated and investigated a case of seizures in a puppy, where a <1-year-old human in the family also had new onset unexplained seizures (a fact which came out in the history when the pup was examined). When the well-water was screened for toxins, high levels of nitrates (although high *normal* for human adults) were found. Seizures in the puppy and the human child ceased once the well-water was replaced with bottled water. The family lived in low-lying farmland, where it was suspected nitrates from fertilizing fields had contaminated the shallow well.

Metabolic screening tests for certain storage diseases (see Table 5.7) may be available and should be performed in all young animals (<12 months) where epileptic seizures are a primary

Table 5.7 Lysosomal storage diseases associated with epileptic seizures.

Disease subgroup/ storage disease	Reported breeds
Glycoproteinoses	
Fucosidosis	English Springer Spaniel
Mannosidosis	Domestic short-haired cats, domestic long-haired cats, Persian cats
Neuronal glycoproteinosis (Lafora disease)	Basset, Beagle, Poodle (mini and standard), Wirehaired mini Dachshund, Chihuahua, Pembroke Corgi, Pointer, mixed-breed dog
Galactosialidosis	Schipperke
Oligosaccharidoses	
Glycogenosis type Ia (von Gierke disease)	Maltese
Glycogenosis type II (Pompe disease)	Lapland dog, domestic short-haired cat
Glycogenosis type IIIa	Curly-Coated Retriever
Glycogenosis type IV (Andersen disease)	Norwegian Forest cat
Sphingolipidoses	
Gangliosidosis GM_1 type I (Norman–Landing disease)	Beagle Cross, English Springer Spaniel, domestic short-haired cat, Siamese cat
Gangliosidosis GM_1 type II (Derry disease)	Alaskan Husky, Portuguese Water Dog, Shiba Dog, Korat cat, domestic short-haired cat, Siamese cat
Gangliosidosis GM_2 type I (Tay–Sach disease)	German Shorthaired Pointer, Japanese Spaniel
Gangliosidosis GM_2 type II (Sandhoff disease)	Golden Retriever, domestic short-haired cat, Korat cat
Glucocerebrosidosis (Gaucher disease)	Sydney Silky Terrier
Globoid cell leukodystrophy (Krabbe disease)	Basset Hound, Beagle, Bluetick Hound, Cairn Terrier, Irish Setter, Miniature Poodle, Pomeranian, West Highland White Terrier, domestic short-haired cat, domestic long-haired cat
Sphingomyelinosis (Niemann–Pick disease)	
Type A	Miniature Poodle, Balinese cat, Siamese cat
Type B	Boxer, domestic short-haired cat
Type C	Domestic short-haired cat
Metachromatic leukodystrophy	Domestic short-haired cat
Mucopolysaccharidoses	
Mucopolysaccharidosis type I (Hurler disease, Scheie disease, Hurler/ Scheie disease)	Mixed-breed dog, Plott Hound, Rottweiler, domestic short-haired cat
Mucopolysaccharidosis type II (Hunter disease)	Labrador Retriever, Miniature Pinscher, domestic short-haired cat, Siamese cat
Mucopolysaccharidosis type III A and B (Sanfilippo disease)	Dachshund (type A), New Zealand Huntaway dog (type A), Schipperke (type B)

(*Continued*)

Table 5.7 (Continued)

Disease subgroup/ storage disease	Reported breeds
Mucopolysaccharidosis type VI (Maroteaux–Lamy disease)	Chesapeake Bay Retriever, Miniature Pinscher, Miniature Schnauzer, Welsh Corgi, domestic short-haired cat, Siamese cat
Mucopolysaccharidosis type VII (Sly disease)	German Shepherd Dog, mixed-breed dog, domestic short-haired cat
Mucolipidosis II (I-cell disease)	Domestic short-haired cat
Proteinoses	
Ceroid lipofuscinosis (Batten disease)	American Bulldog, American Pit Bull Terrier, American Staffordshire Terrier, Australian Cattle Dog, Border Collie, Chihuahua, Cocker Spaniel, Corgi, Dachshund, Dalmatian, English Setter, Golden Retriever, Labrador Retriever, Miniature Schnauzer, Polish Owczarek Nizinny Dog, Queensland Blue Heeler, Saluki, Terrier crossbred, Tibetan Terrier, Yugoslavian Sheepdog, domestic short-haired cat, Siamese cat

Adapted from Dewey, C.W. 2008.

complaint and obvious causes have been ruled out (i.e., portosystemic shunt, toxicity, and metabolic disease).

Bile Acids

The evaluation of fed and fasting bile acids may aid in the diagnosis of epileptic seizures secondary to hepatic encephalopathy. Indications for performing bile acids analysis may include:

- Young patient with epileptic seizures (<3 years old)
- Alterations in liver enzymes on routine biochemical profile
- Low BUN
- Hypoalbuminemia
- Hypocholesterolemia
- Microcytic red blood cells
- Intermittent alterations in mentation status, particularly related to post-meal times

Liver enzyme values are primarily a reflection of hepatic cellular damage or increase secondary to induction through various medications (e.g., phenobarbital, steroids). Bile acids are a measure of liver *function*, and reduced liver function is an early indicator of possible hepatic encephalopathy. Any liver pathology may result in altered liver function; however, the most common conditions are portosystemic shunt and hepatic microvascular dysplasia. Bile is synthesized by the liver, stored in the gall bladder, and excreted into the duodenum in response to a meal. Bile is absorbed through the intestinal walls into the bloodstream and then recycled back to the liver. An increase in serum bile acids, either solely or in response to a meal will suggest liver dysfunction. Bile acids should always be measured with fasting (> 12 h) and fed (2 h after a meal) samples. Occasionally, a postprandial (fed) sample will be lower than the fasting sample. This is more commonly observed in patients with hepatic microvascular dysplasia (Dewey, 2008).

Insulin/Glucose Ratio

Serum insulin and glucose relationships may help in the aid of diagnosing insulinoma and extrapancreatic tumors, which may result in hypoglycemia (Bagley *et al*., 1996b). In the case of beta cell-secreting pancreatic tumor, insulin levels will be increased relative to normal blood glucose levels, although sporadic secretion is possible leading to potential false-negative results. Extrapancreatic tumors (commonly leiomyoma and leiomyosarcoma) causing hypoglycemia will typically have normal insulin levels with low blood glucose levels (Bagley *et al*., 1996b).

Lead and Other Possible Toxins

Serum lead levels should be measured in young patients with a history of inappropriate chewing or eating, especially, if the behavior is present in an environment where lead exposure is possible (old houses). While generally considered rare, exposure to lead is, nonetheless, still a possible differential. Older homes may contain lead pipes or lead paint. Other possible sources of lead include curtain weights, fishing weights, and lead shot, to name a few. If the patient's history is suggestive of exposure to other heavy metals (e.g., mercury and thallium), specific testing of identified heavy metals should be performed. If in doubt, the clinician can call the Americal Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center at 888-426-4435 or www.aspca.org/pet-care/animal-poison-control. Toxic substances, which may induce epileptic seizures, are listed in Table 5.8, although very few confirmatory diagnostic tests are available. The diagnosis is usually based on presumption, unless someone has witnessed ingestion. Treatments consisting of supportive care, specific therapy (such as chelating therapy in

Table 5.8 Toxins associated with epileptic seizures.

Substance	Source
Aluminum phosphide	Rodenticide, insecticide, fumigant
4-Aminopyridine (Avitrol)	Bird control bait
Amphetamine/methamphetamine	CNS stimulant, psychoactive drug
Anatoxin-*a*	Blue-green algae
Benzyl alcohol	Solvent (ink, paint, lacquer), photographic developer
Bromethalin	Rodenticide
Carbamates	Insecticide, organophosphate pesticide
Chlorinated hydrocarbons (organochlorines)	Insecticides such as dichloro-diphenyl-trichloroethane (DDT)—Historically banned
Cicuta sp. (water hemlock)	North American wild plant
Cocaine	Illicit drug
N,*N*-Diethyl-*m*-toluamide (DEET)	Insect repellent
Ethylene glycol	Antifreeze
Fluoroacetate (1080)	Rodenticide, carnivore control (wild dogs, dingo, fox, coyote, opossum, etc.)
5-Fluorouracil	Chemotherapeutic (topical cream)
Hexachlorophene	Surgical scrub, soil fungicide
5-Hydroxytryptophan (5-HTP)	Over-the-counter serotonin precursor
Ivermectin	Broad-spectrum antiparasitic
Lead	Heavy metal (solder, batteries, shot, weights, paint, water pipes)

(*Continued*)

Table 5.8 (Continued)

Substance	Source
Levamisole	Anthelmintic microfilaricide
Cannabis (marijuana)	Psychoactive, medicinal, and recreational drug
Mercury	Heavy metal (thermometers, fluorescent lights, switches)
Metaldehyde	Slug bait
Methylxanthines	Chocolate, caffeine, theophylline
Metronidazole	Antibiotic
Mycotoxins (Penitrem A / Roquefortine	Mold, garbage, compost
Narcissus sp.)	Daffodil plant, jonquil plant
Opiates	Morphine and cats
Organophosphates	Insecticide, pesticide
Organophosphorus	Insecticide, anthelmintics, herbicide
Piperazine	Anthelmintic
Plants	Numerous household, ornamental, and wild plants
Pseudoephedrine	Cold medicine
Pyrethrins	Insecticide
Selective Serotonin Reuptake Inhibitors (SSRIs)	Medication (prescription)—behavioral conditions
Sodium Monofluoroacetate (Compound 1080)	Rodent, fox, opossum bait
Strychnine	Gopher, mole, coyote bait
Tetanus toxin	*Clostridium tetani* infection
Tremorgenic mycotoxins	Penitrem A and roquefortine (garbage, moldy food)
Venom	Amphibians (toads), bees, wasps, reptiles
Zinc phosphide	Rodenticiderus

the case of lead), and detoxification procedures should be used (e.g., activated charcoal, atropine, etc.). Ivermectin and other avermectins should be considered a possible source of toxicity in collies and other breeds known to potentially carry the MDR1 mutation. Certain toxins can be identified in vomitus and feces. Freezing samples of vomitus or feces may aid in the diagnosis.

Metabolic Screen

Metabolic screening tests look for the presence of abnormal metabolites in serum, urine, and cerebral spinal fluid (CSF). The presence of certain metabolites may suggest a lysosomal storage disease or organic aciduria (Table 5.7). If indicated, based on the initial screening test, additional testing such as looking at whole blood or muscle biopsies may be recommended. Specific genetic tests are available for certain diseases, and new genetic identifiers are certain to come in the future. Treatment if possible is directed at replacing the missing enzyme in the case of storage disease, dietary changes, or the addition of vitamin supplementation to compensate for the abnormal metabolism.

THERAPEUTIC DRUG LEVELS

Therapeutic drug monitoring is considered a standard of practice in patients who are receiving certain anti-seizure medications. Drug monitoring is important because certain individuals may

not have the same disposition to drugs relative to the standard population. Monitoring drug levels allows the clinician to make precise adjustments in medications and anticipate needed changes. Not all medications can be monitored, and it is not necessary to monitor many of the current, safer medications. The more commonly monitored drugs include phenobarbital and potassium bromide. The purpose of therapeutic drug monitoring is to develop guidelines for treatment (i.e., add more drug, take away drug), establish a baseline level, help to determine the etiology of possible side effects, determine or modify dosage schedules, and monitor for the possible development of toxicity (Boothe, 1998). Drug monitoring should occur:

- After any loading dose is given (if appropriate)
- Once the patient reaches steady state
- When seizures are controlled (to establish baseline)
- Anytime the dose is changed (if appropriate) including if the patient has a seizure
- Routinely during the course of therapy (at steady state and then based on drug and patient reaction to the drug—typically every 6 months)

It is very important to remember drug failure should not be considered just because a patient is still having seizures and their medication levels are in the "reference range." The reference range is only a guideline from which we would expect the majority of patients to have a favorable response. Some patients will have their seizures controlled at the low end of the range and others at the high end of the range. Furthermore, for a small number of *outliers*, they may have their seizures controlled successfully below or above the reference range. A very common mistake is to add in a second anti-seizure medication because phenobarbital is "not working" when levels are *in the reference range*. Oftentimes, the patient simply needs an increase in the dose of phenobarbital to find the "Goldilocks zone" (see Chapter 6). If above the range, therapeutic monitoring may alert the clinician to more vigilance regarding potential adverse side effects (such as liver failure). Consult your testing laboratory for appropriate sample submission. Serum separator tubes should not be used as the silicone medium may bind certain anti-seizure medications (Boothe *et al.*, 1996). If the half-life of the drug is 3× longer than the dosing interval, the peak and trough samples will be similar. For example, the dosing interval of phenobarbital is every 12 h. Three times the dosing interval would be 36 h. Since the half-life of phenobarbital in dogs (generally speaking) is >36 h, peak and trough levels should be similar. While it is always safest to take a trough level (as close as possible to the next dose), it is not always necessary in regard to phenobarbital (Levitski and Trepanier, 2000). If, however, there are questions as to efficacy and hypermetabolism, trough levels are recommended. In the case of hypermetabolism, where the half-life may be less than expected, the half-life can be calculated by having both serum and trough levels measured (Boothe, 1998). The formula for calculating serum half-life can be found in Chapter 6 and Appendix 3. For specific suggestions for therapeutic drug monitoring, see Table 5.9.

RADIOGRAPHS

Radiographs are not an essential test for the diagnosis of epileptic seizures; however, they can be beneficial as an initial screening test for thoracic metastasis, microhepatica (e.g., portosystemic shunt), or hepatomegaly. Often, three-view thoracic radiographs (right and left lateral as well as ventrodorsal views) are used to screen for obvious metastatic disease in older patients prior to performing advanced imaging such as MRI. If metastatic disease is present, the pathway of diagnostic testing may be altered accordingly. Radiographic evaluation of the thorax may also reveal comorbidities, such as thoracic masses, cardiac disease, and diaphragmatic hernia, which may affect anesthetic protocols and diagnostic recommendations. An enlarged or small hepatic silhouette may suggest underlying liver disease.

Table 5.9 Therapeutic drug monitoring recommendations.[a]

Why performed
Determine the lowest effective concentration in serum
Lack of expected effect at typical doses
Determine if serum steady-state fluctuations are present (chronic therapy)
Prevention of toxicity
Evaluation of compliance
Disease state has the potential to alter drug disposition
Fine-tune serum level for the individual
Assess for hypermetabolism
Phenobarbital
2–3 weeks, 6 weeks, 3 months, 6 months, 1 year, and then every 6 months while on chronic therapy
2–3 weeks after any dose change (3–4 weeks for cats)
Anytime with suspected toxicity
Anytime there are more than two seizures between measurements
Sample in the morning, fasted patient, immediately before next dose
Serum chemistry values every 6 months. Increased alkaline phosphatase (ALP <5× above normal) and alanine aminotransferase (ALT <2× above normal) are expected (hepatic microenzyme induction). Persistently increased aspartate aminotransferase (AST) or gamma-glutamyl transferase (GGT) is a cause for concern (hepatocellular damage). If concerned, check fasting and fed bile acids
Potassium bromide
1 month, 4 months, and then every 6 months while on chronic therapy
1 week after loading and then as above
9 weeks after any dose change
Anytime with suspected toxicity
If increased seizure events or toxicity following diet change or renal disease
Anytime there are more than two seizures between measurements
Sample in the morning, fasted patient, immediately before next dose
Felbamate
2 weeks, 6 weeks, 3 months, 6 months, 1 year, and then every 6 months while on chronic therapy
2 weeks after any dose change
Anytime with suspected toxicity
Anytime there are more than two seizures between measurements
Sample in the morning, fasted patient, immediately before next dose
Serum chemistry values every 6 months to evaluate for liver toxicity
Complete blood count every 6 months to evaluate for blood dyscrasia
Zonisamide[a]
CBC, blood chemistry (incl. bicarbonate), and venous blood-gas analysis at 2 weeks, 1 month, and then every 6 months if on chronic therapy to evaluate for idiosyncratic reactions
Levetiracetam[a]
CBC and blood chemistry at 2 weeks, 1 month, and then every 6 months if on chronic therapy to evaluate for idiosyncratic reactions
Topiramate[a]
CBC and blood chemistry and urinalysis at 2 weeks, 1 month, and then every 6 months if on chronic therapy to evaluate for idiosyncratic reactions, including renal calculi

[a] Many of the newer-generation medications have a wide safety margin and low side effects associated with high serum concentrations, making therapeutic drug concentration evaluation optional.

ABDOMINAL ULTRASOUND

An abdominal ultrasound may be part of a minimal database in older (> 8 years) and younger (< 1 year) patients who present with seizures. Abdominal ultrasound may also be indicated in cases where a history of vomiting, anorexia, diarrhea, CBC, or biochemical profile alterations (e.g., hypoglycemia and changes in liver values) is encountered. Similar to radiographs, abdominal ultrasound can provide a relatively good diagnostic yield with no risk of anesthesia to the patient, for comorbidities, if present.

ADVANCED DIAGNOSTICS (INVASIVE OR REQUIRING ANESTHESIA)

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging is the gold standard for imaging the brain in veterinary and human patients. MRI provides three-dimensional imaging of the brain with excellent soft tissue resolution and contrast between tissues. As imaging techniques, hardware, and software advance, we are now able to not only look at the gross structure of the brain but also at cellular structure, functional alterations of the brain and evaluate the brain for metabolic changes. As we contemplate the possibility of an MRI in a patient, we must balance the inherent risk of anesthesia against the reward of the test. The only reason to perform an MRI is if the results will change the possible treatment outcome (e.g., surgery or specific medications), lead to quality-of-life decisions (e.g., vascular accident vs. neoplasia), or for peace of mind (as in the case of a drug-resistant epileptic). In certain situations (such as toxin ingestion), MRI may be delayed to allow for the natural resolution of the seizures along with the elimination of the toxin (i.e., *reactive* or *provoked* seizures), but changes on MRI examination can be highly suggestive of toxin-induced seizure activity. The changes on the MRI may be reflective of a diffuse encephalopathy (Figure 5.1). However, significant changes on MRI have been documented without toxin exposure and are

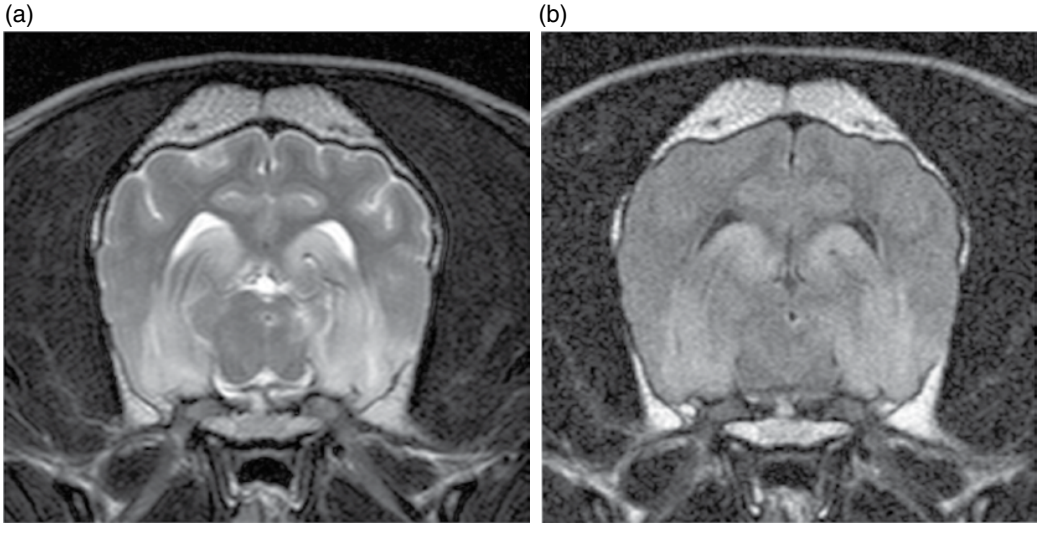


FIGURE 5.1 (a) T2-weighted axial image through the midbrain of a dog 24 h after recovery from status epilepticus resulting from metaldehyde (slug bait) ingestion. There is a bilateral, symmetrical, diffuse, hyperintense signal change involving the hippocampus and extending to the adjacent piriform and temporal lobes. (b) FLAIR axial image of the same area as (a), showing increased contrast between the pathological tissue (hyperintense), normal brain (isointense), and lateral ventricles (hypointense).

presumed to be secondary to ictal-related edema or gliosis in the case of idiopathic epilepsy (early or developing) (Mellema *et al*., 1999; Nagendran *et al*., 2021). MRI allows us to confirm a presumed diagnosis or to ensure a treatable cause of epileptic seizures has not been missed (the *peace of mind* aspect). Some exceptions to this rule may include those patients where the risks associated with anesthesia for an MRI do not outweigh the benefits (e.g., the very sick or patients with suspected increased intracranial pressure), patients who have a long history of epileptic seizures without progression of the seizures or development of any other brain dysfunction (*genetic* or *static structural*), patients with pacemakers, patients with metallic foreign bodies in the face or skull (i.e., can cause poor imaging quality due to *magnetic susceptibility artifact*), and of course financial limitations of the pet owner. Finally, in cases of metabolic/reactive/provoked seizures, if the seizures resolve with treatment, there is no need for an MRI examination.

MRI allows the clinician to "see" the soft tissues of the brain and analyze the brain for structural abnormalities, which may be responsible for epileptic seizures. If the neurolocalization is our *map*, the MRI is our *car*. The true value of a diagnosis is the application of a specific treatment based on the diagnosis. Experienced evaluators of MRI often detect abnormalities as small as a grain of rice. But they (we) have to look for that grain. The development of powerful software helps us see and think beyond our elemental means. Specific instances where employing an MRI examination should be considered include:

- The onset of focal seizures (at any age)
- Any case of status epilepticus or cluster seizures (more common with structural brain disease and reactive/provoked seizures; Zimmermann *et al*., 2009) unless there is a high degree of suspicion the seizures are secondary to metabolic, reactive, or provoked causes.
- The onset of generalized seizures < 6 months or > 6 years old
- Persistent (fixed) neurological deficits—interictal deficits
- Difficulty obtaining seizure control with the first medication (pharmacoresistant epileptics)
- Loss of chronic seizure control with medications
- Change in pattern of seizure (e.g., frequency, intensity, or type)
- Pet owner's "worry" factor (i.e., peace of mind)

We should not underestimate the power of peace of mind. Peace of mind can prevent euthanasia and encourage a pet owner to try one more increase in dosage or one more trial with another anticonvulsant. For the neurologist, this is not the easy route—you are not advocating for the pet but simply being their doctor and their voice. Idiopathic epilepsy is essentially a diagnosis by exclusion. Only 2.2% of dogs <6 years old, with epileptic seizures, have structural lesions identified on low-field MRI (Smith *et al*., 2008). The use of a high field magnet (1.5–3T) is more likely to identify subtle changes in the structure of the brain, such as cerebral disorders of migration and focal cortical dysplasia (Casey *et al*., 2014; Cocchetto *et al*., 2022; Su *et al*., 2024). The author always recommends MRI even after just one seizure but that recommendation is predicated by the fact there is a good chance the MRI will be normal. I tell clients we are looking at an individual and not a statistic. Even if there is only a 1% chance the scan will show a lesion, that may be 1 out of 100. You will not see it if you do not look (Figure 5.2).

A typical MRI evaluation will consist of various sequences used to study the anatomy of the brain (T1 weighted), pathology of the brain (T2 weighted), areas of ischemia (diffusion-weighted), and areas of hemorrhage (gradient echo images) and to distinguish, through increased contrast, the difference between the ventricles and periventricular structures (fluid-attenuated inversion recovery [FLAIR] studies) (Table 5.11). The strength of the magnet will affect the resolution of the

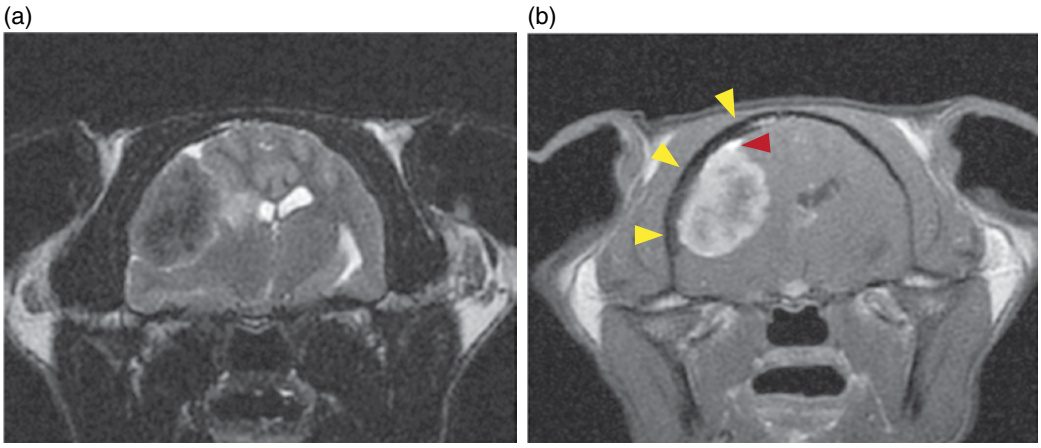


FIGURE 5.2 (a) T2-weighted, transverse image through the midbrain of a 6-year-old, female, spayed cat. A large, roughly spherical, hypointense signal change associated with a mass is present in the left temporoparietal lobe. (b) T1-weighted, post-contrast administration of the same plane as in (a). The mass has a homogeneous peripheral contrast enhancement with a poorly to heterogeneously contrast-enhancing center. Note the hyperostosis (yellow arrows) and the dural tail sign (red arrow). The mass is consistent with a meningioma, unusual for a cat this age. Images provided by Bethany DeVilbiss DVM, DACVIM – Neurology.

scan and the time it takes to acquire the images, as well as the ability to perform advanced analysis such as MRI spectroscopy, diffusion tensor imaging, and other current research-oriented techniques. 1.5 T machines are the most common in private referral practices and veterinary teaching hospitals. Although 3 T units are occasionally used, there is an increase in susceptibility artifacts with machines of higher magnetic field strength. An entire study of the brain should take roughly 45 min depending on the field strength of the machine, the skill of the operator, and of course the number of sequences. Low field magnets (0.5 T and lower) may be adequate for large lesions or obvious pathology; however, the lower spatial resolution has the potential to create false-negative studies.

There are numerous parameters that can be altered in order to change the imaging characteristics. *T1-weighted* images create excellent anatomical studies of the brain where gray and white matter is gray (isointense), CSF is black (hypointense), and fat is hyperintense. Hemorrhage may also be hyperintense on T1-weighted images depending on the various stages of iron degradation in the tissue (Table 5.10) (Figure 5.3). With a T1-weighted image, the *time to repetition* (TR) and *echo time* (TE) are both short. However, because fluid is dark (the exception is hemorrhage at 1–7 days post incident), the contrast between pathological brain tissue (causing cerebral edema) and normal brain tissue is low. In cases where disruption of the blood–brain barrier or increased vascularity of normal brain structures or abnormal tissue (tumor) is present, a contrast agent (gadolinium) can be given through IV injection, in order to . . .you guessed it . . . increase contrast. The gadolinium *enhances* the tissue by affecting the relaxation time of hydrogen ions in the tissue. Tissue that *contrast enhances* has increased vascularity and the contrast *leaks* into the brain if the blood–brain barrier is compromised. Gadolinium is the neurologist's *night vision goggles*. It enhances the contrast between normal and abnormal tissue. T1-weighted postcontrast images should always be evaluated with T1-weighted pre-contrast images.

T2-weighted images highlight fluid changes in the brain. Therefore, any abnormality of the brain resulting in edema (pathological change) is much easier to see. Because of this effect, T2-weighted images, where the TR and TE are long, are an excellent screening study for obvious pathology (Figure 5.4).

Table 5.10 Appearance of parenchymal hemorrhage on MRI sequences.

Stage	Time	Hemoglobin	T1	T2	T2* GRE
Acute	<24 h	Intracellular oxyhemoglobin	Iso	Hyper	Mix
Acute/subacute	24–72 h	Intracellular deoxyhemoglobin	Mix	Hypo	Mix
Early	3+ days	Intracellular methemoglobin	Hyper	Hypo	Hypo
Late	7+ days	Extracellular methemoglobin	Hyper	Hyper	Hypo
Chronic	14+ days	Extracellular hemichromes	Hypo	Hyper	Mix

A *FLAIR* study suppresses the hyperintense signal of the CSF in the ventricles while preserving the hyperintense signal associated with other forms of fluid, such as edema (hemorrhage may have various characteristics depending on numerous factors—see Table 5.10), thereby providing increased contrast between the ventricles and the periventricular tissue.

Gradient echo sequences are particularly useful in the identification of *hemorrhage* in the brain. The iron present in the blood of hemorrhagic tissues creates a magnetic field inhomogeneity, of which the gradient echo sequence is very sensitive. While being very sensitive to hemorrhage, the tissue contrast of the brain is poorly visualized with gradient echo images; therefore, they tend to be limited to the evaluation of hemorrhagic lesions (Figure 5.3b) (Gavin and Bagley, 2009).

Diffusion-weighted images are useful in identifying *ischemic tissue* in the brain. Extracellular water diffuses randomly in normal tissue, whereas it is restricted in ischemic tissue due to cellular swelling or *cytotoxic edema* (the water enters the cells) leading to restricted diffusion. In normal tissue, where the motion of extracellular water is random, the signal will be attenuated—as in *hypointense*. In ischemic tissue, where diffusion is reduced, the signal will be *hyperintense* (Westbrook, 1999) (Figure 5.5f). Changes in the apparent diffusion coefficient following epileptic seizure activity tend to be transient, potentially lasting only a few days (Hasegawa *et al.*, 2003). Diffusion-weighted images may be useful in determining the epileptic focus in patients suffering from status epilepticus (Hasegawa *et al.*, 2003; Hasegawa 2016). This technique may be useful if surgical treatment is considered for the management of epileptic seizures to help supplement, support, or guide additional preoperative diagnostics (i.e., electrocorticography (ECoG).

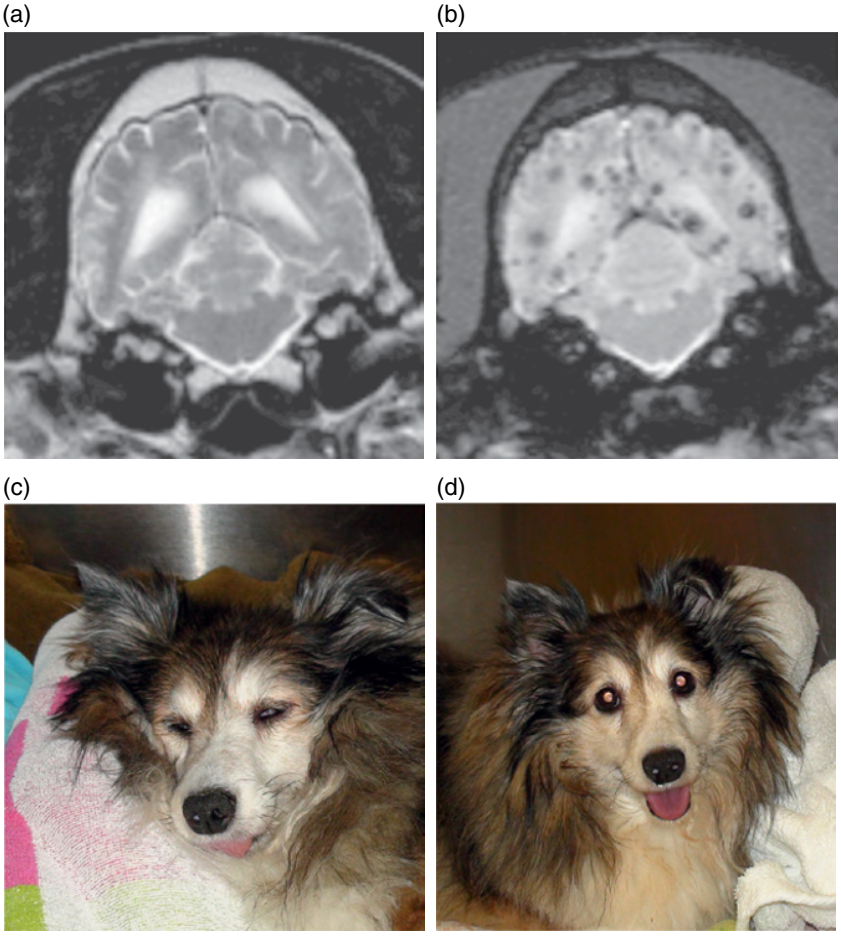


FIGURE 5.3 (a) T2-weighted, axial image through the midbrain of a geriatric dog with hyperadrenocorticism who presented for new onset seizures and decreased mentation. The brain appears essentially normal. (b) Gradient echo imaging in the same dog in the same plane as (a). There are multifocal, hypointense signal changes throughout the cerebral hemispheres, characteristic of diffuse, multifocal hemorrhagic infarcts. (c) Appearance of the stuporous, postictal dog on presentation recovering from an episode of status epilepticus. (d) Despite the significant changes in the brain, the dog recovered within 48 h and was discharged with a normal neurological exam. Phenobarbital was used to manage his epilepsy.

Diffusion tensor imaging provides detailed anatomical images of cerebral white matter tracts which can be created and visualized through three-dimensional post-processing (Jacqmot *et al.*, 2013). Diffusion tensor image atlases have been created of the feline and canine brain (Johnson *et al.*, 2020; Inglis *et al.*, 2024). Tensors are mathematical functions that describe a physical property such as location in space and direction (in this case based on the apparent diffusion coefficient of water—DWI. The individual tensors are made up of three orthogonal vectors. When multiple areas (voxels) share the same tensor, they can be aligned, forming tracts. Color is then added to differentiate the various tracts specific to their individual three-dimensional orientation. With this data, the clinician can evaluate pathology without dissection, as was in the case of Figure 5.6 (Wang-Leandro *et al.*, 2018). This particular dog presented for evaluation of epileptic seizures and was diagnosed with corpus callosum hypoplasia and dysplasia, however, because of a fair prognosis with the condition and adequate management symptomatically, histopathological

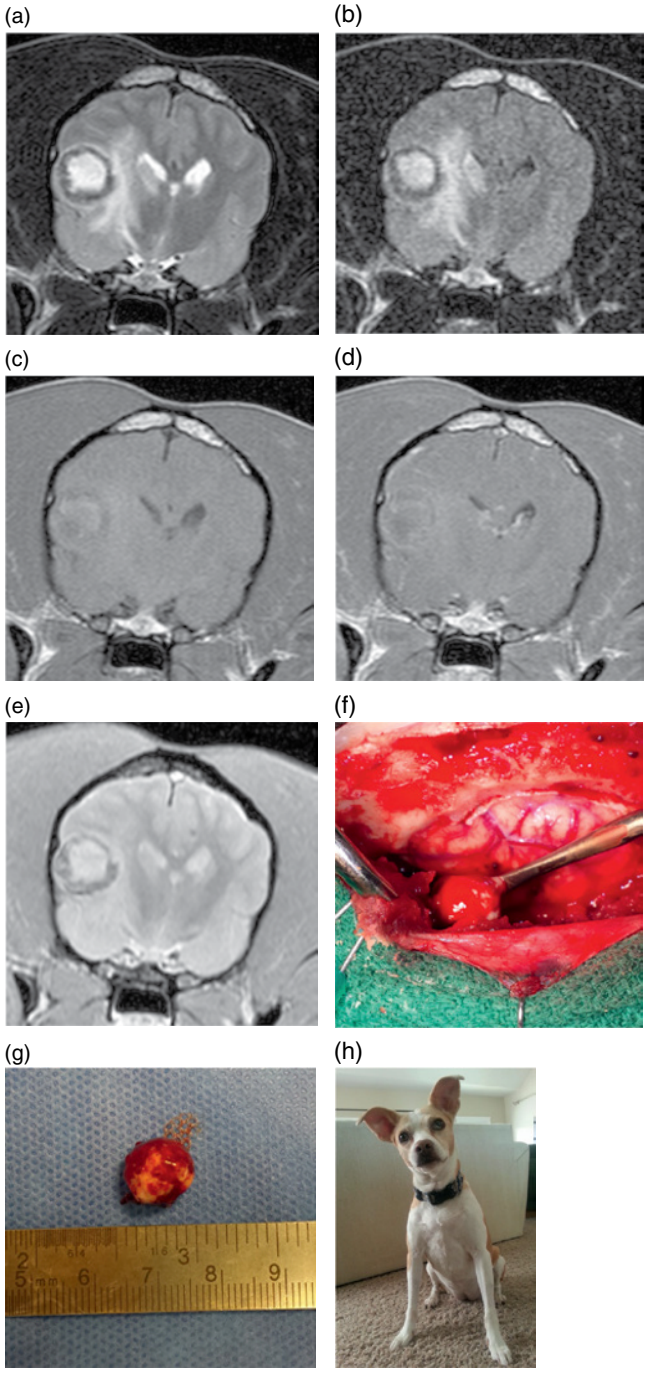


FIGURE 5.4 Standard MRI sequences through the brain of a 10-year-old canine with new onset seizures. (a) T2–weighted, axial images identify a focal, circular, hyperintense signal change in the left cerebral hemisphere surrounded by a ring of hypointense intense signal. A hyperintense signal change extends through the adjacent white matter tracts of the left cerebral hemisphere. There is a midline shift of the falx cerebri to the right and associated compression of the left lateral ventricle. (b) On FLAIR, axial images in the same plane, greater contrast is achieved between the pathological hyperintense signal changes and the lateral ventricles. (c) T1-weighted pre-contrast images show a subtle hyperintense signal change, surrounded by a hypointense ring in the left cerebral hemisphere. (d) Following the administration of gadolinium contrast agent, there is subtle enhancement of the border and interior of the structure. (e) Gradient echo images through the same plane identify hemorrhage surrounding a central, hyperintense core. (f) A semisolid mass, was removed with surgery, through a left, lateral tentorial craniectomy. (g) The mass was confirmed as a non-neoplastic congenital, vascular hamartoma. (h) The dog did not have any more seizures following removal of the mass.

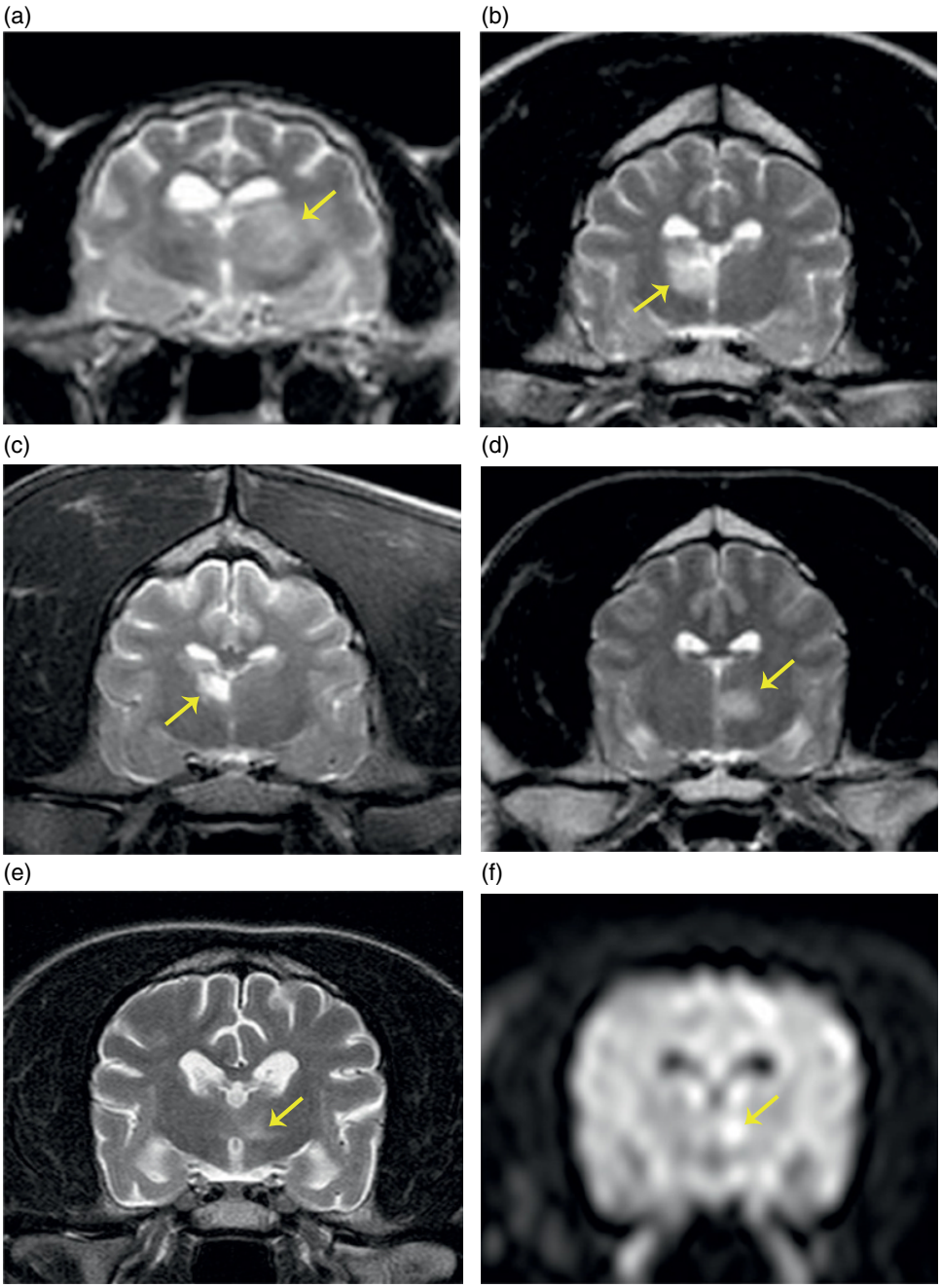


FIGURE 5.5 Various sequences of stroke in veterinary patients on MRI examination. (a) T2-weighted, axial images through the midbrain of a cat showing a poorly defined, hyperintense signal change within the right thalamus. (b) Similar to A, on T2-weighted, axial images through the thalamus of a dog, a more defined, hyperintense signal change is observed in the left thalamus. (c) T2–weighted, axial images through the thalamus of a dog showing a distinct, hyperintense signal change in the dorsal left thalamus near midline. Note also, atrophy of the right temporalis muscles. (d) T2-weighted, axial images through the thalamus in a dog showing a focal, hyperintense signal change. (e) Subtle, diffuse, hyperintense, signal change on T2-weighted, axial images of the thalamus of a dog. (f) Diffusion-weighted, axial, images of a dog through the midbrain, showing a focal hyperintense signal change in the right thalamus indicating an area of ischemia (see text). Note, in all images, no mass effect is present.

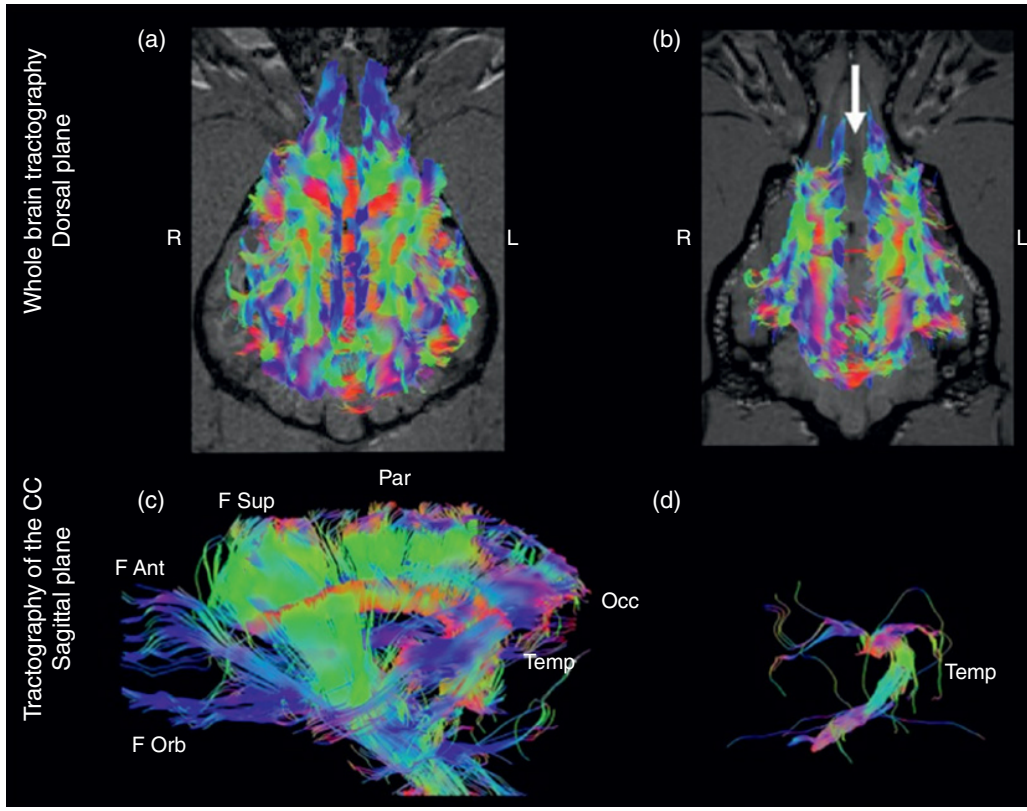


FIGURE 5.6 Diffusion tensor imaging. Whole brain tractographies registered to T1-W images at the level of the caudal colliculi depicted in a dorsal plane and corpus callosum tractographies in the sagittal plane (rostral to the left) of a 4-year-old, male healthy Beagle (a and c) and the 4-year-old, male Staffordshire Terrier mix with corpus callosum abnormalities (CCA) (b and d). The majority of axonal bundles crossing hemispheres are absent in the dog with CCA (white arrow; (b) in comparison to the healthy Beagle. Tractography of the CC revealed that only temporal fibers were present, corresponding to the discrete area of remaining white matter noticed in T2-weighted sequences (d) Color coding of tracts: Red, laterolateral axis; green ventrodorsal axis; blue, rostrocaudal axis. F Ant, frontal anterior; F Orb, frontal orbital; F Sup, frontal superior; Occ, occipital; Par, parietal; Temp, temporal. Wang-Leandro, A et al. (2018)/Frontiers Media S.A./CC BY 4.0.

evaluation (thankfully for this dog) was not possible. Diffusion tensor imaging was used for *in vivo* quantitative and visual representation of the microarchitecture of the axonal bundles. Demyelination and axonal cell loss disrupt the normal integrity of white matter tracts. This disruption is identified by measuring alterations in anisotropic diffusion (or disruptions in the common diffusion pathways of water through the *normal* tissue). Lesions of gray matter, associated with epileptogenic sites, will have an accompanying reduction in white matter tracts. This reduction can be traced to the epileptogenic area of origin. White matter changes have been demonstrated in dogs with idiopathic epilepsy (Beckmann *et al.*, 2023). In this study, dogs with idiopathic epilepsy have subtle changes in diffusion tract imaging of the cingulate area. New MRI techniques, as well as post-acquisition processing, are continuing to be developed, allowing for faster scan times and greater resolution and evaluation modalities. Diffusion-weighted and diffusion tensor images have the potential to replace the difficult-to-attain and expensive positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans often employed in human medicine to help detect the epileptogenic focus. MRI allows us to "open the door to the brain" and see what's going on.

MRI PROTOCOLS FOR EPILEPSY

The International Veterinary Epilepsy Task Force (IVETF) has developed a consensus statement regarding a veterinary epilepsy-specific MRI protocol, both for high-field and low-field machines (Table 5.11) (Rusbridge *et al*., 2015). Although the protocol recommendations are specific for the evaluation of epileptic patients, following them will not lessen the diagnostic yield of the test for other forms of brain disease. These recommendations are based on the current (at the time—2025) literature review and the opinion of a bunch of highly respected and intelligent veterinarians. At a minimum, they should be performed but additional investigation of the patient, is of course, at the discretion of the neurologist. And on that point, we should also remember an abbreviated study may also be necessary or prudent in some instances (e.g., postoperative MRI and anesthetic complications) A high-field magnet (1.5 T) or stronger is recommended with a slice thickness of 3 mm or less to maximize the chance of lesion identification. A consideration for low-field magnets (< 1 T) is also made with slice thicknesses of 4 mm minimum. Other considerations must also be taken into account in addition to coil strength. These include:

- Coil position: The closer the better. Choose a coil with the least distance from the brain surface to the receiving coil.
- Channel availability: The more the better. An 8-channel brain coil is common but a 32-channel will give better images.
- MRI operator: An experienced MRI operator will be able to adjust scanning parameters to give the best images in the least amount of time.
- MRI interpreter: An experienced interpreter is more likely to find significant lesions and less likely to miss an abnormality.

Table 5.11 IVETF suggested MRI brain imaging protocol.

High Field Magnet >/= 1.0 T, 3 mm or less slice thickness	Low Field Magnet < 1.0 T, 4 mm or less slice thickness
T2 Sagittal: Identify long axis of hippocampus	**T1 Sagittal**: Identify long axis of hippocampus
T2 Dorsal: perpendicular to long axis of hippocampus	**T1 Dorsal**: perpendicular to long axis of hippocampus
T2 Transverse: parallel to long axis of hippocampus	**T1 Transverse**: parallel to long axis of hippocampus
T2 FLAIR Dorsal: perpendicular to long axis of hippocampus	**T2 Dorsal**: perpendicular to long axis of hippocampus
T2 FLAIR Transverse: parallel to long axis of hippocampus (optional)	**T2 Transverse**: parallel to long axis of hippocampus
T1 3D Technique: 1mm voxel size (if possible).	**T2 FLAIR Dorsal**: perpendicular to long axis of hippocampus
T1: Dorsal perpendicular to long axis of hippocampus	**T2 FLAIR Transverse**: parallel to long axis of hippocampus (optional)
T1 Post-contrast (if indicated): Orientation(s) determined by clinician	**T1 Post-contrast** (if indicated): Orientation(s) determined by clinician
Hemosiderin/Calcification Sequences (e.g, Gradient Echo Transverse: parallel to the long axis of the hippocampus)	

Adapted from Rusbridge *et al*., 2015.

- "On the Fly" interpretation: Being able to direct scanning as sequences are acquired will potentially allow for more complete exams (i.e., "go over there and look at that . . .").
- Time: Adequate time must be given for quality images. The more time, usually the better the images but this must also be balanced with increased anesthesia time.

The IVETF recommended protocols for epileptic patients are semi-customized to the investigation of hippocampal sclerosis. Human TLE is the most common cause of complex focal epilepsy. A major pathological finding with TLE is mesial temporal sclerosis, consisting of gliosis, necrosis, and severe neuronal cell loss, especially in the hippocampus, ipsilateral to the seizure focus (Goldberg *et al*., 2014). Generally speaking, with most forms of epilepsy (human), some degree of atrophy of brain structures is identified. A standardized MRI protocol designed to include investigation of the hippocampus would allow for further investigation into the pathogenesis and treatment of seizures. Hippocampal sclerosis in cats and hippocampal atrophy in dogs has been described (Kuwabara *et al*., 2010; Wagner *et al*., 2014; Klang *et al*., 2018; Pakozdy *et al*., 2023). While an association appears to be present with changes to the hippocampus in epileptic dogs and cats, it is not always a recognizable MRI finding (Lőrincz *et al*., 2021). Recognition of abnormalities of the hippocampus such as increased hyperintensity of the temporal lobe, as well as, contrast enhancement of the mesial temporal lobe may be enhanced through standard sequences (and simply *knowing* what you are looking for). However, volumetric studies of the hippocampus require high-resolution MRI, specific operator training and are labor intensive at this time. Future developments utilizing automated software have the potential to make these measurements standard. Surgical removal of an epileptic focus (confirmed by EEG diagnosis), while certainly not commonplace in human or veterinary medicine, could provide a successful treatment for drug-resistant epilepsy and patients identified on MRI with suspected lesions of the hippocampus may be further evaluated with histopathology to characterize the lesion and clarify the etiology in order to help further our understanding of the pathophysiology of epilepsy (Chambers *et al*., 2022; Zilli *et al*., 2022). Improved understanding will likely lead to better treatments.

COMPUTED TOMOGRAPHY (CT SCAN)

Computed tomography (CT) scans utilize X-rays to produce a three-dimensional image of the brain. CT produces excellent bone detail but poor soft tissue detail, especially when compared to that obtained with MRI (Figure 5.7). If MRI is not available, metal artifacts prevent imaging of the brain or extended anesthesia is not safe, CT imaging may be helpful in identifying more obvious gross lesions of the brain. CT scans often provide complimentary images to MRI in the case of skull fractures or bony malformations. Patient accessibility is easier, and because scan times are shorter, CT may be preferred when patient safety is compromised by anesthesia. CT is often preferred in cases of acute head trauma, especially in human medicine, but generally less preferred under MRI for imaging of the CNS. When malformations of the skull are identified, 3D reconstructions of the skull may assist with surgical planning.

CEREBRAL SPINAL FLUID ANALYSIS

Cerebral spinal fluid (CSF) has been shown to only provide a specific etiological diagnosis in 2% of cases of CNS disease in dogs (Bohn *et al*., 2006). In cats, likely due to a higher percentage of structural epilepsy compared to dogs, the diagnostic yield of CSF is much higher (Quesnel *et al*., 1997; Barnes *et al*., 2004). In the Barnes study, 33% (1/3) of cats with structural epilepsy had a diagnosis made with CSF (*Cryptococcus neoformans* organisms identified in sample), whereas all cats with normal advanced imaging and normal exam findings (5 with MRI and

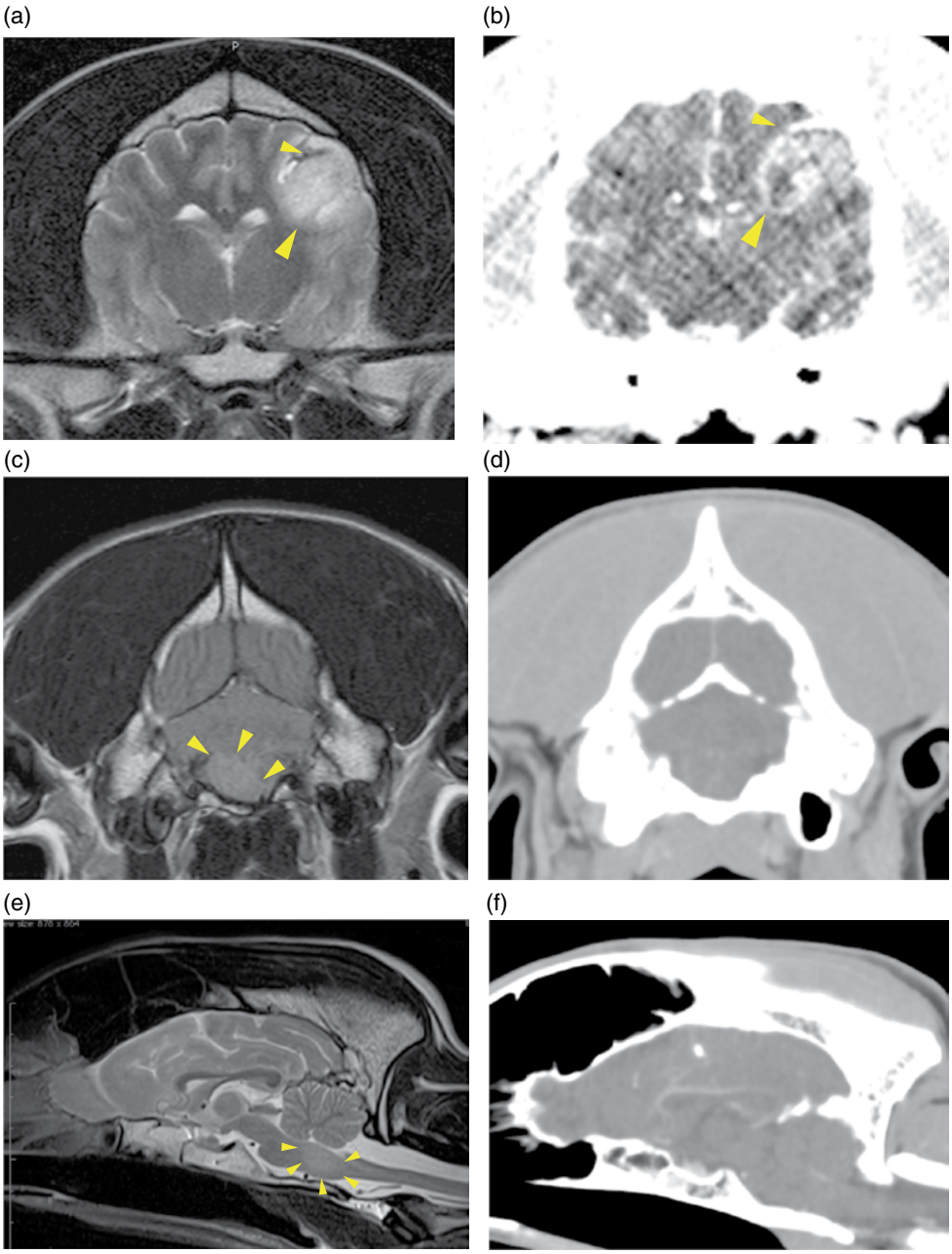


FIGURE 5.7 Comparison of MRI and CT. (a and b) Images acquired through the same anatomical plane in the same dog. (a) T2-weighted axial, image of the brain showing a focal, hyperintense signal change in the upper right cerebral hemisphere (frontal lobe, large arrow) with an angular, hypointense signal change extending from the periphery of the circular mass to a deeper level of the mass (small arrow). At the tip of the angular component of the mass is a hyperintense signal change, which is more hyperintense than the bulk of the mass. The hypointense signal change is suggestive of mineralized tissue and the more hyperintense component at the tip of the angular change is suggestive of hemorrhage. (b) Post-contrast, CT scan of the same lesion shows a poorly defined, circular, radiopaque mass in the right frontal lobe. The angular component of the mass identified in the MRI is confirmed to be mineralized tissue on the CT. Following surgical resection, a meningioma with partial mineralization was confirmed. (c–f) MRI and CT comparison of a 4-year-old Golden Retriever diagnosed with MUO. (c) T1-weighted, transverse image through the caudal cerebellum and myelencephalon. There is mild, homogenous contrast enhancement of the left side of the brainstem, crossing ventrally to the right side (arrows). (d) CT of the same dog as (c) in the same transverse plane. (e) T2–weighted, sagittal image through the middle of the brain, showing a diffuse and poorly defined hyperintense signal change in the caudal brainstem (myelencephalon). (f) CT sagittal in the same plane as (e).

2 with CT) had normal CSF. In the Quesnel study, all cats evaluated for epileptic seizures were diagnosed with structural brain disease (contrary to the Barnes study or Schwartz-Porsche and Kaiser, 1989). Furthermore, in the Quesnel study, 19/26 cats had abnormal CSF and 15 of those 19 were considered to be mild changes (increases in protein or cytological abnormalities with no pleocytosis). Cytological abnormalities with a normal cell count (no pleocytosis) were considered to be significant and a final diagnosis of structural brain disease was confirmed (or highly suggestive) in 14/15 cases either by MRI or histopathological examination. To contrast these studies with a more modern evaluation we look at Majercikova (2023). In this study, 87 epileptic cats with either a normal MRI (80) or MRI with changes to the hippocampus (17) were evaluated. Only 4 cats had abnormal CSF, however, "abnormal" meant a pleocytosis was present (> 5 nucleated cell count) and 3/4 cats had normal protein (one cat's protein was not evaluated) (Majercikova *et al*., 2023). From this study, the CSF was abnormal in 4.6% of the cases, and the diagnostic yield of the CSF analysis (*abnormal*) was 0%. CSF analysis did not contribute to the diagnosis nor did it change the treatment. One cat with abnormal CSF was diagnosed with MUO on necropsy. While the author's question the value of obtaining CSF in cats with a normal MRI or only changes to the hippocampus, they conclude CSF analysis is an important diagnostic test for animals with central nervous system disease, however, the risk and benefits should be considered on an individual basis.

CSF analysis is primarily a supportive test in most cases, although for certain disease entities, it can be at the very least, categorically diagnostic (i.e., inflammatory disease, inflammatory vs. neoplastic, etc.). CSF is primarily used to diagnose encephalitis (i.e., inflammation of the brain). However, even in cases of MUO (those cases *labeled* as such due to lack of a definitive histopathological diagnosis) where we expect to find an abnormality, CSF may be normal (Granger *et al*., 2010). Research into the use of CSF "fingerprinting" using gas chromatography-mass spectroscopy (GCMS) has shown dogs with idiopathic epilepsy will have a GCMS profile significantly different than those with structural causes of epilepsy (Hasegawa *et al*., 2014). An advanced method of metabolic fingerprinting aims to establish a baseline of metabolomics (characterizing an individual's biological phenotype) using ultra-high performance liquid chromatography (UHPLC) coupled with high-resolution mass spectrometry (HRMS) (Verdoodt *et al*., 2024). This method found significant differences in the CSF of dogs with IE compared to dogs with nonbrain-related disease. Encephalitic changes in the brain may be visualized on MRI, if they are severe (i.e., contrast enhancement of the meninges), however, it is reported that 7% of cases of MUO will have a normal advanced imaging (MRI and/or CT), and many dogs diagnosed with inflammatory brain disease with have normal CSF (Granger *et al*., 2010). In another study, 33% of dogs with CNS inflammatory disease had a normal MRI (Bohn *et al*., 2006). In the author's experience, the chances of a dog or cat with encephalitis, having a normal MRI are fairly common, making the necessity of CSF analysis even stronger to reach a diagnosis (not to mention infectious causes which are even less likely to show up on advanced imaging). Encephalitis may cause epileptic seizures; therefore, a CSF analysis is often combined with an MRI to rule in or out encephalitis. CSF may also help to distinguish between two different etiologies that have similar MRI appearance (e.g., metastatic neoplasia from encephalitis). Certain forms of neoplasia may also be apparent in CSF analysis and not visualized in MRI studies (e.g., lymphoma) (Bohn *et al*., 2006; Whitney *et al*., 2020). While MRI is highly sensitive and specific in reaching a diagnosis of CNS disease, it is often combined with CSF analysis. In general, if the MRI is considered normal, a CSF tap is performed following the study, while the patient is under the same anesthesia. We typically aim to collect CSF caudal to the suspect lesion (brain in this case), therefore, a cerebellomedullary cistern tap is more often performed. Most clinicians find this site easier to collect, and with less possible contamination of blood, although with a greater risk of iatrogenic damage to the nervous system (i.e., possible puncture of the brainstem). The lumbar cistern tap has a greater chance of identifying pleocytosis and elevations of protein compared to a

cerebellomedullary cistern tap (Early *et al*., 2019). However, any increase in cell count (*pleocytosis*) or protein may not necessarily be related to disease of the brain as you may have downstream disease in the spine for which you will be sampling. If the patient is presumed to have increased intracranial pressure, through clinical evaluation, MRI demonstration of a mass, or visualization of herniation on MRI, a lumbar puncture may be performed to lessen the risk of herniation to the patient (Speciale *et al*., 1995). Some clinicians (including the author) will preferentially perform lumbar punctures when structural disease of the brain is identified on MRI, to lessen this risk. In the Speciale report, dogs did not seem to be at risk, while cats may be at a greater risk for herniation. Other reports show herniation in dogs, as well as cats, following cerebellomedullary cistern collection in cases where intracranial pressure was increased (Kornegay *et al*., 1983; Parent and Rand, 1994). An abundance of caution is ok. However, if unsuccessful in obtaining a lumbar tap, the clinician should weigh the potential risks against the benefits of performing a cerebellomedullary cistern tap. The author has not experienced any complications with a high tap in dogs or cats who had demonstrated structural brain disease. Spinal fluid is collected and immediately submitted for evaluation. Additional spinal fluid (saved at the time of collection) may be submitted for culture and sensitivity (if indicated), as well as evaluation for infectious organisms (fungal, viral, protozoal, etc.). Spinal fluid is most commonly collected after an MRI in order to make sure the patient is not at significant risk or in the process of herniating the brain. Because of this potential in neurological patients, many clinicians prefer to not collect spinal fluid without an MRI evaluation. The average spinal tap takes less than 5 min. While there is potential for complication (even death) associated with a spinal tap (cerebellomedullary cistern), complications are rarely encountered. Many pet owners will also express concerns about possible pain associated with CSF collection, either due to personal experience or knowledge of the procedure (up to 40% of humans experience a headache after a spinal tap) (Turnbull and Shepherd, 2003). To the best of our ability to detect it, dogs and cats do not display the discomfort associated with CSF collection that humans often complain of. This is likely due to the position of the neuraxis of the veterinary patient in the horizontal plane as opposed to the vertical plane of a standing human. The exact pathophysiology of the headache people may experience is thought to be due to leaking CSF from the puncture site with an associated drop in CSF volume and intracranial pressure. When humans experience discomfort associated with spinal fluid collection, they often lie down or walk bent forward at the waist, in order to relieve the headache pain; essentially the way all veterinary patients ambulate (Bishop *et al*., 2023). Another factor is the weight of the CSF column on the puncture site, also exacerbated by our bipedal ambulation.

Is a CSF collection necessary if a patient is suspected to have idiopathic epilepsy? That's a debatable topic. Some authors have questioned the necessity of CSF collection when the MRI exam is normal and the patient fulfills the other criteria of a Tier I level of evidence suggesting idiopathic epilepsy (see Table 5.1) (Coelho, *et al*., 2019; Gilbert *et al*., 2021). CSF analysis is recommended as part of the diagnostic algorithm put forth by the IVETF, even if a patient has a normal MRI and otherwise fits the criteria for idiopathic epilepsy (De Risio *et al*., 2015). Certainly, many factors may contribute to the decision-making process, including the risk to the patient (which is low), the confidence of the clinician in obtaining a diagnostic sample safely, and the additional cost associated with a low diagnostic yield test. Still, most neurologists would probably feel "weird" if they did not perform a CSF evaluation when an MRI was normal, even in the case where a patient was highly suspected to have idiopathic epilepsy. We may also consider the future diagnostic utility of tests, not yet commercially available (such as anti-antibody screening or mass spectroscopy) on collected CSF (Stafford *et al*., 2019; Huenerfauth *et al*., 2022). Neurologists may save CSF samples for future possible diagnostic testing. Spinal fluid collection is a very common and necessary component of the critical and complete evaluation of a veterinary patient with epileptic seizures. Similar to advanced imaging, it may not be performed in those patients too frail for anesthesia, suspected to be suffering from metabolic/reactive/provoked seizures or where time has demonstrated a nonprogressive disorder.

ELECTROENCEPHALOGRAPHY (EEG) (SEE ALSO CHAPTER 10)

Perhaps the greatest difference between the diagnostic evaluation of epileptic seizures in humans and in veterinary patients is the use of the EEG. Historically, this test would have required anesthesia, but we are now able to perfrom this advanced diagnostic with minimal sedation (and sometimes no sedation). For veterinary neurologists, the MRI has become the single most valuable diagnostic tool for the evaluation of epileptic cats and dogs. As advanced neuroimaging became more common and available as a veterinary neurodiagnostic, the use of the EEG declined. A survey of ACVIM and ECVN neurologists found less than 50% of neurologists used EEG and it was used infrequently (Luca *et al*., 2023). The trend is shifting thanks to the work of some very talented, curious, and persistent veterinary neurologists and electrodiagnosticians. For human neurologists trying to solve the epilepsy puzzle, the EEG assumes the role of the *most useful diagnostic tool* (Engel, 2013). MRI and CSF analysis are a way to look at the *structural* features of the nervous system, while an EEG is a tool used to evaluate the *functional* elements of the brain. The sensitivity of EEG in veterinary medicine in detecting abnormal electrical activity is variable and reported to be anywhere from 0 to 100% in the detection of epileptic discharges (Pakozdy *et al*., 2012). Taken at face value, this looks pathetic compared to the sensitivity and specificity of MRI. But we are evaluating two separate elements. Trying to compare the two is like blaming your car for taking you to the wrong location (i.e., the car is the MRI and the map is the EEG). You need both elements of the trip in order to have the greatest success. MRI, CSF, *and* EEG are complimentary tools.

The difficulty in evaluating the benefit of the use of EEG in a clinical setting may be partly due to the variability of the application, including the form of sedation or anesthesia used, the techniques applied, and the purpose of the EEG study for the patient population (i.e., genetic vs. structural epilepsy, epileptic seizure vs. movement disorder, etc.). Standard EEG protocols are in place for human applications. A veterinary literature review identified 15 different montage techniques combined with various forms of anesthesia between 1970 and 2024 (Everest *et al*., 2024). A strong correlation exists between the clinical description of a seizure (i.e., its classification) and changes observed on an EEG recording in dogs (Holliday *et al*., 1970; Jaggy and Bernardini, 1998; Berendt *et al*., 1999). In a long-term intracranial EEG (iEEG) study in dogs, researchers found after observing over 200 epileptic events, there was a remarkable similarity between the electrographic activity, seizure onset patterns, and background activity between dogs and humans (Ung *et al*., 2016). One of the historically greatest obstructions to the use of the EEG in veterinary medicine was the need for anesthesia or heavy sedation in order to complete a recording. Variations in sedative and anesthesia techniques, as well as activation procedures (e.g., hyperventilation, photic stimulation), may increase the sensitivity of the EEG (Brauer *et al*., 2012; Engel, 2013). Short-term sedation, to place electrodes, followed by reversal and awake EEG monitoring is a reasonable and valid application in *dogs* and probably increases the sensitivity of EEG in detecting epileptiform activity (Wrzosek *et al*., 2024). The same mild sedation, followed by awake evaluation technique, would also seem reasonably valid in cats (as long as you avoid ketamine). So historically, the need for anesthesia to perform the test, while not only complicating the procedure by adding time, cost and risk to the patient, had the potential to mask our findings, by suppressing electrical activity in the brain (let's not forget the purpose of anesthesia). We are overcoming this hurdle with the availability of lower-cost, ambulatory, awake EEG (aEEG) units (Figure 5.8). This allows the clinician to use light (reversible) sedation to place electrodes, if necessary, and then monitor the patient in an awake state for hours, in order to "capture" an event, even in a home setting (James *et al*., 2017; Folkard *et al*., 2024). This one tool can be a game changer in a clinical setting, placing the EEG more in the realm of MRI or blood work as far as practicality. Prior general anesthesia, sedation, or AED use does not limit the ability of an ambulatory EEG (aEEG) in its diagnostic sensitivity (recommended recording time of at least 4 h) (Parmentier *et al*., 2020). In addition to its diagnostic utility for the etiological and therapeutic investigation of epilepsy and the ability to

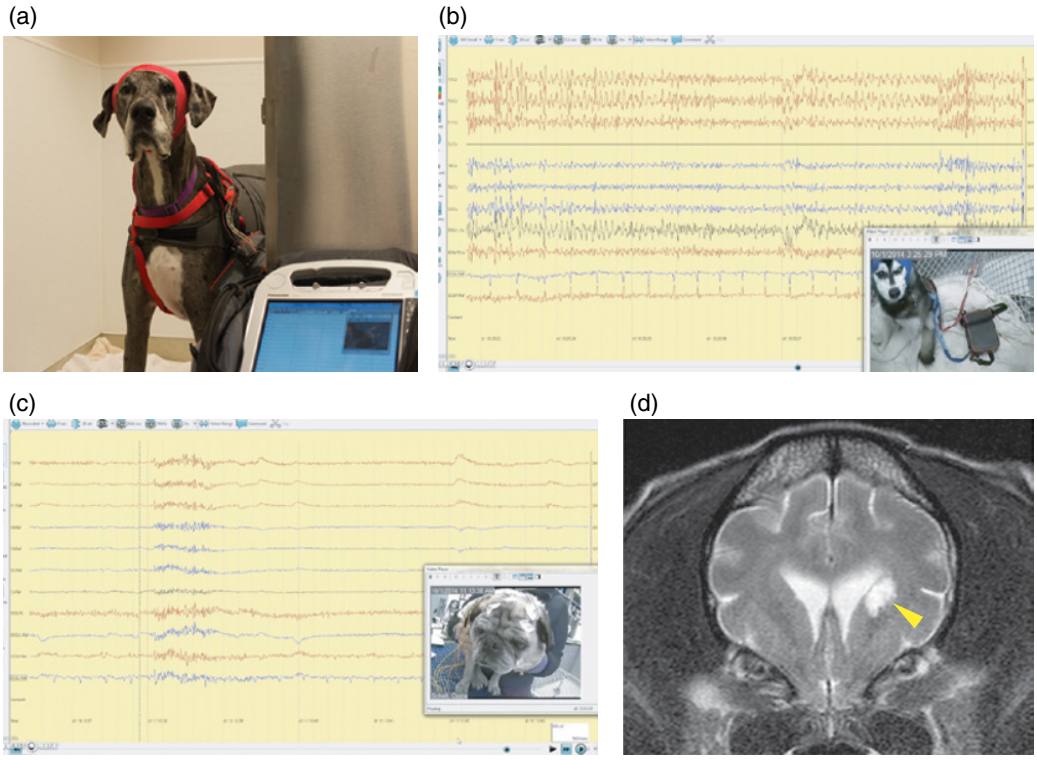


FIGURE 5.8 Ambulatory, video EEG (aEEG or vEEG) in various dogs. (a) an older Great Dane is set up for in hospital, 24-hour video EEG evaluation. (b) A young Klee Kai is examined for myoclonic facial twitches. The EEG showed paroxysmal discharges immediately preceding the facial twitches captured on video. (c) An older pug is examined for myoclonic facial twitches. EEG was normal which prompted an MRI examination. (d) T2-weighted, transverse MRI of the pug in (c) just rostral to the optic chiasm. A focal, hyperintense signal change (suggestive of an infarct) is seen in the right caudate nucleus. Among its many functions, the caudate helps plan and execute voluntary movement.

distinguish epileptic from non-epileptic events, EEG has also been shown to be a useful tool in the early diagnosis of canine cognitive dysfunction syndrome (Mondino *et al.*, 2022). Just as with humans diagnosed with Alzheimer's disease, an early diagnosis of canine cognitive dysfunction may be helpful in treatment outcomes. This section will undeniably be a lobbying effort to convince veterinary neurologists to use EEG as a first-line, diagnostic tool in their practice. Remember back when looking at an MRI was maybe slightly clearer than an abdominal ultrasound? Now it is second nature. The more we use a tool the more comfortable we get with it. Change is good. Embrace the EEG.

The EEG is a recording of the electrical activity of the brain. The EEG is performed by inserting small, fine, scalp needle electrodes in the skin overlying specific areas of the brain. Alternatively, surface electrodes may be used (Lyon *et al.*, 2024). The EEG electrode will record the electrical potential between two locations (an individual channel or *derivation*). The combination of multiple locations is referred to as a *montage*. Multiple locations are recorded at once creating a temporal sequence of brain electrical activity (Figure 5.9). The normal brain electrical activity will change depending on the state of awareness of the patient and external stimulation. Abnormal activity is typically characterized by either depressed electrical activity relative to the state of the patient (e.g., an awake patient with depressed activity may be abnormal) or excessive activity (i.e., spike-and-wave activity in a patient having seizures). *Paroxysmal*

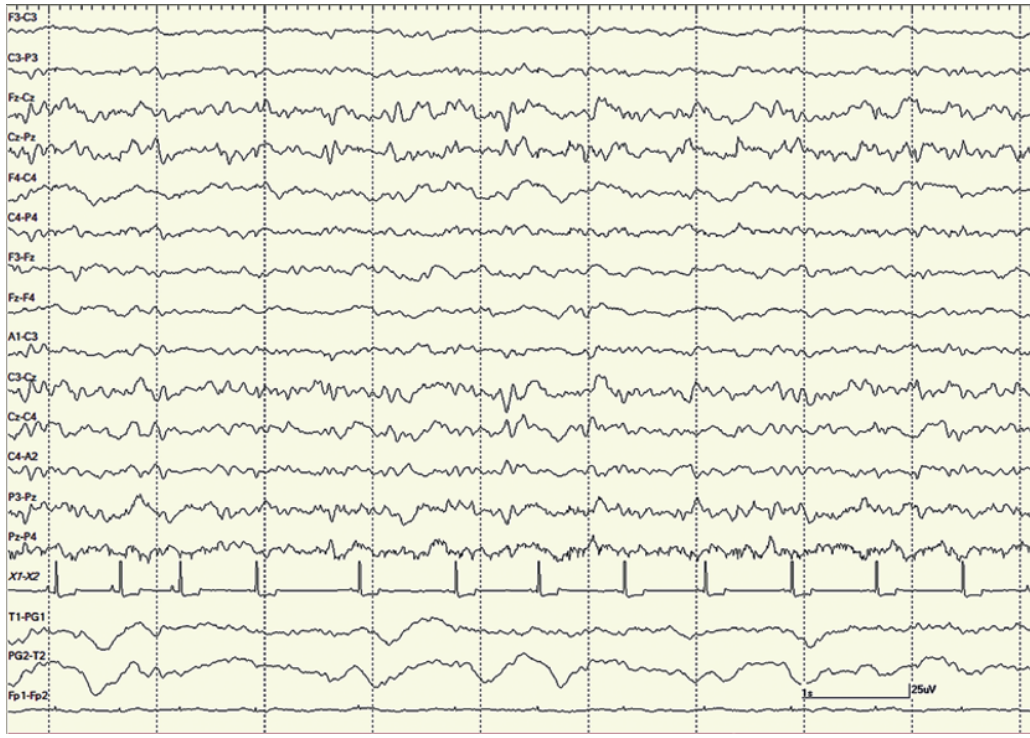


FIGURE 5.9 Normal electroencephalograph (EEG) of a dog in slow wave (i.e., synchronized) sleep. The amplitude of the waves increases and the frequency of the waves slows because neurons are firing together instead of randomly (a summative effect). An epileptic dog or cat may have a normal EEG and non-epileptic patients may have an abnormal EEG. The EEG should not be oversimplified. It should be considered a complementary tool. Courtesty of D. Colette Williams, PhD., William R. Pritchard Veterinary Medical Teaching Hospital, Clinical Neurophysiology Lab, University of California.

discharge(s) is a general term to describe sudden and recurring electric activity found in the brain as a waveform on the EEG (Ukai *et al*., 2021). These electrical discharges have a sudden onset, rapidly reach a maximal amplitude, and suddenly terminate. They are the "breadcrumbs" we are looking for. Abnormal electrical activity may confirm and help to localize a seizure disorder or provide a definitive electroclinical syndrome, where findings on the EEG, correlated with the clinical picture, can direct the clinician to other confirmatory diagnostic tests (Demeny *et al*., 2020). In the Demeny case reports, the signalment of the patients, along with typical EEG findings associated with Lafora disease (polyspike slow waves triggered by photic stimulation) led to genetic testing and muscle biopsy confirmation of the condition. So, in a classic sense, the diagnostic test (EEG) led the clinician down the path to more specific diagnostics tests. Ultimately, a definitive diagnosis and the ability to treat and prognosticate in a more accurate and specific manner were attained. The EEG may help determine if the patient has epilepsy (especially in cases of focal epilepsy vs. a behavioral disorder, sleep disorder, or movement disorder), what kind of epilepsy the patient has (absence or generalized seizure as opposed to focal) and the location of the origination of the seizures (the epileptogenic area), especially in cases where epileptic seizures are focal and cannot be identified with advanced imaging techniques. The EEG may be especially useful in confirming the diagnosis of epileptic seizures when the "events" have not been observed by the clinician and the description of the "events" by the owner does not exactly correspond with the definition of an *epileptic event* (Berendt *et al*., 1999). The EEG may also be useful in determining the efficacy of medical management by evaluating the suppression of paroxysmal discharges by a specific AED.

EEG is commonly used in the study of human epilepsy to help classify epileptic seizures based on electroclinical syndromes (Engel, 2001; Berg *et al*., 2010). Not all patients will fit into "standard" classification schemes based on symptomology and semiology. Electroclinical syndromes provide an alternative classification system (Parisi *et al*., 2011; Seneviratne *et al*., 2012). As part of an *operational or specific syndromic* classification (the Holy Grail of classifications), veterinarians can use EEG findings in conjunction with elements of the signalment and history to "predict" what disease the patient may have and treat according to a classification based on the patient fitting into the particular syndrome. For example, EEG was used to essentially classify a form of epilepsy in Finnish Spitz Dogs, where the origination of the epileptic discharges and response to phenobarbital were characterized with EEG (Jeserevics *et al*., 2007). With this information, veterinarians presented with a Finnish Spitz Dog, who fit the signalment, may choose phenobarbital as their first choice AED *for this syndrome*. Particular attention is made to the location of an epileptogenic site as surgical resection of abnormal tissue or disconnection of tissue (see Chapter 10) may be a treatment option in certain cases.

The practical use of EEG in veterinary medicine may allow for the recognition of *electroclinical syndromes*, which may help clinicians further recognize those epileptics without typical semiology, characterize the underlying etiology, and apply the most efficacious treatments (i.e., targeted therapy) for a particular identified epileptic syndrome (Srenk *et al*., 1994; Jaggy and Bernardini, 1998; Jeserevics *et al*., 2007; Poma *et al*., 2010). For example, when children are diagnosed with childhood absence epilepsy (i.e., *petite mal epilepsy*) or juvenile absence epilepsy, by demonstrating typical absence seizures with or without myoclonia and a classic EEG pattern characterized by 2.5–4 Hz generalized spike-and-slow-wave discharges, treatment with drugs such as ethosuximide, sodium valproate or lamotrigine is specifically chosen (Kessler and McGinnis, 2019). This is a similar procedure to the use of phenobarbital, described in the Finnish Spitz Dogs earlier. Furthermore, the syndromic classification may also correspond with classic MRI changes including thalamic atrophy and changes in cortical gray matter (micro-dysgenesis) (Engel, 2013). By realizing the similarities between veterinary and human patients (either through EEG or MRI), we may be able to apply more effective treatment. After all, animal models of epileptic seizures are used in order to determine therapeutic drug efficacy. It makes sense we would be able to "reverse engineer" the successful application of a treatment corresponding to a human epileptic syndrome, if the same syndrome could be identified in a veterinary patient and the corresponding therapy is tolerated. We are already starting to apply this to similar cases of *limbic encephalitis* between species. As investigators continue to unravel the often nebulous causes of epileptic seizures, EEG may be a useful tool to suggest further diagnostic testing, treatment options, and prognosis associated with the underlying cause. For example, cats presenting with orofacial seizures may fit into a syndromic classification of TLE associated with hippocampal sclerosis (Fatzer *et al*., 2000; Pakozdy *et al*., 2014). Furthermore, this syndromic classification may lead to alternative treatments such as the use of corticosteroids or surgery.

There are many practical limitations to the everyday use of EEG in veterinary practice, which creates a highly specialized diagnostic test with a potentially low diagnostic yield when compared to MRI; however, the type of data one can access is not comparable to MRI. EEG, MRI, and CSF analysis are complementary tests. Some of the practical limitations in veterinary medicine include:

- Patients may be intolerant of electrodes.
- The muscle mass and relatively thick skull of veterinary patients overlying the brain may attenuate the electrical signals by the time they reach the surface electrodes.
- The muscle mass of veterinary patients may create excessive movement artifacts (e.g., eye blinking or facial twitching). Topical lidocaine has no effect on muscle artifacts (Ward *et al*., 2016).
- Historically, sedation or anesthesia was necessary, which could alter the normal or abnormal EEG recordings. This complication has largely disappeared with new devices.

- Alterations of electrical activity of a diseased brain (evaluated independently from other factors) are not pathognomonic for any particular disease (low specificity).
- Complete recordings need to be made in the awake and sleeping patient. It is difficult to obtain artifact-free recordings in awake patients (Holliday and Williams, 1998).
- Small lesions or alterations in electrical activity, indicative of disease, may be overlooked as the EEG is a *summation* of cortical electrical activity.
- Until recently (2024), no specific, generally accepted operating parameters (i.e., montage, anesthetic or sedative use, etc.) have been developed and adopted in veterinary medicine (Brauer *et al*., 2012; Lyon *et al*., 2024).
- The ability to detect abnormal activity is related to the time of the epileptic seizure to the EEG recording, as well as the severity of the seizure (Berendt *et al*., 1999).
- A *single* period of EEG recording may not be adequate to detect an ictus (Cuff *et al*., 2014).
- Interpretation requires specialized training and experienced interpreters of EEG data of veterinary patients are few (at this time).
- Because of breed variability, accurate placement of electrodes is subjective, possibly leading to abnormal or inconclusive recordings (Rogers *et al*., 2024).

While there are many debatable limitations to the practical and justifiable diagnostic yield of EEG recording in a clinical situation (as opposed to research or teaching), an EEG recording may be useful in the following situations:

- Determining if the patient is actually having seizures (focal vs. absence vs. nonconvulsive) or simply displaying abnormal behavior, syncope, or a sleep disorder (Penning *et al*., 2009; Poma *et al*., 2010, Packer *et al*., 2015, Knipe *et al*., 2023) (Figure 3.1).
- Determining if a postictal patient is actively having seizures or a stereotypic movement disorder (Kube *et al*., 2006; Musteata *et al*., 2023).
- Determining if the patient is "brain dead" and helping to determine prognosis in critical patients (Firosh Khan *et al*., 2005; Scozzafava *et al*., 2010; Iannucci *et al*., 2023).[1]
- Classifying epileptic *syndromes* among veterinary patients (Jeserevics *et al*., 2007; Srenk *et al*., 1994; Jaggy and Bernardini, 1998; Poma *et al*., 2010).
- Identifying nonconvulsive status epilepticus (Bush *et al*., 2013; Cuff *et al*., 2014; Granum *et al*., 2019). (Figure 5.10).
- Evaluating the effectiveness of chronic and pulse anti-seizure medications (Frost *et al*., 1986; Cuff *et al*., 2014).
- Determining the localization of an epileptogenic focus for possible surgical removal (Bagley *et al*., 1996a; Jaggy and Bernardini, 1998; Hasegawa, 2016; Drobot *et al*., 2024).
- Classifying seizure types adds to our etiological and epidemiological understanding of epilepsy in veterinary patients (Chawner *et al*., 2023).
- Determining the effectiveness of an anti-epileptic drug AED in an individual drug–resistant patient through evaluation of suppression of paroxysmal discharges (Bocheńska *et al*., 2014).

[1] A very interesting case report.

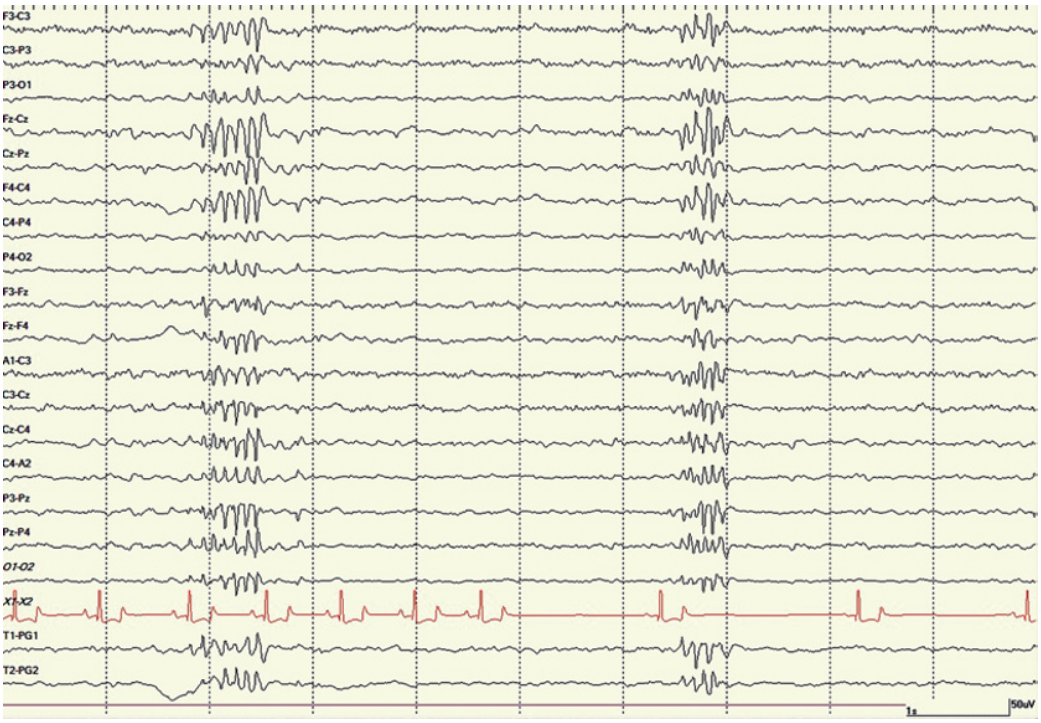


FIGURE 5.10 Bursts of multiple spikes/sharp waves, which are synchronized over a background of slow-wave sleep. Courtesty of D. Colette Williams, PhD., William R. Pritchard Veterinary Medical Teaching Hospital, Clinical Neurophysiology Lab, University of California, Davis.

The EEG can be very useful in cases where the determination of actual epileptic seizures cannot be made by visual observation alone. In a clinical setting, the patient who is actively having seizures may physically stop having tonic–clonic convulsions; however, repetitive movements such as paddling or facial twitching may be present in the unconscious and "relaxed" patient. Using an EEG can help the clinician determine if abnormal brain electrical activity is continuing—allowing for possible alterations in therapy in order to stop *subclinical* epileptic activity (Kube *et al.*, 2006; Poma *et al.*, 2010; Bush *et al.*, 2013; Musteata *et al.*, 2023; Tästensen *et al.*, 2024) (Figure 5.10). Nonconvulsive status epilepticus may also be diagnosed and it is stressed that the interpretation of an EEG to diagnose nonconvulsive status epilepticus is user-dependent and quite subjective (Cuff *et al.*, 2014; Tästensen *et al.*, 2024). Making this determination with EEG may help prevent brain damage associated with continuous abnormal electrical activity (e.g., glutamate-mediated excitotoxicity, kindling, and development of mirror focus) associated with refractory convulsive status epilepticus, nonconvulsive status epilepticus (NCS), or subclinical status epilepticus (Majores *et al.*, 2007) (Figure 5.11). Electrographic seizures (ES), subclinical seizures, or nonconvulsive seizures are visible only with EEG recordings. Outwardly the patient appears clinically normal (although they may also appear a little somnolent). Electrographic status epilepticus (ESE) or nonconvulsive status epilepticus occurs when the electroclinical abnormality lasts longer than 10–15 min. Dogs and cats are diagnosed with nonconvulsive seizures (ES or NCS) and ESE with no overt clinical signs at a rate similar to humans (Granum *et al.*, 2019; Chawner *et al.*, 2023). In the Granum study, 19% of dogs and 27% of cats were diagnosed with ES on EEG and displayed no overt clinical signs. In the same study, 9% of dogs and 27% of cats were diagnosed with ESE. Animals with ES or ESE were 4× more likely to die in the hospital, showing the utility and benefit of early diagnosis with EEG. Dogs and cats with a history of cluster seizures may also be at



FIGURE 5.11 Periodic complexes with a frequency of 2–3 per second consistent with status epilepticus. EEG recording was obtained with 10 electrodes interpreted in a 13-channel bipolar montage. The EEG recordings were reviewed in a bipolar modified double banana montage (two rows of rostral to caudally arranged electrode pairs over each brain hemisphere [one row laterally and one medially]) for the upper eight tracings and in a transverse pattern for the lower five tracings. The scale for voltage and time is indicated. A1, left auricular electrode; A2, right auricular electrode; C3, left central electrode; C4, right central electrode; F1, left frontal electrode; F2, right frontal electrode; O1, left occipital electrode; O2, right occipital electrode; T3, left temporal electrode; T4, right temporal electrode. The image is from a cat with nonconvulsive status epilepticus who was later treated with high doses of phenobarbital to induce a burst suppression pattern. Courtesy of Daniel Cuff DVM, Bush Veterinary Neurology Service.

a higher risk for ES and ESE (Tästensen *et al*., 2024). Similar to the Granum study, those patients diagnosed with ES or ESE had a significantly higher mortality rate (73% mortality for patients with ES, 67% for patients with ESE compared to 27% of patients with no EEG seizure activity). It is estimated absence seizures (i.e., nonconvulsive-generalized seizures) affect one-third of the canine population presenting with epileptic seizures (Chawner *et al*., 2023). EEG may be useful in the actual and correct determination of the frequency of epileptic seizures, as the observed reported seizures are often not consistent with the actual epileptic seizure activity (Ukai *et al*., 2021). EEG may also be helpful when monitoring the effect of a medically induced coma. Medically induced comas may be employed as a treatment following severe brain injury or intractable epileptic seizures. An EEG indication of the coma being generated is the presence of *burst suppression* of electrical activity. A burst suppression pattern appears as reduced to quiet electrical activity following bursts of electrical activity (Cuff *et al*., 2014). Drugs used to induce a medical coma (e.g., propofol, pentobarbital, and ketamine) can be titrated to achieve this effect through EEG monitoring (Rossetti *et al*., 2004; Raith *et al*., 2010). The burst suppression pattern is indicative of deep sedation as an effect of the anesthetic agent and commonly regarded as an *artificially induced*

end point of status epilepticus. It is the author's opinion that all veterinary emergency facilities should have the ability to perfrom an EEG, especially those where a neurology service is part of the group.

The application of wireless transmitted EEG data to alert pet owners of potential epileptic activity is being explored and promises to provide for earlier treatment, as well as reduced incidences of status epilepticus, visits to emergency rooms, identification of subconvulsive states, and complications associated with untreated epileptic seizures when used in conjunction with *seizure prediction* algorithms (Lehnertz *et al*., 2007; Davis *et al*., 2011; Coles *et al*., 2013). A combination of at-home EEG monitoring, an activity monitoring device, and owner questionnaires has been shown to be successful for at-home EEG monitoring similar to a Holter monitor device (Folkard *et al*., 2024). Machine learning combined with iEEG shows promise in being able to distinguish the abnormal, preictal electrical activity of the brain from normal background activity, allowing for artificial intelligence (AI)-generated predictions of future epileptic seizures (Varatharajah *et al*., 2017). Non-EEG, pet activity and biological, collar-mounted devices show promise for predicting and alerting pet owners of abnormal, potentially epileptic activity (Folkard *et al*., 2023).

One of the hurdles we face in applying any technology for the diagnosis and treatment of disease is standardization. MRI is an excellent example, where over the years, a standard protocol of sequences delivers the most diagnostic information in the least amount of time with the greatest accuracy. Given the infrequent use of EEG in a clinical setting and the proportionally greater use in research or academic settings, a natural discrepancy and significant variations in the application of EEG exist, heaped on top of our already inherent biases. A standard protocol for video EEG (vEEG) has been developed and published (Lyon *et al*., 2024). It is hoped this standardized protocol will encourage veterinary neurologists to use vEEG as a first-line diagnostic tool. Much like MRI, veterinary neurologists may have their individual sequence and positioning preferences but the ultimate goal would be to gather the necessary data in a quick, accurate, and inexpensive manner while at the same time being available to similar if not identical interpretation by any other clinician.

The interpretation of EEG data is often regarded as more of an art than a science. A significant amount of *overinterpretation* exists. *Computer-enhanced EEG* and *ambulatory or "awake" video-monitoring EEG* have improved the diagnostic yield of the EEG recording in veterinary medicine as it has in human medicine. Brain mapping software is available and routinely used in human medicine to provide a topographic representation of EEG activity (Nuwer, 1988). The combination of EEG data, MRI, and topographical mapping utilized together to provide a comprehensive study of the abnormal brain promises to advance the diagnosis and treatment of epilepsy whether through early intervention and prevention or treatment utilizing medical or surgical modalities (Drobot *et al*., 2024). The Drobot study demonstrates a cooperative use between MRI volumetric studies (of the hippocampus) and correlated EEG change to diagnose TLE in a subset of dogs, otherwise diagnosed with idiopathic epilepsy. As in humans, this may lead to more effective treatments, such as surgery, for this typically, drug-resistant form of epilepsy (see Chapter 10).

RESEARCH AND FUTURE DIAGNOSTIC MODALITIES

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (*TMS*) uses a rapidly changing magnetic field to induce weak electrical currents in the brain, which results in the depolarization of brain neurons and the generation of an action potential. The area depolarized is controlled by the use of various magnetic coils overlying distinct regions of the brain (Nollet *et al*., 2003). This noninvasive method of stimulating the brain may be useful in mapping cortical function and brain excitability, as well as

being used as an aid in distinguishing between different epilepsy syndromes (Badawy *et al*., 2012, 2013). A measurement of cortical excitability can be useful in determining the effectiveness of anti-seizure medications. TMS is also a useful tool allowing researchers to connect data obtained from *in vitro* experimentation with *in vivo* information. Repetitive TMS may hold therapeutic promise in the future for the treatment of brain diseases including stroke, neurodegenerative conditions, psychological disturbances, and trauma (Hsu *et al*., 2012; Villamar *et al*., 2012; Cristancho *et al*., 2013; George *et al*., 2013). Think of it as physical therapy for the brain.

MAGNETOENCEPHALOGRAPHY

Information regarding both structure and function of the brain can be combined to create an anatomical image of the brain using magnetoencephalography (MEG). This neuroimaging technique is periodically used in human medicine to aid in the identification of discrete areas of epileptiform activity through the detection of abnormal interictal electrical activity. The technology has been applied experimentally in one dog, which shows electrical activity of the brain similar to EEG but without the electrical potential attenuating artifacts such as muscle mass and the skull (Jäntti *et al*., 1995). With MEG, a collection of superconducting detectors and amplifiers, also known as a *superconducting quantum interference device* (*SQUID*), detects the naturally occurring magnetic fields generated by the brain. Magnetic fields are created by the electrical activity of single neurons (axons). Once the fields are detected, they are analyzed to find their source in the brain. The source information is then superimposed over an MRI image of the brain to create a *magnetic source image* (*MSI*). This noninvasive analytical method creates a map of both the structure and function of the brain. It does not require any injections or exposure to a magnetic field (MRI) or X-rays (e.g., CT, SPECT, and PET scans). Methods such as functional MRI (fMRI), SPECT, and PET scans are secondary measures of function (i.e., function is measured following an injection of a metabolized compound), whereas MEG is a *direct* measure of brain function. Other benefits of MEG include precise temporal resolution, with the ability to distinguish events happening on the order of milliseconds, and excellent spatial resolution, with the ability to localize a source down to millimeters. Furthermore, unlike electrical recordings of the brain, magnetic fields are not distorted by the incongruities of the skull or overlying tissues and are not susceptible to tissue electrode interference (Barth *et al*., 1984a). MEG is primarily used for precise surgical planning, often combined with other imaging and functional studies (such as EEG), to specifically localize the source of epileptic spikes for surgical removal and eloquent areas of the brain to avoid during surgery (Barth *et al*., 1984b; Velez-Ruiz and Klein, 2012). As with many of the advanced neuroimaging technologies, large space requirements, magnetic shielding, and expensive cryogenic cooling make MEG an expensive and difficult-to-attain technology. Advances in atomic magnetometer technology, which do not require super cooling and are smaller in size, have the potential to open this technology to a greater application (Shah and Wakai, 2013).

FUNCTIONAL NEUROIMAGING

FUNCTIONAL MRI (FMRI)

The use of MRI is most well-known for the anatomical and structural evaluation of the brain. *fMRI* utilizes the fact that oxyhemoglobin is paramagnetic, while deoxyhemoglobin is diamagnetic. Paramagnetic substances produce an increased MRI signal. Neuronal activity results in increased blood flow to active areas of the brain, resulting in local increases in oxyhemoglobin and a subsequent increased signal. The *blood oxygen level-dependent* (*BOLD*) fMRI utilizes this concept to evaluate patterns of blood flow in different anatomical areas of the brain through averaged,

repeated acquisitions and subtracting baseline studies from EEG-triggered studies (Krakow *et al*., 1999). Using this methodology with MRI has the advantage of superior *temporal* resolution over functional PET studies, which require up to an hour following injection of radiolabeled ligand to evaluate metabolism. fMRI allows *near-immediate* image acquisition following an epileptiform discharge. The BOLD image identifies the anatomical substrate where the epileptiform discharge originated. Additionally, fMRI may identify hemodynamic changes associated with underlying *networks*, which help to classify certain epilepsies related to a specific syndrome by way of an *imaging fingerprint* (Gotman, 2008; Moeller *et al*., 2013). Another role of fMRI is to identify an epileptogenic zone as part of a presurgical evaluation. The area of the brain where the EEG-associated epileptiform discharges occur is referred to as the *irritative zone* and is often a closely related but distinct site to the cortical area where epileptic seizures are initiated, known as the *ictal onset zone* (Engel, 2013). The purpose of multiple sophisticated diagnostics is to identify the epileptogenic zone with the ultimate goal of surgical resection for medically intractable epilepsy and preserving *eloquent* brain tissue (e.g., speech centers) (Moeller *et al*., 2009). Even with extensive diagnostics workups, lesion identification is not always possible, particularly in frontal lobe epilepsy (FLE) of humans. These patients are often pharmacoresistant, and surgical treatment may be an option; however, approximately 15% of the patients are rejected as surgical candidates due to the inability to identify the epileptogenic zone with standard diagnostics. The combination of EEG and fMRI helps to identify occult lesions for surgical resection in many of these patients (Zijlmans *et al*., 2007). Surgical treatment of epilepsy in veterinary patients has been reported, although the cause of the epileptic seizures was a mass effect from a fungal lesion (Parker and Cunningham, 1971). While not always expected, epileptic seizure cessation occasionally occurs following the removal of discrete brain lesions (i.e., neoplasia or developmental malformation), in the author's experience (Figures 5.4 and 5.12). Advanced surgical techniques for the surgical treatment of epilepsy in companion animals are becoming more common (see Chapter 10). Even with reported cessation of seizures, unless the patient cannot tolerate anti-seizure medications, they should be maintained on chronic maintenance therapy. The use of fMRI has been employed experimentally in dogs and cats to evaluate the auditory and visual pathways (Willis *et al*., 2001a, b; Aguirre *et al*., 2007; Bach *et al*., 2013; Brown *et al*., 2013) (Figure 5.13). Despite requiring anesthesia and the concerns naturally revolving around decreased cerebral metabolism, BOLD fMRI has been demonstrated to be effectively utilized *in a research setting* with anesthetized animals and in a single report of highly trained canines *without* anesthesia (Berns *et al*., 2012) (Figure 10.2). fMRI remains a research tool at this time in regard to veterinary medicine. As high-field strength MRI units become more available, the use of this technology holds promise to provide improved classification of epileptic syndromes in veterinary patients, identification of lesions not visible with conventional imaging, and potential targeted surgical resection of epileptogenic zones.

POSITRON EMISSION TOMOGRAPHY (PET)

Brain function information derived through observation of brain tissue metabolism can be obtained with *PET* scans. For focal epilepsy, a discrete area of abnormal brain tissue may be identified with PET scanning (Alavi *et al*., 2011). Although PET scanning technology has been in development and utilization longer than MRI, the contemporary advances in MRI technique have resulted in a reduction in the use of PET scans (Duncan, 1997). A PET scan is essentially a CT scan of the brain but utilizes a scintillation detector to "see" gamma photons. Gamma photons are produced when a positron (the antiparticle of an electron) emitted from a biologically radioactive tracer isotope collides with an electron. The most commonly used radioactive tracer isotope is ^{18}*F-fluorodeoxyglucose* (*FDG*), which allows the measurement of glucose metabolism in the brain. Other labeled compounds utilized to measure oxygen

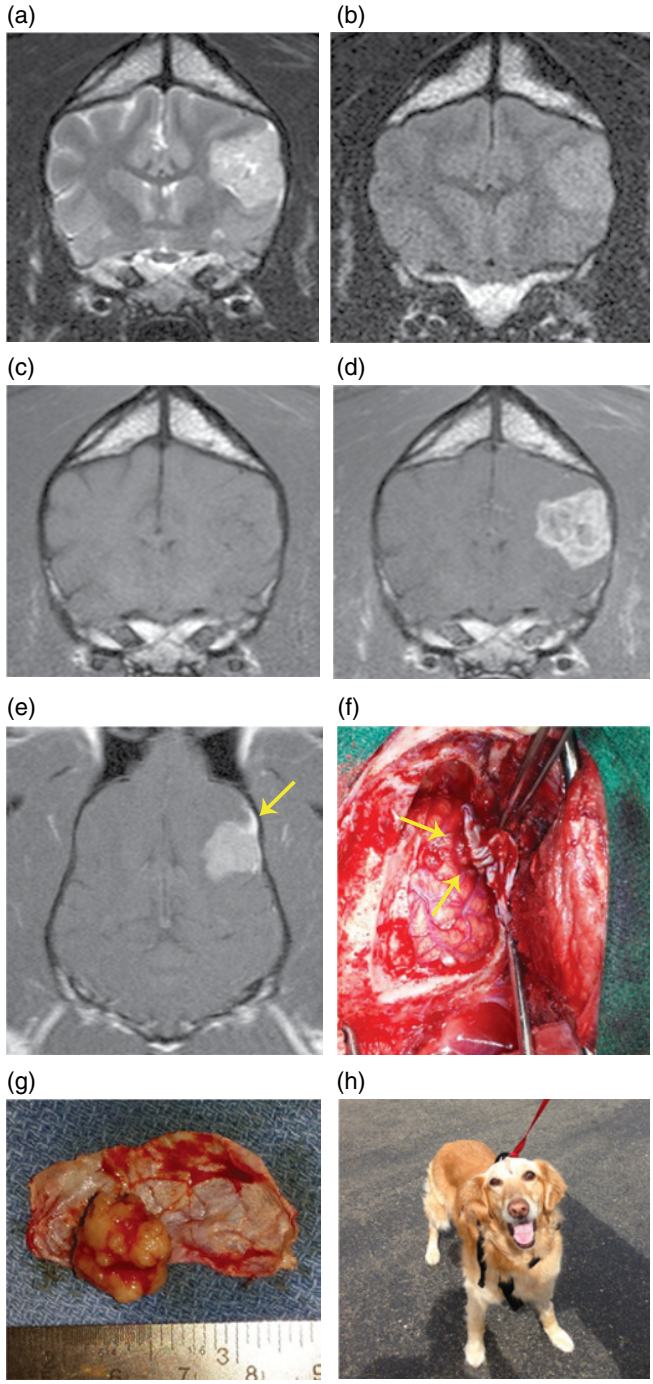


FIGURE 5.12 Magnetic resonance images of a 10-year-old, male neutered, Golden Retriever, who had experienced a single seizure. (a) T2-weighted axial image through the forebrain identifying a focal, heterogeneous, hyperintense signal change with mass effect in the right temporal lobe. (b) Same plane as A T1-weighted FFE. (c and d) Pre- and post-contrast T1–weighted, axial images (respectively) of the same plane as (a) and (b) showing a focal, superficial, heterogeneously contrast-enhancing mass in the right temporal lobe. (e) T1-weighted, post-contrast, the dorsal image of the same dog showing a dural tail sign (arrow) of a typical meningioma. (f) Appearance of the mass during surgery (arrows). The mass was solid and attached to the overlying meninges by a narrow stalk. (g) The mass after excision. The histopathological diagnosis was a meningioma. (h) The patient a few days after surgery prior to discharge. No further seizures occurred following surgery.

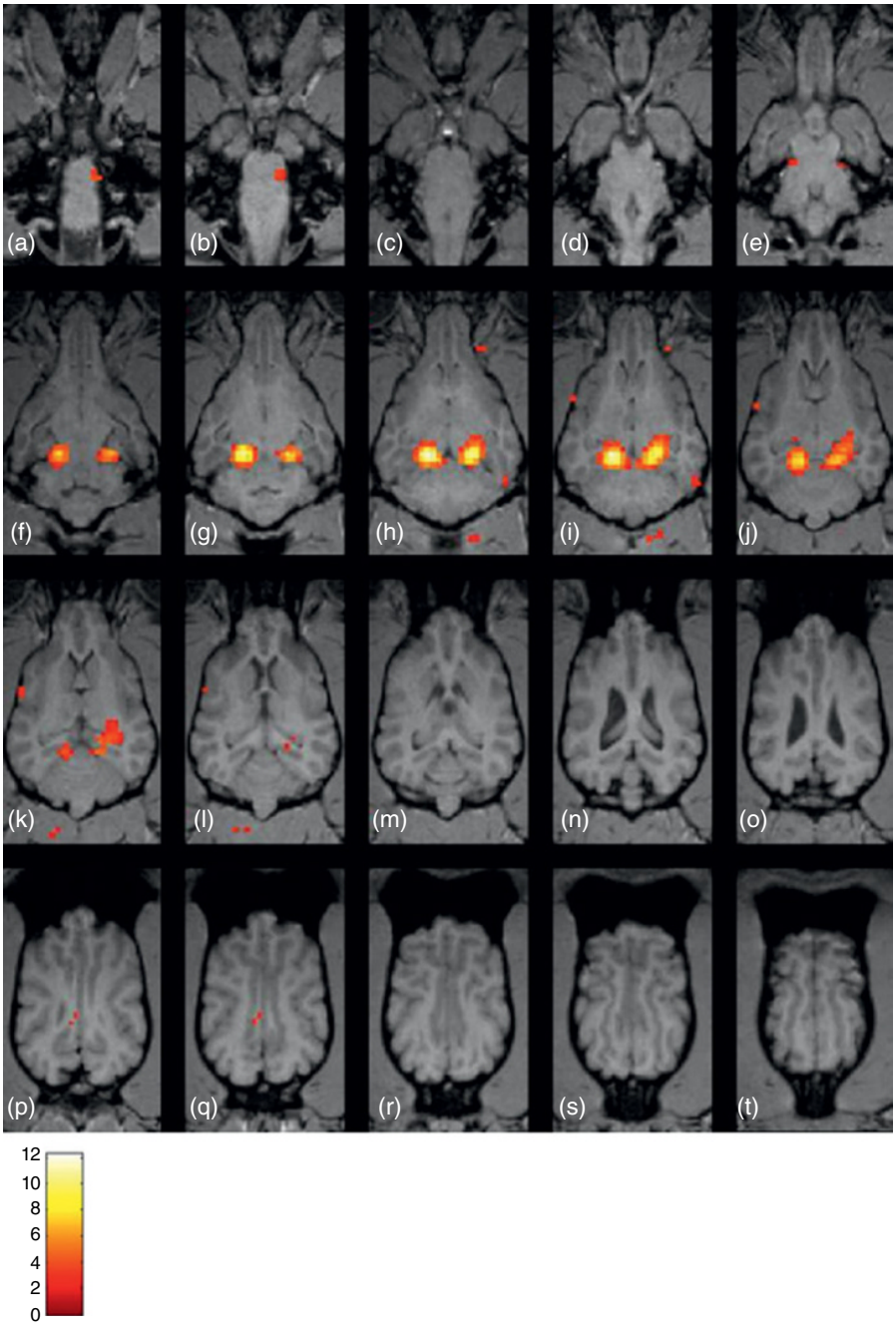


FIGURE 5.13 Multiple dorsal sections from the brain of a dog with superimposed BOLD-activation following auditory stimulation (a–t). T2*-weighted functional data were obtained using sequence 1 to identify voxels responding to auditory stimulation. These voxels were afterward superimposed on T1-weighted anatomical images of the subject (slice thickness between adjacent dorsal sections 2 mm) as colored pixels. The color bar indicates the *t*-values of the activated voxels. The pictures show the most significant activation in the region of the caudal colliculi (slices f–k) followed by the medial geniculate nuclei (slices h–k). Few activated voxels were found in the cortex and other regions of the brain. This activation pattern is representative of all functional data obtained with sequence 1. Bach et al. (2013)/BioMed Central Ltd/CC BY 2.0.

metabolism and blood flow can also be employed. Prior to the scan, the isotope is injected into the venous circulation (typically) of the patient. After an appropriate waiting period for the isotope to be integrated into the target tissue (about 1 h for FDG in the brain), the patient is scanned while the isotope decays. As the isotope decays, it emits positrons, which travel approximately 1 mm or less in the tissue, until a point where a reduction in kinetic energy allows it to interact with an electron. The positron–electron interaction destroys both elements and creates two gamma photons, which are detected by the scintillator. A focal area of epileptogenic activity will appear as zones of *hypometabolism* and reduced blood flow in the interictal period. Conversely, during an epileptic seizure, cerebral metabolism and cerebral blood flow are generally increased (Duncan, 1997). Capturing ictal activity can be a challenge due to the special facilities needed on-site to prepare the isotopes and the lag period between metabolism and analysis. In humans, one of the primary uses of a PET scan is in the presurgical planning for medically refractory epilepsy. Using specific ligands, researchers are developing techniques to determine the specific neurochemical abnormalities, which may lead to the development of epileptic seizures. Future development of ligands may help to elucidate the ligand–receptor interactions, which may be deranged, leading to the predisposition or direct development of epileptic seizures. PET scans are also used to help distinguish between various seizure syndromes (i.e., typical childhood absence from atypical absence conditions) and help in prognostication (Ochs *et al*., 1987; Gaillard *et al*., 1995).

As the technology improves, the resolution of PET scanners is allowing neurologists to examine areas of the brain, which hold an interest in the study of epilepsy (e.g., hippocampus, amygdala, and substantia nigra) (Engel, 2013). The availability of PET scanning to veterinary patients may provide an impetus for more exploration into surgery for the treatment of medically intractable epilepsy when a discrete lesion cannot be identified (e.g., neoplasia or malformation).

SINGLE-PHOTON EMISSION COMPUTERIZED TOMOGRAPHY (SPECT)

Gamma-ray-emitting radionuclides are bound to ligands and visualized in the brain by the use of a gamma camera. Similar to PET scanning, a SPECT scan will "see" the area of the brain where the gamma-emitting tracer has concentrated or where it is attenuated. An advantage over PET is that the single-photon-emitting isotopes have a much longer half-life and are practically more easily handled when compared to PET isotopes. Gamma cameras are more readily available compared to PET scanning equipment but are still considered primarily for research interests. SPECT scans may be used to measure cerebral blood flow, blood volume, and blood–brain barrier permeability through the use of technecium-99m-labeled *tracers* such as *(99m) Tc-hexamethylpropyleneamine (HMPAO)* and *(99m) Tc-ethylcysteinate (ECD)*. HMPAO and ECD are taken up into the brain in a proportional manner to cerebral blood flow, allowing the camera to detect the increased areas of blood flow in the brain during focal ictal events. Following injection, ECD is trapped intracellularly within 2 min (Peremans *et al*., 2001). This information is subtracted from interictal studies to identify a discrete area of increased blood flow (Figure 5.14). The same area would be expected to have decreased blood flow during the interictal time period (Oommen *et al*., 2004). Subcortical hypoperfusion and alterations in regional cerebral blood flow have been reported in epileptic dogs using 99mTc-ECD (Lass *et al*., 2006; Martlé *et al*., 2009). Studies of this nature may help identify some of the similarities between epileptic seizures in humans and veterinary patients. Because of its ease of preparation and rapid temporal resolution (another advantage over PET), imaging can be carried out during and shortly after an ictal event. Similar to PET and fMRI, SPECT scanning may be routine in presurgical planning in order to identify an epileptogenic site for resection. SPECT scans have lower resolution than PET scans and are typically co-registered with an MRI to allow for interpretation of both sets of data and a consensus diagnosis (Zubal *et al*., 1995).

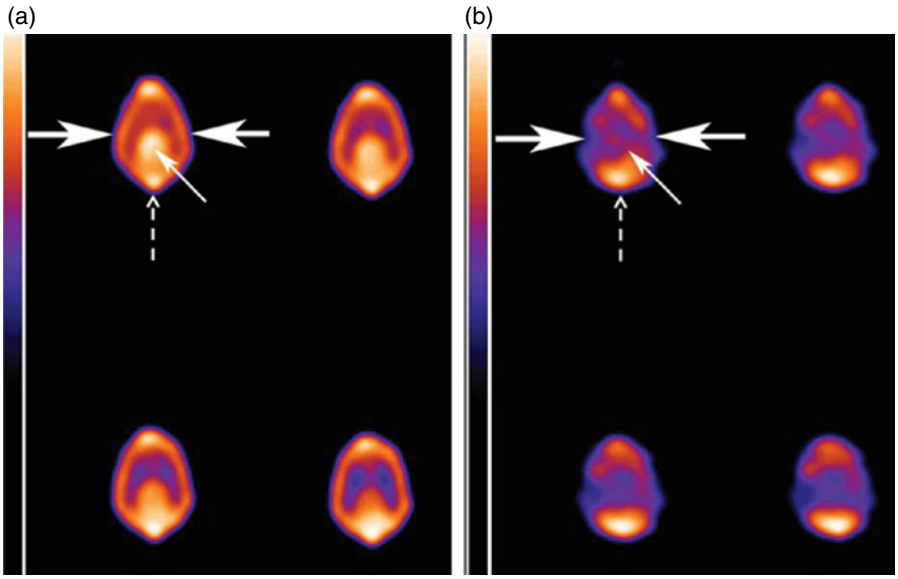


FIGURE 5.14 (a) Normal SPECT perfusion (a measure of neuronal function) images (four consecutive horizontal slices) acquired from a 5-year-old female Border Collie. The tracer used is technetium-labeled hexamethylpropylene amine oxime (HMPAO). Neuronal tracer uptake is seen in the cortical (two large arrows focused on the temporal cortex) and subcortical areas (small arrow) and cerebellum (interrupted arrow). The cortical uptake forms a nice delineated rim. (b) SPECT perfusion images (four consecutive horizontal slices) acquired from a 1-year-old female Scottish Sheepdog with neurological signs (including epileptic seizures) secondary to a portosystemic shunt. On visual inspection, decreased perfusion is apparent in several cerebral cortical (two large arrows focused on the temporal cortex) and subcortical (small arrow) areas (cerebellum indicated with an interrupted arrow), resulting in heterogeneous tracer uptake as opposed to the delineated homogeneous uptake in the normal dog (a). On quantification, general decreased activity was registered in all cortical and subcortical areas with significant decreases in frontal, temporal, and subcortical regions. Courtesy of Dr. Kathelijne Peremans, Division of Nuclear Medicine, Medical Imaging Department, Faculty of Veterinary Medicine, University of Ghent, Belgium.

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) utilizes the resonance frequency of a nucleus similar to MRI; however, instead of a two-dimensional structural image being created, MRS looks at the concentration of specific metabolites in discrete areas of the brain (Duncan, 1997). This noninvasive diagnostic provides biological information in regard to cerebral energy metabolism, tissue composition, and pH (Engel, 2013). The presence or absence of certain chemicals may provide information regarding the pathophysiology and MRS "fingerprinting" of various epileptic syndromes (Table 5.12). Due to their abundance in cerebral tissue, the most common nuclei examined are ^{1}H and ^{31}P. These nuclei are also present in compounds of interest in the brain including *N*-acetyl aspartate (NAA), creatine + phosphocreatine (CR), choline-containing compounds, lactate, myoinositol, γ-aminobutyric acid (GABA), glutamate, and glycine. With MRS, the tissue in the brain under examination is analyzed for commonly found metabolic compounds. The "peaks" show up in various areas corresponding with the specific compound. The area under the peaks can be measured to quantify the amount of the questioned substance essentially providing a noninvasive "biopsy" of the brain (Figure 5.15). ^{1}H-MRS metabolites have varying clinical importance. NAA, a cerebral amino acid and mitochondrial neuronal component, is recognized as a marker of neuronal density and viability. It is present in neurons, axons, and

Table 5.12 Summary of magnetic resonance spectroscopy metabolites

Metabolite	Location	Marker of	Significance of
N-acetyl aspartate (NAA)	Neurons, axons, myelin	Neural, health, density, and viability	↓ = neuronal loss or dysfunction
Creatine + phosphocreatine	All neuronal cells. Concentrated in glial cells	Energy metabolism and used as an internal reference	Control variable
Choline	Cellular membranes, myelin, oligodendrocytes, astrocytes	↑ with synthesis/destruction of cellular membranes	↑ = myelin breakdown, gliosis, and ↑ cellular density
Lactate	Diffuse cerebrum	↑ with prolonged seizures	↑ = brain ischemia. ↑ epileptogenic areas
Myoinositol	Astrocytes	↑ glial changes and changes in osmolality	Indicates osmolality disturbance (i.e., ↑ Na^+)
GABA	Diffuse cerebrum		Eval. efficacy of AED
Glutamate/ glutamine	Diffuse cerebrum	↑ = neurotoxicity	Cerebral damage

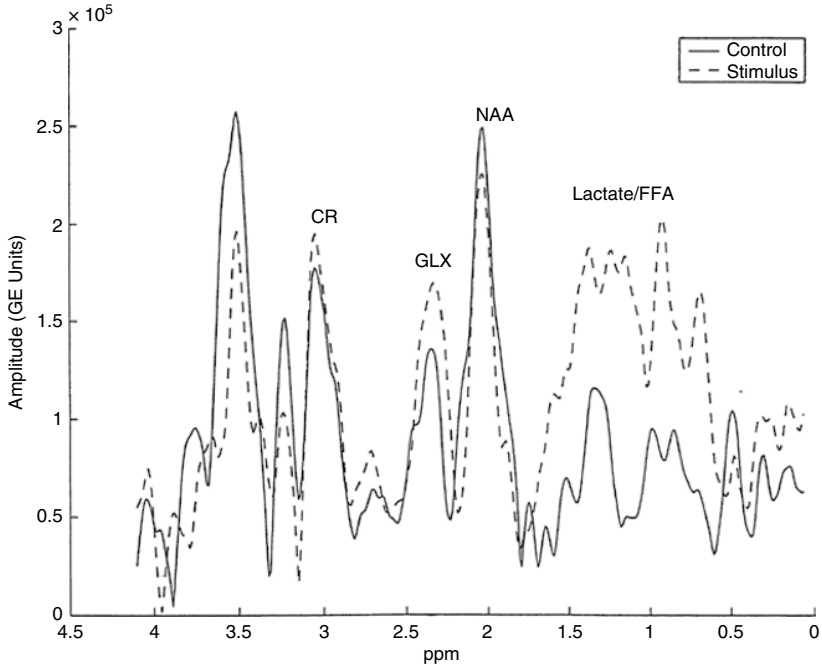


FIGURE 5.15 A control and postictal (stimulus) spectrum obtained from a mixed-breed dog. Stimulus MRS was obtained after 30 min of experimentally induced, pentylenetetrazol (PTZ, 20 mg/kg Q3–10 min) seizures. Note the postictal increase in glutamate and glutamine (GLX) amplitude and the emergence of lactate and free fatty acid peaks, an indication of tissue acidosis as an indicator of brain ischemia. Reproduced with permission from R. Neppl, C.M. Nguyen, W. Bowen, T. Al-Saadi, J. Pallagi, G. Morris, W. Mueller, R. Johnson, R. Prost, and S.D. Rand. 2001. In Vivo Detection of Postictal Perturbations of Cerebral Metabolism by Use of Proton MR Spectroscopy: Preliminary Results in a Canine Model of Prolonged Generalized Seizures. *American Journal of Neuroradiology*. 22(10):1933–1943. © by American Society of Neuroradiology.

myelin. Its presence is detected exclusively in the central and peripheral nervous systems. The absence of NAA in examined tissue is a marker for neuronal loss or dysfunction (Hammen *et al*., 2003). Choline is bound to cellular membranes and myelin. Choline levels will rise depending on the synthesis and degradation of cellular membranes. Its increase is suggestive of membrane destruction and gliosis. Oligodendrocytes and astrocytes contain increased amounts of choline, and resulting increases may suggest increased cellular density, as well as myelin breakdown and gliosis (Hammen and Kuzniecky, 2012). Creatine and phosphocreatine (CR) serve as an internal reference to other metabolites (Hammen *et al*., 2003). Lactate levels will increase and tissue pH will decrease (acidify) during prolonged seizures. An increase in lactate is a sensitive indicator of brain ischemia, and it is locally increased in epileptogenic regions of the brain, postictally (Neppl *et al*., 2001). Information regarding these changes can help in the study of the pathophysiology of epilepsy (Petroff *et al*., 1984). Myoinositol is primarily located in astrocytes, and its increase represents glial changes in the brain and disturbances of osmolality (i.e., hypernatremia) (Hammen and Kuzniecky, 2012). The measurement of GABA and glutamine is complicated due to their presence under the strong peaks of NAA and Cr. Additionally, they are found in small quantities in the brain. Special editing sequences are necessary to filter out the surrounding signals. The evaluation of these compounds, in particular GABA, may be helpful in evaluating the efficacy of antiepileptic drugs, for example, the ability to screen drugs against seizure types much like culturing a bacterial infection in order to select an appropriate antibiotic (Petroff *et al*., 1995; Cai *et al*., 2012). MRS has been utilized in the investigation of *biomarkers*, which may help predict epileptic seizure frequency, intensity, and response to medications (Filibian *et al*., 2012). A goal of biomarker discovery and analysis is the development of pharmacological means to prevent the formation of epilepsy and hinder its progression (Lesko and Atkinson, 2001; Pitkänen and Lukasiuk, 2011). MRS was used in a beagle dog with Lafora disease and demonstrated a decrease in NAA, much like that in humans affected with the same condition (Alisauskaite *et al*., 2020). In this case, Lafora disease was suspected based on the presenting clinical signs of *episodic reflex myoclonus* and confirmed with genetic testing. The MRI of the dog was structurally normal. MRS can be helpful in the presurgical evaluation of epileptics and in determining which surgery would be most beneficial (Spencer *et al*., 2005, Hasegawa, 2016). Much like other functional methods of evaluating the brain discussed previously, the application of this technology to clinical practice will potentially become more widespread as availability and access to high-strength MRI scanners become more commonplace. Many 1T MRI units have the ability to perform MRS if appropriate software is also present. The clinical application of MRS in classifying epileptic syndromes, elucidating the underlying pathophysiology of epileptic seizures, predicting response to therapy, identifying epileptogenic foci, prognosis, and potential for adjunctive therapy (e.g., surgery) will likely parallel that of human medicine.

MAGNETIC RESONANCE ELASTOGRAPHY

What if you could palpate the brain? Magnetic resonance elastography (MRE) is a technique where low-frequency "shear" waves are created and then monitored as they travel through the tissue in order to measure the visco-elastic properties of tissue. It is a noninvasive way to measure the stiffness of various areas of the brain (as well as other soft tissues such as liver and muscle). The shear waves will travel through different densities of tissue at different speeds (much like how sound travels differently through air or water). The information gathered is then processed into a colored map, known as an *elastogram*. This technique can be used to assess the consistency or "stiffness" of a brain tumor (i.e., meningioma) which may help with surgical planning (Murphy *et al*., 2013). In regards to epilepsy, the technique has been used to assess microstructural changes to areas of the brain, such as the hippocampus, before the area has grossly changed to the point where an abnormality of volume can be appreciated. Hippocampal sclerosis is characterized by

cell loss and reactive gliosis. Reactive glial cells are more stiff than normal cells (Lu *et al*., 2011). In one study, investigators were able to show a significant difference in the hippocampal stiffness ratio (comparison between ipsilateral affected hippocampus and contralateral, unaffected hippocampus) between humans affected with mesial temporal lobe epilepsy (MTLE) and control subjects (Huesmann *et al*., 2020). In humans, MTLE is considered one of the most common forms of drug-resistant epilepsy but also one of the most amenable to surgery. Early diagnosis is critical as progressive sclerosis of the hippocampus leads to resistance to treatment. If the condition is allowed to continue to develop (typically due to under treatment), the disease will progress to a contralateral seizure onset, whereby surgery is no longer an option (Wiebe and Jette, 2012). Initial presenting signs in humans (olfactory aura, episodes of anxiety, and/or déjà vu) can be vague (can dogs and cats experience déjà vu . . .? Imagine what that might look like in a dog or cat . . .) and early treatment is often delayed. If there is a way to diagnose the disease before other biomarkers are evident or the hippocampus is grossly changed, surgical resection may be performed earlier leading to typically, better outcomes and better quality of life (for people) (Engel *et al*., 2012).

EPILEPSY BIOMARKERS

What if there was a blood test, which could diagnose epilepsy before seizures occur? The benefits of early identification of a pathological process include early intervention and assessment of the efficacy of a treatment modality such as initiation of anti-seizure medication—identifying a need for earlier nonmedical intervention (e.g., surgery) and preventing the need for expensive and often invasive diagnostic testing. A biomarker is defined as "a physical sign or laboratory measurement which occurs in association with a pathological process and has putative diagnostic and/or prognostic utility" (Lesko and Atkinson, 2001). Bile acids are a biomarker for hepatic disease, as they indicate the presence of dysfunction or the progression of disease. Blood glucose is a biomarker for diabetes. Using gas GC-MS, researchers are able to identify specific biomarkers associated with drug-resistant epilepsy in humans (Kong *et al*., 2025). Biomarkers differ from *risk factors*. A risk factor only suggests an increased incidence or chance of developing disease but is not a reliable indicator. For example, severe head trauma may be a risk factor for the development of epileptic seizures but is not definitively associated with the development of epileptic seizures. An ongoing, long-term study looking at observable biomarkers for post-traumatic brain injury-induced epilepsy holds promise to identify blood biomarkers that may predict which patients need to start AED therapy *before* they start having seizures (Vespa *et al*., 2019). A *surrogate biomarker* is "a laboratory measurement or physical sign which is used in therapeutic trials as a substitute for a clinically meaningful endpoint that has a direct measure on how a patient feels, functions or survives and is expected to predict the effect of the therapy" (Temple, 1999). An example of a surrogate biomarker related to epilepsy could be an imaging modality which determines if a drug localized to a specific area of the brain or altered certain brain metabolites associated with epileptic seizures (i.e., as identified with MRS). Quantifying seizure burden, much like HBA1c is used to monitor diabetic control would be another ideal application (Banote *et al*., 2022). Discovering a reliable surrogate biomarker for epilepsy is a rapidly growing area of research. The importance of the identification of biomarkers of epileptogenesis (the identification of epilepsy before epileptic seizures begin) and epileptogenicity (a measurement of the severity or existence of epilepsy in the interictal state) was emphasized in the National Institute of Neurological Disorders and Stroke (NINDS) 2007 Epilepsy Research Benchmarks (Kelley *et al*., 2009). Biomarkers of epileptogenicity could (Engel, 2011):

- Determine *when* or *if* to start anti-seizure medication in a patient who presents after a single seizure event (i.e., differentiating epilepsy from a reactive seizure).
- Help to assess the efficacy of an anti-seizure medication before another seizure event (i.e., avoid the *trial-and-error* model of anti-seizure medication evaluation).

- Identify the epileptogenic region of the brain responsible for the generation of spontaneous seizures. This would reduce the cost and time associated with diagnostic testing and increase the efficacy of presurgical evaluation.
- Similar to a *culture and sensitivity* used in bacteriology and antibiotic selection, provide more immediate efficacious anti-seizure medications for treatment and screen new potential anti-seizure medications through clinical trials.

Several investigatory pathways have been proposed, and likely, many more will be propositioned as the research in this area expands (Pitkänen and Lukasiuk, 2011). They include but are not limited to:

- The identification of specific genomic expressions (Glasscock, 2014).
- Biomarkers of inflammation associated with epileptic seizures (Vezzani and Friedman, 2011).
- Changes in the expression of certain mRNAs related to epileptogenesis or epileptogenicity, known as *transcriptomics* (Redell *et al*., 2011).
- Alterations in metabolites such as glutamate, *N*-acetyl aspartate, lactate, pyruvate, etc. These metabolites may be measured in serum or CSF or through MRS (Dash *et al*., 2010).
- Measurement of certain proteins in serum or CSF, which may be reflective of changes in tissues during epileptogenesis and epilepsy (Xiao *et al*., 2009, 2010).

Targeted candidate biomarkers at this time include: S100 calcium-binding protein B, glial fibrillary acidic protein, neurofilament light protein, neuronal-specific enolase, and ubiquitin C-terminal hydrolase 1 to name a few (Banote *et al*., 2022). Biomarkers of neuroinflammation (e.g., cytokines), as well as, blood biomarkers of seizure burden, such as brain proteins (neuronal specific enolase increases even after a single seizure) hold promise (Rabinowicz *et al*., 1996).

The basic research associated with the investigation and identification of specific biomarkers of epileptogenesis and epileptogenicity is a rapidly expanding and emerging field in the study of epilepsy. This field holds a significant amount of potential to affect the way epilepsy is diagnosed and managed. Veterinary applications, in particular, are encouraging, as our patients typically have to *show* us signs of disease rather than *telling* us about their condition. If we have the ability to look for disease markers, more effective treatment outcomes may be possible. Advances in this field are already becoming apparent in basic veterinary research in the area of biomarkers associated with steroid-responsive meningitis (Schwartz *et al*., 2008; Maiolini *et al*., 2013).

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Medical Management of Seizures

CHAPTER 6

KEY TAKEAWAYS

"Pseudoresistance" is the premature failure of a medication.

Fail a drug only when:

- Side effects (or client-related factors) outweigh the benefits.
- You have reached the upper end of the serum concentration reference range or double the starting dose.

Many strategies can be utilized to treat epilepsy.

What is treatment success? A 50% reduction in the epileptic seizures without toxic side effects of the medications.

What is a drug-resistant epilepsy?

- Failure to attain seizure freedom after two therapeutic trials of appropriately chosen and managed antiepileptic drugs.

A significant number of drug-resistant epileptic patients can still have improvement when other drugs are failed, although the rate of success declines.

QUICK JUMP

When to start treatment p. 201 (Table 6.1)

Formula for calculating $t½$ (Table 6.4)

Maintenance medications for dogs (Table 6.6)

Maintenance medications for cats (Table 6.7)

Status epilepticus medications for dogs and cats (Table 6.8)

Stability of benzodiazepines when dispensed for home use (Table 6.9)

Therapeutic drug monitoring—why and when? (Table 6.10)

How do I stop a medication? Table 6.11

Introduction	198	Treatment Strategies	228
Why Treat Epileptic Seizures	199	Drug Monitoring	247
Dosing	205	Discontinuation of Medication	247
Pharmacological Principles	208	Conclusion	248

Myelominutia: Could antiseizure medications create resistance through artificial selection of drug resistant seizure circuits?

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INTRODUCTION

The most important element accompanying the discussion of epileptic seizures is treatment. It is what the owner of the pet and the veterinarian is most interested in. Regardless of the cause of the epileptic seizures, early and effective treatment allows the patient to have a better quality and *quantity* of life. Of all treatment modalities available, medical management using drugs will be the most common, effective, and financially feasible approach. Proper management improves the pet's quality of life *and* the owner's quality of life (let's never discount the impact of epileptic seizures on a pet owner's mental status), helps to reduce the chances of seizure progression (including status epilepticus), helps to prevent sudden death or debilitation secondary to epileptic seizures, and gives the clinician time to elucidate the underlying etiology of the epileptic seizures.

The basic tenant underlying medical management is:

Treat the patient early and treat them effectively.

The above statement means—do not wait until seizures get "bad" before you treat them and above all, use the correct, published dose of a medication. Underdosing an antiepileptic drug (AED) is like underdosing an antibiotic. Why would you do that? One of the most common mistakes I see is starting a patient on a "low dose" of phenobarbital, not seeing adequate control of the epileptic seizures, and then adding in a second medication without failing the first (i.e., increasing to effect or side effect). This is a common theme you will read often in this book. Multidrug treatment creates *pseudoresistance* and a "tangled" knot of medications, which is often difficult to unravel down the road.

A significant amount of trepidation surrounds the medical management of epileptic seizures both for the clinician and the pet owner. Most pet owners have access to the same information as veterinarians regarding available medications and typically a significantly greater amount of time to devote to research regarding the medications the veterinarian may prescribe. Many pet owners will be well-prepared and knowledgeable when it comes to medical management options, through their own research. However, since much of the information they have access to is in regard to the human application of the same mediations you may prescribe, it is the veterinarian's responsibility to help the client determine which medications may be helpful or harmful in addition to a multitude of other factors, such as side effects, availability, cost, and efficacy. The veterinarian will be able to help the client understand why treatment is necessary, when treatment is needed, which medication to use, and what strategy or strategies to employ for each particular patient (things we will cover in this chapter).

While the basic understanding of treatment principles will be the same (if not identical), in regard to dogs and cats, the medication options which can be used will be s*lightly* different, with cats typically having fewer options and in general less empirical and scientific data surrounding those options. Additionally, cats tend to be more difficult to dose (thankfully ...there are some workarounds).

A veterinarian must also help the client monitor seizures, seizure patterns, response to medications, seriousness of side effects, and when to change medications or their dosages. Helping the client to determine the right *balance* between effective seizure control and medication side effects (or potential side effects) is also important. This also includes the very critical element of a *combined* professional approach to the management of an epileptic patient. Relying on specialists alone to make medical decisions for the patient will lead to delay in treatment, potentially unnecessary progression of disease, and increased suffering to the patient and its caregiver. The triangle of management depends on the patient's caregiver, the primary care veterinarian, *and* the specialist. Therefore, it is important the *primary care veterinarian* takes an active role in the management of the case, relying on the specialist when needed.

Finally, the veterinarian will likely be placed in the situation of being a sort of "therapist" for the client. The client, the patient, and your practice will be well served by having someone to guide the animal caregiver through the confusing journey of medical management of epilepsy. The client will look to the veterinarian for support and guidance. As stated before, epileptic seizures are frightening and are a very emotionally charged medical condition for the caregiver. Feelings of helplessness on the part of the pet owner and assuming the patient is "suffering" may lead to premature euthanasia. As you help guide your clients through the medical management of epileptic seizures, keep in mind some clients will communicate at the slightest degree of worry, whereas others may wait until the situation has degraded to a point where intervention and successful management become more difficult. One of my fears is I will hear a patient was euthanized without my knowledge or consultation [usually through an emergency room (ER) visit], especially when we were at the beginning of the management journey. For that reason (and a few others), I tend to spend an inordinate amount of time mapping the future treatment of the patient on the first visit, as well as encouraging the doctors I work with to seek out my consultation when they need it but not to be afraid of making decisions for the pet (this goes for primary veterinarians, as well) when the specialist is not available. I need the pet owner to know I am there to help. If you are able to teach the client and give them a basic understanding of epileptic seizures and their management, they will have more confidence in treating the condition, be better prepared to make decisions regarding treatment, and above all, be less reactive when treatment fails or needs to be modified.

WHY TREAT EPILEPTIC SEIZURES

Some would argue that statistically whether we treat or do not treat idiopathic epileptics makes no difference in the outcome of the case. I would remind the reader that our patient is not a statistic. Our patients are individuals and members of a family. Even if there is a 1% chance of making a difference in that pet's life, we will not see success if we do not try. We try to prevent epileptic seizures from occurring in order to slow down or prevent their propagation, improve the patient's and pet owner's quality of life, and reduce the risk of serious neurological or medical impairment due to uncontrolled seizures; to give the clinician more time to elucidate the underlying cause of the epileptic seizures; and above all to prevent the unnecessary euthanasia and suffering of our patients. The purpose of treatment is foremost to prevent the continuation and progression of epileptic seizures. Epileptic seizures can be thought of as a "memory" in the brain. The neural connections that develop in an epileptic patient make them prone or *primed* to have more seizures. The more seizures they have, the more likely neurons will "learn" to fire uncontrollably or with synchronicity. Like a memory that is reinforced and becomes harder to forget (e.g., your name), seizures occurring over and over again will become more difficult to treat as the brain is less likely to "forget" the specific neural connections. If we can stop or significantly reduce the epileptic seizures, the brain is more likely to "forget" the circuit which has developed and use those neurons for another task (similar to forgetting an inconsequential bit of information—such as the price of a gallon of milk 2 months ago). Think of the seizure as becoming *short-term memory* as opposed to *long-term memory*.

Epileptic seizures are very frightening to pet owners. Feelings of *helplessness* even add more to the emotional equation. Many pet owners may think their friend is in the process of dying if they are uninitiated to the event. Epileptic seizures can be very emotional and draining to a pet owner and family. Sleep deprivation, constant worry, compassion fatigue, and feelings of helplessness may lead to the transposition of "suffering" from the owner who is experiencing a heightened emotional state to their pet. It's even more difficult to explain the situation to children. When the pet is labeled as "suffering," an owner may justify the premature euthanasia of the pet either from the perspective they are "helping" their animal by eliminating suffering or helping themselves by eliminating an unnecessary burden on their own life (which a pet owner will *occasionally* admit).

Animals do not really *suffer* when they are having seizures. Most likely they have the same feelings as humans who experience seizures. Humans who "suffer" through epileptic seizures will describe feelings of extreme fatigue, being disconnected from the environment, or just waking up and not really being sure where they are or what they were doing (i.e., "brain fog"). Explaining this to pet owners can help tremendously with their ability to accept the problem. The veterinarian's role is trying not only to prevent or reduce the seizures from the beginning but also to provide a source of information, reassurance, and guidance to the pet owner through the process. Early and consistent communication with the pet owner will help tremendously to prevent premature euthanasia, improve the pet owner's quality of life, and extend the pet's *quantity and quality* of life. The natural place of the veterinarian is to be the pet's advocate. To do this, you must effectively go through the pet owner (see Chapter 4).

Epileptic seizures will rarely cause harm to the brain. However, states of status epilepticus or prolonged clustering may lead to neural tissue damage and metabolic derangements. Of paramount concern in the case of status epilepticus is the potential for hyperthermia due to sustained and protracted muscle activity. Body temperatures over 105 ºF (40 ºC) for a sustained amount of time may lead to organ dysfunction and metabolic derangement (this is concerning but thankfully, rare). Liver failure, renal failure, metabolic acidosis, aspiration pneumonia, and disseminated intravascular coagulation are examples of the potential complications associated with severe epileptic seizures. Self-trauma or accidental trauma is not common; however, falling down stairs or off decks and drowning are possible secondary sources of injury or death even with mild seizures. Most seizures are self-limiting; however, it is *impossible* to predict which seizures will come to an end on their own and which may progress either to secondary generalization, status epilepticus, or clustering. Therefore, until convinced based on long-standing patterns (and even then, it is a gamble), assume all seizures have the potential to be dangerous. Sudden unexplained death in epilepsy (SUDEP) is rare but a potential outcome with any single seizure event, although more likely to occur in younger patients, suffering from poorly controlled generalized, tonic–clonic seizures and on multiple AED treatments (Hamamoto *et al.,* 2016). Euthanasia remains one of the greatest risk factors, leading to decreased lifespan in canine patients with epilepsy (Berendt *et al.,* 2007). Several studies report that dogs with idiopathic epilepsy do not have a shorter lifespan compared to non-epileptic dogs (Gulløv *et al.,* 2012; Hamamoto *et al.,* 2016). We can probably assume the same goes for cats. However, other studies report a shorter lifespan (Berendt *et al.,* 2007; Saito *et al.,* 2001). The clinician should always remember, the more seizures a patient has, the more likely they are to be euthanized (Berendt *et al.,* 2007; Fredsø *et al.,* 2014). We need to remember epilepsy affects not only the quality of life of the patient but also of the caregiver (Wessmann *et al.,* 2014).

Finally, reducing the number of hospital visits, stress on the patient, stress to the owner, and financial stress over emergency hospitalization is a good reason to work hard to prevent or reduce all seizures. Achieving a balance between the incidence and severity of seizures against the downsides of medical treatment (cost, dose, frequency, side effects) should be your goal and the pet owner's goal. Never try to assume what a pet owner is willing or not willing to do. Always be optimistic and assume the best outcome until demonstrated otherwise. Another potential trap the clinician may inadvertently fall into is assuming the pet owner understands concepts the veterinarian may think of as common sense. Keep in mind:

> *Common sense to one person may be critical thinking to another.*

Your clients are more interested in understanding their pet's ailment than your command of *medicaleze* (i.e., flooding the conversation with excessive medical vocabulary, they most likely do not understand but will continue to look at you and nod their head in agreement). Successful treatment, whether reducing the frequency or severity of the seizures, will buy the veterinarian "time" to

elucidate the cause. Even without diagnostic tests to rule in or out certain disease processes, the lack of progressive neurological dysfunction over time will allow the clinician to make a relative assumption as to the syndromic classification of epileptic seizures (see Figure 4.6). When faced with a new diagnostic "puzzle," the clinician will either look for other pieces of the puzzle through diagnostic test results or wait for new pieces through the development of or absence of neurological dysfunction (which can *only* be localized to the brain). Treatment of seizures does not mask the underlying problem or make it more difficult to detect with diagnostic testing (with the exception of the electroencephalogram (EEG) and corticosteroids). While it is very important to make sure you are indeed treating *epileptic* seizures and not a "seizure-like" event, once the determination that epileptic seizures are occurring has been made, treatment should be recommended regardless of the underlying cause (note: the use of corticosteroids to treat autoimmune causes of seizures is ...nuanced to say the least).

WHEN TO TREAT

One of the most common questions asked is, "when to start treatment?" We can place several general guidelines which can help with the determination of when to start treatment; however, this determination is not absolute (Table 6.1). Early treatment results in a better long-term control of seizures (Heynold *et al*., 1997). The decision of when to initiate treatment may depend on *absolute* and *arbitrary* variables. Think of it as a sliding scale of *relative necessity to treat* (Table 6.2). There are certain absolute variables in the equation which would lead us to initiate treatment, whereas there are other variables which may slide the decision-making scale to a decision not to treat or at least conditionally delay treatment. We may consider some elements to be more *subjective* or *arbitrary* determinants of treatment. For example, a pet owner's fear-based emotions concerning the possible detriments of a seizure or the emotional stress involved in watching a seizure may lead to earlier treatment compared to the same patient who belongs to a client who

Table 6.1 Guidelines for treatment.

Absolute	• Any seizure secondary to trauma
	• After any episode of status epilepticus
	• Multiple seizures in a short period of time. ≤6 months (i.e., clusters)
	• Any seizure secondary to a known or *highly suspected* cause (tumor, encephalitis, etc.)[a]
	• A trend toward increased frequency or severity of seizures
	• Excessive or prolonged postictal deficits
	• ≥2 seizures within a 6-month period
Recommended	• Significant emotional stress on family members
	• Tendency toward trauma or multiple ER visits
	• "Threats" of euthanasia
	• Attacks by other dogs in family or "stress" to other pets

[a] If you suspect the patient may be suffering from a structural cause of epilepsy.

Table 6.2 Relative treatment scale.

Status/trauma	ER visit cluster	Patient concerns	Owner concerns	Medication concerns	Single seizure
◀					▶
Treat					**Don't treat**

is more concerned about the possible side effects of treatment, potentially leading to a delay in treatment. There is no absolute correct answer and making the determination can be frustrating for an owner. The veterinarian who can objectively weigh all the variables can help guide the pet owner to the correct decision for themselves and *their* pet. Generally, the goal would be to have *no* seizures with *no* side effects, as soon as possible. A secondary goal would be to reduce the frequency and/or intensity of seizures, status epilepticus, and clustering, relative to pre-treatment levels. Defining the underlying etiology should always be attempted; however, when the cause is elusive or diagnostic testing is not practical or possible, treatment of the seizures is still recommended. If you are waiting for a referral to a neurologist and afraid treatment may alter diagnostic tests, treating epileptic seizures (with standard AEDs) will only potentially alter the results of an EEG (not the minimal data base, MRI, or CSF analysis). Successful treatment depends as much on the pet's guardian as the veterinarian who is making recommendations. The client must understand the disease, know what treatment entails, and be aware in many cases treatment may be chronic (if not lifelong); can lead to potential adverse side effects, may be expensive, time-consuming; and, unfortunately, is rarely 100% successful. A more reasonable goal, rather than complete cessation of seizures, would be a 50% reduction in the frequency of epileptic seizures without toxic side effects of the medications (Farnbach, 1984; Marson *et al*., 1997). The veterinarian should always strive for complete control, but a balance must be achieved between medical management and lifestyle consequences for the pet and its owner. Previous studies have estimated only 30% of dogs treated will have their seizures eliminated (Lane and Bunch, 1990). This is about the same success rate as with humans. Furthermore, only 15–24% of dogs go into seizure remission between 1 and 3 years (Berendt *et al.,* 2002; Hülsmeyer *et al.,* 2010; Gulløv *et al.,* 2012). Other epidemiological studies have validated previous estimates when referring to older antiseizure medications with seizure-free dogs approaching 30%, a reduction in seizures at 53%, and no improvement or worsening with treatment at 27% (Heynold *et al*., 1997). Client education is paramount to successful treatment. Clients will be inundated with information from multiple easy-to-access sources, such as websites, online forums, neighbors, others who experience seizures personally or in their own pets, and paraprofessionals in the veterinary world (rehabilitation therapists, pet store employees, animal psychics, trainers, etc.). A client handout highlighting the key points of epileptic seizures and its diagnosis and management can be very useful. The more educated the client is at the beginning and the more questions answered, the less frustrated they will be, which often translates into better compliance and more successful treatment (see Chapter 4). Furthermore, your credibility as a knowledgeable and capable clinician will be enhanced by providing information upfront before a crisis ensues. As we advance in the study of epilepsy, more refined treatment protocols will be developed which are specifically tailored to treat various subgroups of canine and feline seizure disorders. Finally, check the literature periodically. This is an ever-evolving subject.

Our treatment guidelines are generally reflective of the recommendations from the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement published in 2016 (Podell *et al.,* 2016). We can divide the guidelines into "absolute reasons to treat" and "recommended reasons to treat" (Table 6.1). Certain absolute reasons to treat are less negotiable with a client, and an emphasis on early treatment should be given. Any seizure secondary to *head trauma* should be treated. Clients should be aware epileptic seizures secondary to head trauma may show up anywhere from months to years after known head trauma, likely due to the development of *glial scarring* (Dewey, 2000). Whether or not to preemptively treat following an incidence of head trauma and prior to the first seizure is the subject of much debate. Generally speaking, even in the event of known head trauma, one would not prophylactically treat epileptic seizures unless certain circumstances occur (see below). The advantage of treatment is a potentially more successful long-term seizure-free period along with the reduced possibility of developing comorbidities associated with seizures. The disadvantage would be the potential

stress, cost, and side effects on the caregiver and patient when an anticonvulsant is not necessary. With the development of newer AEDs, which have few if no side effects and are relatively inexpensive, the author prefers to initiate treatment prior to the development of the first seizure, *if* the head trauma resulted in the patient becoming unconscious or there is *demonstrated structural damage* to the brain through advanced imaging (MRI or computed tomography [CT] scans). If you proactively treat the patient and they are seizure-free for 6 months, then the medication may be gradually withdrawn. Of course, client concerns may overrule the decision to treat early. If a *reactive* (toxin) or *metabolic* cause of seizures is suspected, treatment may be stopped after the cause has been eliminated (but warn the pet owner a "rewiring" of the brain could have occurred making the seizures more likely to return).

Treatment should be instituted after any episode of *status epilepticus*. To remind the reader, status epilepticus is defined as a seizure showing no clinical signs of stopping after a time, which would represent the typical cessation of that type of seizure for that patient *or* recurrent seizures without interictal resumption of baseline central nervous system function (Blume *et al*., 2001). Practically, this could also include any seizure lasting longer than 5 min or three or more epileptic seizures occurring within a 24-h period (i.e., a cluster in this sense) (Podell *et al.,* 2016). There is no strict definition, but it is generally accepted the longer the seizure, the more likely it is referred to as status epilepticus (relative to the patient's previous seizures). The increased concern underlying an episode of status epilepticus is the desire to prevent physical harm to the patient (hyperthermia), metabolic derangement, or damage to the brain and the general tendency of patients who experience status epilepticus to visit the ER in order to stop their epileptic seizures and give supportive care for the often-extended postictal time periods associated with status epilepticus.

Multiple seizures over a short period of time (days or weeks) or epileptic seizures classified as a *cluster* would indicate the need for treatment. A cluster is defined as multiple seizures within a given period of time (usually 1–2 days) exceeding the average incidence over a longer period *for the patient* (Blume *et al*., 2001). We would also consider treatment to be more imperative if there were a general *tendency* toward an increased frequency or intensity of seizures. Recognition of a change in the pattern of epileptic seizures may allow earlier treatment, thereby preventing a less successful outcome, *kindling*, or the development of *mirror foci*. Kindling is the phenomenon whereby the duration or generation of seizures is induced preferentially through the experience of repeated seizures (one seizure causes another) (Bertram, 2007). Following a discharge of electrical activity, some neurons may experience *after discharges*. This grouping of electrical discharges following a stimulus may promote the generation of synchronous firing activity of neurons and be a source of potential epileptogenesis. A *mirror focus* is an area of the brain where seizures are generated, which is homologous to an actively discharging epileptiform region on the opposite side of the brain (the primary epileptogenic site) (Gilmore *et al*., 1994).

Suspected or verified *structural brain disease* should be treated. Typically, this would be verified by neurodiagnostics, such as advanced imaging or cerebrospinal fluid analysis. This may include etiologies, such as stroke, hemorrhage, tumor, encephalitis, or any other structural abnormality of the brain. The justification is based on the notion a known cause exists and those epileptic seizures secondary to structural brain disease tend to be more difficult to control and are more likely to be associated with recurrent epileptic seizures. We know they will happen; therefore, it is highly recommended to treat. One may argue (admittedly, successfully) treatment in the face of nonprogressive disease, such as developmental malformation (hydrocephalus), stroke, or hemorrhage, is not necessary as these conditions *may not* progressively worsen with time. A reasonable tactic would be to treat these seizures similarly to the case with known head trauma. Start with a safe, inexpensive, and effective medication and discontinue therapy (through gradual withdrawal) if after 6 months there are no further seizures.

Finally, there are a few more conditions where it is recommended to treat epileptic seizures. If the patient is demonstrating a trend toward increasing frequency or intensity of seizures. For example, you may be presented with a 3-year-old cat who has had two seizures in 24 months. However, the last seizure was 8 months ago and the cat has had two more since then. This may demonstrate an increase in frequency is ensuing. Additionally, if seizure frequency is maintained but the seizures are lasting longer or have progressed from focal to generalized, it might be a good idea to start treatment (but that is not to say "don't treat focal seizures"—we should treat them if necessary). Along those lines, if the patient is experiencing excessive or prolonged postictal deficits, treating the seizures may help prevent or even lessen the excessive postictal time period. Even for those patients whose seizures are considered infrequent, treatment should be initiated if there are more than two seizures in 6 months.

The guidelines which garner the label of "recommended reasons to treat" are a little more on the subjective side; however, their reasons still have merit. These cases may be argued by pet owners who are afraid of the potential consequences of therapy (side effects) or the hardship it would confer on their lifestyle (the need for compliance). They may be opposed to the necessity of routine therapeutic drug monitoring or have financial concerns regarding therapy. They may be "antidrug" or insist on homeopathic, naturopathic, herbal, or folk treatments. While these integrative treatment options may (or may not) have merit, they should not replace a treatment, which is proven to work (see Chapter 9). Epileptic seizure events may be so brief (lasting only a few seconds), possibly nonconvulsive (e.g., behavioral arrest), with a quick recovery and no demonstrated progression over time, whereby the necessity of treatment is not warranted. In these cases, the potential *benefits* do not outweigh the potential *risks* or *costs*.

Epileptic seizures, which are infrequent and nonprogressive, may still have a significant impact on the pet owner or family members, and treatment could be arguably justified based on the emotional stress to the family. Conversely, the emotional stress, lifestyle change, cost, or worry about potential side effects may also slide the scale toward not treating in certain cases. We should not underestimate the potential hardship a family may experience when watching a beloved pet have a seizure. We are all "wired" differently when it comes to the ability to handle certain stressors or experiences. As a clinician, we should be giving the client all the relevant information regarding epileptic seizures, the prognosis, and their treatment. We should then listen to the clients' concerns and try to alleviate those, which may be unreasonable (without pressure), and remind the client we are there to give *recommendations* and *options*. One of the main roles of our profession is to advise and recommend within the guidelines the pet owners set forth. They may not be aware of their own limitations, but many fears and much trepidation can be alleviated by sincere conversation. Stay empathetic and compassion will happen naturally.

Even where epileptic seizures are considered mild by the professional or not frequent enough to justify therapy, occasionally clients will *threaten* euthanasia because of the hardship an animal having seizures may bestow upon the household. Do not take these threats lightly and do not *dismiss* a client's concerns. There is nothing to stop them from nodding their head in agreement with your arguments and then going down the street to the next available clinic or worse ending a pet's life on their own. Take their concerns seriously and try to educate but again, do not pressure. Many clients may not be aware of the newer, safer, and less expensive medications, which require little or no therapeutic monitoring. These cases can easily slide the treatment indicator toward treatment rather than euthanasia as an alternative.

A significant cost and concern regarding chronic epileptic seizures is the multiple (and often late night or early morning) visits to the ER clinic either to stop a seizure or provide supportive care when there is an extended postictal state. These visits can be trying on a pet owner and expensive. These instances may justify earlier treatment.

Finally, some owners may express concern about stress to other pets in the house or attacks by one pet on the pet having seizures. A pet having an epileptic seizure may appear threatening to other animals. Attacks on a pet having seizures by other pets in the household are likely.

Some general rules may also be applied to the decision-making process in the treatment of animal seizures adapted from those decisions used to treat humans (Engel, 2013):

- It is generally well accepted minor focal motor seizures, brief myoclonic seizures, or absence seizures do not need to be treated if the medication or hardship to the caregiver in giving medication would cause more harm than good. Be aware, however, of the potential for secondary generalization and changing patterns toward increased severity or intensity.
- Tonic–clonic seizures and focal dyscognitive seizures should always be treated as there is an increased chance of sudden death, structural damage to the brain, extended hospitalization, or premature euthanasia.
- It is acceptable to allow an occasional event in a patient who may be already compromised rather than risking additional compromise in order to gain better control.
- Drug-resistant epilepsy is considered when the patient has tried two drugs at maximum dosages either alone or in combination. These patients should be referred to a neurologist. A significant number of patients may still benefit from other therapies.
- The veterinary neurologist may be able to identify more appropriate treatment modalities or medical therapies. It is in the patient's and client's best interest to be co-operatively managed by a neurologist *and* primary care veterinarian when the case is complicated.
- Consider each patient as an individual and not a population. Achieving a balance between seizure control and side effects of medications is the primary goal.

These "rules" are meant to be guidelines to help the clinician with decisions regarding the aggressiveness of therapy. Epidemiological data concerning epileptic seizures in dogs and cats is significantly lacking compared to humans. The approach to the treatment of epileptic seizures in dogs and cats should focus on the individual patient and not the *population*. What works for one patient may not work for another, hence the necessity to forewarn a pet owner of the potential degree of commitment necessary to help these patients. Try to avoid painting a "doom and gloom" picture and focus on the positive.

DOSING

When considering the dosing of an antiseizure medication, the goal is to use as little medication as possible but as much as necessary. We dose to achieve a *steady-state* concentration in the blood. Steady state is the concentration in the blood where the amount of the medication given and the amount of the medication eliminated are equal and the serum concentration of the drug is maintained. Published doses and guidelines are to achieve a steady state. Use them. With standard doses, we try to maintain the concentration within an established therapeutic range (Figure 6.1). Steady state is achieved at approximately 5½ half-lives of the medication (Figure 6.2). The *reference range* is a statistical concept, which is determined by the level of seizure control or side effects within a population of patients and therefore should only be used as a guide with individual patients. The specific disposition of a medication may vary among individuals and idiosyncratic effects must also be considered as possible consequences to novel medications. Some patients require more medication to achieve the desired effects, whereas some do not require as much. The *therapeutic range* is the concentration within the blood, which is high enough to produce desired results (efficacy) but below a level of intolerance or the development of adverse side effects (Figure 6.3). The therapeutic range is not dependent on a population but is determined by the individual's reaction to a single medication at a particular dose. Any one individual patient may have their seizures controlled by a dose which is below the reference range and therefore would not need to have an increased dose, whereas another individual may require a dose that creates a serum concentration above the reference range to control

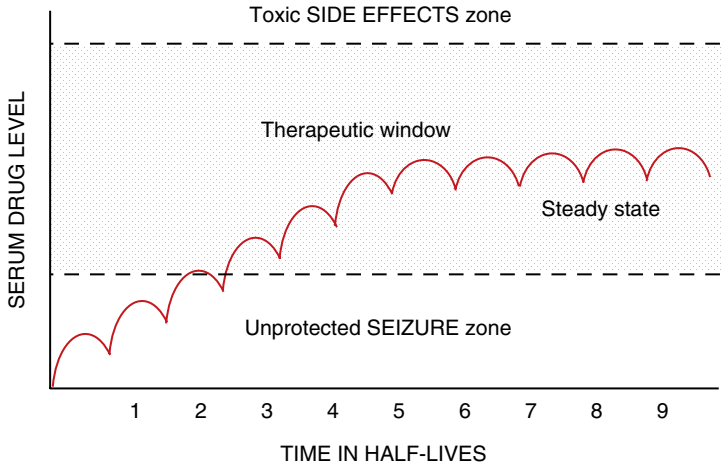


FIGURE 6.1 Steady state is achieved by 5½ half-lives after consistent administration of a drug at intervals of one half-life or less. When steady state is achieved, the amount of drug coming into the patient equals the amount being eliminated. The "therapeutic window" for the patient is the amount of drug necessary to achieve the desired results (i.e., seizure control) with minimal or no side effects.

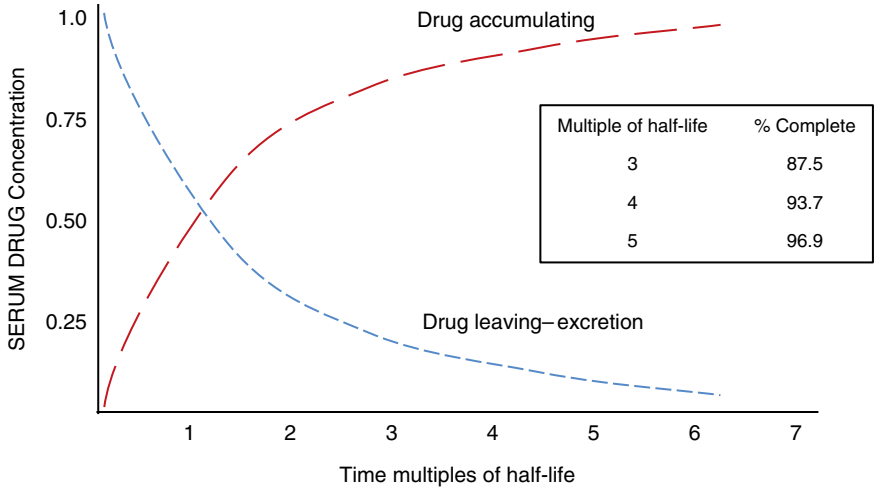


FIGURE 6.2 Serum drug level elimination over time following a single oral dose. At a multiple of three half-lives, 87.5% of the drug is eliminated. At a multiple of 5 half-lives, nearly 100% of the drug is eliminated (blue dashed line). Time to steady state is the converse whereby at a multiple of 5 half-lives, the drug is at 96.9% of steady state (red dashed line).

seizures. This is ok, if there is an adequate balance between the toxic side effects *at that particular dose*, the patient's dose would *not* need to be reduced in order to fall within the reference range. So essentially, if seizures are controlled at a dose that is below the reference range—great! If seizures are controlled above the reference range—also great! But, watch out for side effects (this may include more warnings to the owner and more frequent surveillance). Actually, watch out for side effects at any level. Remember, these patients are outliers when compared to the general population for which the reference range was established but have their individual therapeutic range achieved. Remember to treat the patient, *not the lab work*.

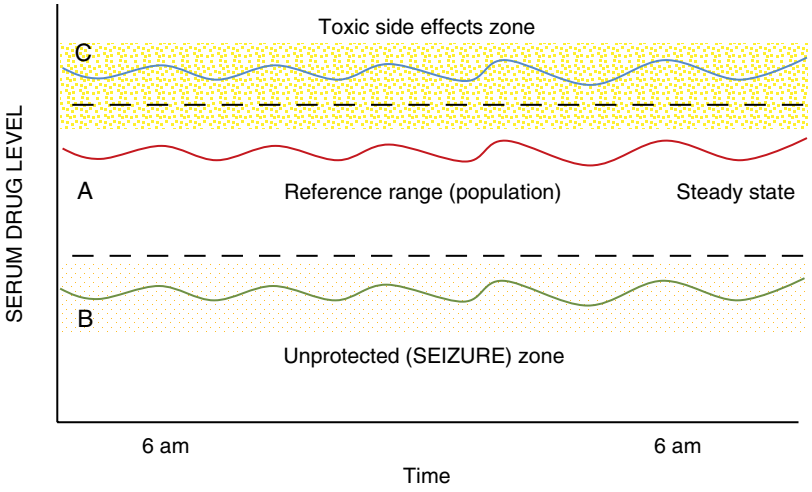


FIGURE 6.3 The relationship between the *reference range* of a medication and the *therapeutic range* of a medication. (A) For the population, the reference range is the amount of drug, which provides effective seizure control with no side effects. (B) For this patient, its own therapeutic range (no seizures and no side effects) may be below the reference range (the orange area). An increase in medications is not necessary if the blood concentration is below reference range (as long as seizures are controlled). (C) For this patient, an amount of drug outside of the reference range is necessary to manage seizures (the yellow area). A medication reduction is not necessary unless the *individual* develops negative side effects or there is concern of impending side effects (i.e., liver failure). For patients (B and C), the stippled area represents the *individual* therapeutic range (hypothetical). For example, in regards to patient (C), a slight decrease in the dose of the medication may drop the serum concentration out of the side effect zone while still maintaining good seizure control.

When beginning a novel antiseizure medication in a patient, a determination needs to be made as how important it is to achieve rapid serum concentration. This determination will be made based on factors, such as how severe the seizure(s) was, the presence of any other underlying disease states (comorbidity), the age of the patient, and the owner's concern for seizure control or possible side effects. A comorbidity may alter the medication you choose. For instance, a dog with pre-existing suspicion for liver disease or a patient with a portosystemic shunt would need careful consideration when choosing the medication or dose of the medication, if the medication is significantly eliminated by the liver or has the potential to exacerbate liver dysfunction (e.g., phenobarbital, phenytoin, or primidone). The clinician needs to balance the desire for rapid and efficacious seizure control against the potential for side effects. To add to the challenge, the pet owner's own misconceptions, reluctance, or *alacrity* to start any certain medication can help steer the clinician in the right treatment direction. In human medicine, the practitioner tends to take a slow, steady approach to treatment. They begin with low doses of medications and titrate up to effect. In veterinary medicine, because of the potential for premature euthanasia or the increased likelihood of physical or metabolic damage from an untreated or unseen seizure, we should strive to treat early and use appropriate doses of medications to stop seizures as soon as possible. We may *overmedicate* and then back into a therapeutic range for the particular patient. This is certainly acceptable if it saves the patient's life and they do not suffer from untoward side effects. *The most common mistake made by clinicians is to underdose*. The second most common mistake is to add on a second medication before the first has been given an adequate dose and time to work. Fear of side effects is the primary motivator which is usually due to an unfamiliarity with the medication. Stick with the published doses to begin, unless you have a compelling reason to alter the recommended dose.

Certainly, there is much variation to this approach. It would be reasonable and expected to begin with a low dose of medication and slowly increase it to effect in a patient with comorbidities, owners who are reluctant to treat, or patients whose seizures are not considered "life threatening" (for whatever reason, potential for euthanasia included). We may all be faced with the menacing threat "if you don't get these seizures under control, I'm going to have to put her down." In that situation, the *start low and go slow* approach would *not* be appropriate. Clear communication regarding side effects (and their typical transient nature) is paramount. Regardless of the approach, many of the complications associated with therapy can be avoided with good, if not exceptional, communication. As explained in Chapter 4, spending time with the client to gauge their level of insecurity and anxiety associated with treatment, along with discussions to help dispel misconceptions associated with treatment can go a long way in the beginning stages of treatment to prevent unhappiness, uncertainty, and dissatisfaction at a later date. Warning a client about the potential consequences of either *going slow* or *going fast* regarding treatment will help ease potential future frustration with either suboptimal control of epileptic seizures or tolerance of negative side effects associated with certain medications. An elementary understanding (review) of pharmacokinetic and pharmacodynamic principles is helpful to be able to educate your clients.

PHARMACOLOGICAL PRINCIPLES

A basic understanding of pharmacology is required to prescribe antiseizure medication, help owners monitor effectiveness of medications, evaluate the severity and acceptability of side effects associated with antiseizure medications, and help with the construction of a therapeutic plan. The clinician fills the gap between the pharmacist and the patient. Drug dosing schedules are not arbitrary and should be followed as close as possible by the patient's care provider. Dosing schedules are determined by:

- Uptake and elimination of a medication as determined by the interactions of the chemical with the body. How long does it take to reach therapeutic concentration?
- Bioavailability of the medication as determined by its pharmacokinetic characteristics.
- The medication's serum concentration as related to the patient.
- The medication's unique and *variable* effects on the patient.
- The owner's ability to comply with medication dosage schedules.

The first two aspects create a starting point for medication dosing. Several other variables will determine which medication to start with, when to *fail* a medication, and when to provide *add-on* medications. Failure of a medication to have the desired effect should be well documented and the patient labeled as "drug-resistant" to that particular dug. The clinician will help the client navigate the often-confusing journey of medical management of epileptic seizures. The routes of medication, dosages, and pharmacological principles including absorption, protein binding, distribution, metabolism, and elimination are important concepts to at least have a rudimentary understanding. These *pharmacodynamic* (a drug's physiological effects or actions due to its molecular and biochemical characteristics) and *pharmacokinetic* (how the body interacts with the drug) principles will build a foundation for the construction of treatment strategies (Figures 6.4 and 6.7).

ROUTES OF ADMINISTRATION

Multiple routes of administration are available to deliver antiseizure medications. Determining the route to use will depend on the setting in which the medications are given, the necessity for rapid

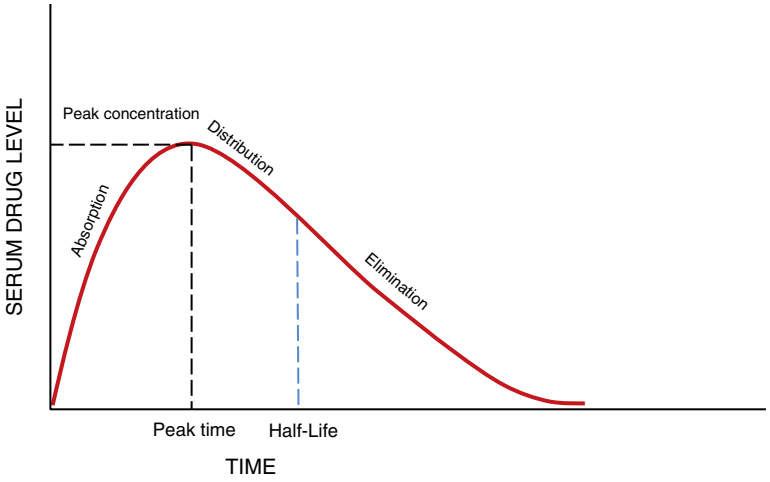


FIGURE 6.4 The pharmacodynamic parameters of a drug after a single oral dose. An initial rapid increase to a peak concentration will occur during the absorbance phase. Following absorption, the drug will decrease in two phases. An initial slower phase representing distribution to various tissues of the body followed by the elimination phase, which is more rapid and represents both metabolism and clearance. The *peak time* is the time it takes the drug to reach peak concentration in the serum, and the *half-life* is the time it takes 50% of the serum concentration to be eliminated from the body.

delivery, the ease of medication delivery, and the preparation of the medication. Routes of medication administration include:

- Oral (PO)
- Intravenous (IV)
- Intramuscular (IM)
- Rectal (PR)
- Intranasal (IN)
- Transdermal
- Intraosseous
- Intraperitoneal

Oral administration (PO) has the advantage of ease (in most cases) of administration by the pet owner. However, special considerations are often anticipated as in the oral dosing of cats. Oral dosing is a method which can create considerable variability in serum concentrations due to disparities in absorption and compliance of dosing, especially when considering most medications are formulated to be absorbed based on the gastric chemical composition of humans. For example, extended-release (XR) medications formulated for humans may have wide swings in medication availability in dogs and cats. The bioavailability of these preparations may make them not suitable for veterinary patients. Other commonly used human medications may be eliminated from the dog or cat so rapidly that more frequent (and usually unreasonable) dosage schedules may be necessary. For example, a very effective drug in humans may work well in dogs and cats; however, if it must be given every 6 h due to accelerated elimination in veterinary patients, compliance and cost can be significant factors, which may lead to it not being an acceptable choice. Other medications

commonly used for humans may produce toxic metabolites or create unwanted side effects, further preventing their use in veterinary patients.

The oral route for emergency dosing of antiseizure medications may also be considered in a nonhospital setting. In this case, we are speaking of the buccal transmucosal absorption of medications, which would otherwise be given through an IV, IM, or IN route, such as lorazepam and midazolam. Studies are lacking on the bioavailability of this route, although in the author's experience, pet owners have reported a beneficial use in a home setting. This use stemmed from the occasional difficulty of hitting a "moving target" (as in the nostril) in a dog or cat who was actively having an epileptic seizure. I always advise to try the IN route for home use but if the case arises where the pet owner cannot reliably get to the nostril, they can squirt it in the mouth. I do caution them to avoid the oral route if the pet is hypersalivating or foaming saliva from the mouth. What few studies we do have (in dogs only) indicate absorption is dependent on the pH of the formulation (in the case of midazolam) and improved when the viscosity of the injectable medication is altered by compounding it (again, midazolam) into a gel formulation (Zhang *et al.,* 2002; Aldawsari *et al.,* 2018). The advantage (empirically) of lorazepam is a lower volume of the injectable liquid (in the concentrated form) given either through the buccal or IN route when compared to midazolam. Once dispensed, the shelf life of the injectable midazolam formulation, when mixed with a vehicle, is reported to be up to 102 days (Steedman *et al.,* 1992; Walker *et al.,* 1997). Midazolam has been shown to be shelf-stable for up to 90 days in a diluted form, stored in a polypropylene syringe at room temperature (Gilliot *et al.,* 2020). Midazolam is commonly used as an oral syrup, prepared from the injectable form, for pediatric sedation. Lorazepam, however, does not stay stable once diluted and stored for more than 2 days (Colsoul *et al*., 2020). However, the *undiluted injectable* form of lorazepam, stored in a glass vial (syringe in the study), is stable for up to 150 days at room temperature (Gottwald *et al.,* 1999). Oral lorazepam tablets are rapidly disintegrating once they are exposed to saliva.

IV administration has the advantage of rapid bioavailability to the brain (assuming the medication crosses the blood–brain barrier (BBB)), ease of administration by professional care providers in hospitalized patients, and 100% compliance (assuming a patent catheter or clean IV puncture). The disadvantage of IV administration lies in the lack of its use in the home care situation, as well as the cost associated with in-hospital use.

IM injections can be used when venous access is not possible (hospital or home setting) and rapid availability to the brain is desired, assuming the medication is compatible with IM injection. Some medications may create significant tissue reaction when injected into the muscles. These injections can cause pain and abscesses at the injection site if given incorrectly and may be difficult, cumbersome, and potentially dangerous when used in the home setting (due to the use of tiny, very sharp needles and their proper disposal). The only antiseizure medications which can be given through IM injection are phenobarbital, levetiracetam, midazolam, and lorazepam. Giving these medications IM may be suitable when IV access is not available, however, the time to peak concentration and bioavailability are likely to be altered (i.e., slower).

Rectal administration (PR) can be used with certain medications (potassium bromide, levetiracetam, and diazepam) to achieve near-rapid absorption when IV access is not available and IM injection is not possible or practical. Proper rectal administration will allow the home care provider to treat seizures more rapidly when they occur. This advantage has been shown with rectal diazepam to reduce the number of cluster seizures and hospitalization visits while at the same time giving the pet owner a sense of "control" over the epileptic seizures through reduced anxiety (Podell, 1995; Kähn *et al.,* 2023). While historically, rectal diazepam was the most widely used in this form, it has for the most part been replaced by IN midazolam (Charalambous *et al.,* 2017). Rectal administration of injectable levetiracetam or a levetiracetam suspension may also be beneficial for the control of epileptic seizures (Peters *et al.,* 2014; Cagnotti, *et al.,* 2018, 2019).

Transdermal administration allows the pet owner to medicate patients who are difficult to pill or take oral solutions of medications (yes, we're talking about you, cats...). The limitations of this route of administration are the inability of certain medications to be compounded to transdermal forms and the reduced ease of accessibility to the medication because of the need to be compounded. Absorption variations are also possible depending on skin oil concentration, cleanliness of the pet, temperature of the skin, and hair coat coverage. Typically, these medications are applied to the inside (pinna) of the ear. They require the pet owner to wear gloves to prevent accidental self-absorption. While owners may find this route preferable to the oral route, close monitoring of serum concentrations may be another consideration, as well as increased dosages over the oral route (Gasper et al. 2015; Krull *et al.,* 2019; Barnes Heller *et al.,* 2019).

For young animals and neonates, where venous access may be more limited, intraosseous infusion can be a rapid way to deliver antiseizure medications. The delivery of diazepam and phenobarbital has been shown to reach comparable concentrations in the blood via intraosseous infusion in experimental models. This delivery route is considered safe for the developing animal (Brickman *et al*., 1987, 1990, 1996). Phenobarbital may also be delivered through intraperitoneal injection in an emergency (Coates and Bergman, 2005). Finally, diazepam, lorazepam, and midazolam have been shown to reach serum therapeutic concentrations when delivered intranasally (Platt *et al*., 2000; Mariani *et al*., 2003; Eagleson *et al*., 2012).

ABSORPTION

Once a drug enters the body, it must be absorbed into the bloodstream. The absorption rate and amount will affect the degree of efficacy and the time to peak antiseizure effect (Boothe, 1998). The fraction of the oral dose of a medication which ultimately reaches the systemic circulation is referred to as the *bioavailability* of the drug. This can be simply expressed as a relationship between the amount absorbed from the oral route and that from the IV route (100%) and is expressed as a percentage of absorption:

$$\text{Absorption} = \frac{\text{drug}_{\text{oral}}}{\text{drug}_{\text{intravenous}}} \times 100$$

Most antiseizure medications are well absorbed through the oral route. In general, about 75% of a drug given orally is absorbed within 1–3 h (Rang, 1995). Numerous factors may influence this rate, such as:

- The presence of food in the stomach
- The presence of other drugs
- Gastrointestinal (GI) motility
- The pH of the gastric secretions
- Splanchnic blood flow
- Particle size and the formulation of the drug
- Various other physiochemical factors, such as intestinal or chemical binding complexes of certain drugs

Certain medications (e.g., phenytoin) may be slowed by the presence of food in the stomach. The absorption of a medication into the bloodstream is going to depend on certain biological factors, such as its lipid or water solubility. Water solubility will determine how easily the medication goes

into solution within the blood and is transported into cells through passive diffusion via membrane channels if the molecules are relatively small (or large in the case of endothelial cell pores). However, the capillaries of brain blood vessels lack these pores (hence, the BBB). Lipid-soluble medications will be more soluble within the cell plasma membrane and will be transported via a concentration gradient into the cell. Various medications are absorbed via carrier-mediated facilitated transport whereby plasma transport mechanisms will actively transport certain molecules if they "fit" the endogenous transport mechanism. For an antiseizure medication to reach the brain, it must first be absorbed into the bloodstream, be in a "free" state (as opposed to "protein bound"), and cross the BBB, and only then can it exert its cell- or receptor-specific action. Drugs which are given via an oral route will need to be absorbed into the bloodstream through the gastric mucosa. Because the lipid solubility of a drug depends on its ionization state and the ionization state can change with the local pH (e.g., gastric secretions), the absorption of the drug into the bloodstream from the GI epithelial cells may be influenced by pH differences of the gastric secretions. The more lipophilic a medication, the greater the permeability; however, lipophilicity is not predictive of permeability (Alavijeh *et al.*, 2005). Many factors can alter gastric secretions and pH of gastric secretions, such as the presence of food, other concurrently given drugs, and disease states. Gastric blood flow may also alter drug absorption. The formulation of the drug can also affect its solubility and absorption (solution, capsule, tablet, XR, etc.).

Generic Versus Brand Name

Consumers save billions of dollars every year by buying generic AEDs as opposed to brand-name drugs. The Food and Drug Administration (FDA) governs the approval of generic drugs within the USA. Manufacturing processes and inactive components of the formulation may also affect the bioavailability of the medication. When a drug patent runs out, the manufacturer of the generic drug must "reverse engineer" its creation. The drug companies which spent millions on the development of the drug in clinical and safety trials do not provide a "recipe" for its creation to the generic manufacturers. The patent will list the ingredients but not instructions on how to put it all together. The bioavailability of a drug may vary from individual preparation; therefore, the term *bioequivalence* is used. Generic drugs can have a certain "allowable" variation in bioequivalence by the FDA. Bioequivalence means the generic drug will work in the body in the same way and will be as safe and as effective as the brand-name drug. No two preparations of the same drug by different manufacturers are identical and variations in bioequivalence may lead to dramatic changes or swings in therapeutic concentration within the blood:

- Bioavailability: The fraction (usually expressed in percent) of an orally ingested drug, which gains access to the systemic circulation.
- Bioequivalence: A term which implies a similar disposition of a drug. If another drug is substituted and is *bioequivalent*, there will be no clinical difference between the two.

The FDA rules allow for a disposition variance of 20% less than or 25% more of the active ingredient in the blood of a generic preparation when compared to the brand name. This effectively means when switching from one manufacturer to another, there may be an almost 50% difference in the bioequivalence of the drug (Krauss *et al.*, 2011). This could lead to wide swings in therapeutic concentrations, resulting in reduced epileptic seizure control and the development of negative or toxic side effects (more on the importance of drug monitoring later). While the manufacturer of a generic drug must show it is as close to the original, proprietary form, they do not have to show it is *therapeutically equivalent* (it is assumed). Additionally, the generic drug does not have to contain the same *inactive* ingredients or be of the same quality as the brand-name medication. These differences may also affect the bioequivalence of a drug. In some cases, the time to maximum concentration or the speed of absorption may also be significantly different. In the case of time-released drugs, this

can lead to either the rapid delivery and high concentrations in the blood leading to negative side effects or the slow delivery of the drug leading to a possible increase in epileptic seizures. For drugs with a narrow therapeutic index, such as AEDs, even small changes can have significant results. While the FDA states bioequivalence of a generic is comparable to a brand name, instances have occurred where a formulation of a drug is withdrawn or recalled due to concerns of bioequivalence or the use of substandard ingredients. Granted, most medications are going to be safe and provide the same bioequivalence. However, it is important for the prescribing and managing clinician to be aware of possible complications, when complaints of either ineffectiveness or adverse side effects are noted, particularly when they revolve around recent changes in medications in a patient previously well-controlled. Those changes may occur within a few days of a switch or up to several months (depending on time to steady state).

Following absorption from the GI tract, the medication must pass through the liver prior to reaching the brain. The liver may metabolize the drug or activate the drug into the therapeutic component prior to the medication reaching the brain. This *first-pass effect* exerted on the drug by the liver may reduce the amount of the drug, which ultimately reaches the brain.

PROTEIN BINDING

Most drugs are bound to proteins within the bloodstream and in various tissues throughout the body. The protein-bound portion of the drug is the component *not* therapeutically effective. The protein-bound potion of the drug will remain in the vascular compartment, and conversely, if bound in a specific tissue, that portion of the drug will be prevented from leaving the compartment and potentially concentrating the drug to a higher level in that tissue than in the blood. It is the *free* form of the drug, which makes its way to the brain to exert its therapeutic (or toxic) effect. In general, the more fat-soluble (lipophilic) the medication, the greater the degree of protein binding. Albumin is by far responsible for most protein binding in the plasma. The degree of protein binding of a drug and the variability of protein binding either due to disease states or the presence of other drugs in the body can alter the therapeutic effect of the drug. For example, if a patient is hypoalbuminemic, the free form of the drug will be in a greater concentration and may therefore assert a greater therapeutic effect or cause a toxic side effect. Younger animals are expected to have a lower serum albumin concentration, resulting in decreased protein binding of certain drugs. Some drugs may displace others from protein binding (e.g., aspirin displaces diazepam), and therefore, their presence, in combination with a well-tolerated and well-balanced antiseizure drug, may disrupt the balance (see individual drug monographs). Protein binding, to a degree, will influence the disposition of a drug in the body. This may lead to alterations in distribution, metabolism, and elimination of the medication.

DISTRIBUTION

Following an initial rise in the serum after absorption, the serum concentration will start to drop as the drug is distributed among the various tissue compartments of the body. In general, the more lipid soluble a drug, the greater its protein binding and subsequent distribution to the various compartments of the body. The *volume of distribution* (V_d) is a proportionality factor relating the total amount of drug in the body to the amount in a biological fluid (blood). It is a primary pharmacokinetic value used to derive secondary pharmacokinetic values. The value is dependent on the specific *physiochemical* properties of the drug and how it interacts with the *physiological* properties of the body. It is determined by the molecular weight of the molecule (the larger the molecule, the less likely it will diffuse out of the blood), how much plasma protein binding it undergoes (the more binding to plasma proteins, the less likely it is to leave the plasma), and whether it is lipophilic or hydrophilic (the more lipophilic, the more it will leave the blood—which is a hydrophilic

environment). The volume of distribution of a drug is a known value and helps to determine what the correct dosage is to achieve a certain plasma concentration of a drug:

- If a drug has a *low* V_d, it is less likely to be distributed out of the blood and will therefore have a low tissue concentration (more stays in the blood).
- If a drug has a *high* V_d, it is more likely to be distributed out of the blood and will therefore have a high tissue concentration (more leaves the blood or is *distributed*).

If a drug has a low V_d, you can give less to achieve a desired plasma concentration (because less distributes to the tissue). Conversely, if a drug has a high V_d, you need to give more drug to achieve a desired plasma concentration (because more will be leaving the blood). Why does all this matter? Because we look at the plasma concentration of the drug assuming it is proportional to the target tissue concentration (with certain exceptions, i.e., inhaled drugs and topical drugs like lotions and ophthalmic drugs). The degree of the volume of distribution will influence the half-life of the drug and when considered with the redistribution among the tissues in the body (e.g., fat) will determine the duration of action of the drug.

Most antiseizure drugs, except for potassium bromide, are lipid soluble and have a high volume of distribution. The more lipid soluble a drug, the more tissues it will reach, including the brain. Although diazepam is highly protein bound, it is extremely lipophilic, leading to a very rapid distribution to the tissues of the central nervous system, therefore making it one of the most effective immediate-acting antiseizure medications (i.e., its recommendation for the treatment of status epilepticus) (Boothe, 1998).

METABOLISM

It is important to discuss and understand the metabolism of antiseizure drugs to help with the formulation of treatment plans, prognosticate success or failure of certain medications, adjust medications, and understand potential toxic consequences or side effects of various antiseizure medications or their combinations. The primary route of elimination of most drugs from the body is via the urine (secondarily through bile and feces and occasionally through the lungs). One of the primary reasons dogs and cats do not have a similar repertoire of antiseizure medications when compared to people is due to their metabolism of those drugs. Many commonly used antiseizure medications for humans are either metabolized too quickly in dogs and cats or metabolized into toxic compounds. It is important to remind animal caretakers the same drugs used to treat human epileptics are not always compatible or effective for dogs and cats. In some cases, death or serious and irreversible side effects may occur. To be eliminated through the kidneys, the drug must become hydrophilic, which occurs through various metabolic processes, most of which take place in the intestinal wall or the liver. If a compound is lipophilic, it must be transformed into a more hydrophilic product. This is done through three main forms of biotransformation reactions (and numerous other minor mechanisms):

- Oxidation–reduction
- Conjugation
- Hydrolysis

Most antiseizure medications are lipid soluble and therefore must be partially or completely metabolized by the liver. Most metabolites are less biologically active or inactive when compared to the parent compound. However, some metabolic processes will create the active metabolite (e.g., primidone metabolized to phenobarbital), and occasionally, metabolism will create a toxic or carcinogenic metabolite. There is a very close relationship between the biotransformation of drugs

and routine biochemical processes. Biotransformation, in many instances, is accidental, such that the biochemical processing is designed for endogenous substances in the body and the metabolism of drugs only occurs because the compounds resemble endogenous substances.

There are two phases to metabolism of drugs by the liver. They tend to occur sequentially. *Phase I* metabolic reactions will convert the parent compound into a *hydrophilic* compound, which is commonly an inactive form of the parent compound. These reactions are mainly oxidation, reduction, and hydrolytic cleavage. Many compounds will be sufficiently hydrophilic to be excreted after this phase. Phase I reactions often proceed to phase II reactions. *Phase II* reactions involve conjugation with endogenous compounds, which make the parent compound more water soluble. These conjugates will often attach to the moieties that are introduced during phase I reactions. Conjugates such as glucuronide, acetate, amino acids, and sulfate are employed. *Glucuronidation* is by far the most abundant conjugation pathway in the liver. This process allows products to be excreted through the bile. Almost all products of phase II reactions are *inactive* metabolites.

Most drug-metabolizing enzymes are found in the liver. The cytochrome P450 enzyme family is one of the most important and potentially (genetically) diverse oxidative enzyme groups. It is located within the mitochondria and endoplasmic reticulum of cells in the liver and the intestinal wall. Cytochrome p450 is a hemoprotein, which contains an iron atom, which can alternate the ferrous (Fe^{2+}) and ferric (Fe^{3+}) states, making it an electron acceptor. This allows it (iron) to be a very potent oxidant used in phase I reactions.

The *first-pass effect* refers to the rapid metabolism of certain drugs (e.g., diazepam) when given orally before they reach systemic circulation. The metabolic biotransformation occurs in the intestines and the liver. This generally protective mechanism is responsible in many instances for the inefficacy of an otherwise very potent drug if the drug is given orally. In most instances, it means a greater dose of the medication must be given to achieve the desired pharmacological response and is responsible for a degree of unpredictability in bioavailability of certain drugs with potentially dramatic individual variation. It is the reason that *oral* diazepam is relatively *ineffective* in dogs. Very little diazepam survives the first-pass effect to make its way to the brain after being given orally.

Because the liver is important in the metabolism of many antiseizure medications and the metabolites of those compounds can cause local tissue destruction (e.g., the creation of reactive oxygen species), hepatotoxicity is one of the greatest safety concerns with many antiseizure drugs. When multiple drugs are combined to help control seizures, the probability of hepatotoxicity increases (Boothe, 1998). The enzymes used by the liver to metabolize drugs may be induced by certain drugs (e.g., phenobarbital) and inhibited by others. Enzyme induction may lead to a more rapid metabolism of the parent compound (and therefore reduced effect) or a reduced metabolism in the case of enzyme inhibitors (resulting in potential toxic effects). Microsomal enzyme *induction* is a process whereby certain drugs bind to cytosolic receptors, stimulating DNA transcription, which leads to increased protein synthesis. Induction of microsomal enzymes usually results in an increased metabolism of the inducer, as well as other drugs. Enzymes, such as cytochrome P450, produce oxygen-free radicals through their oxidative processes. This has the potential to damage surrounding tissue (i.e., liver). Phenobarbital is one of the better-known antiseizure enzymatic inducers which can create liver damage secondary to enzymatic induction (Dostalek *et al*., 2007). Phenobarbital will increase the rate of metabolism of many drugs. We must also consider the use of other concurrent drugs when giving antiseizure medications as those drugs may also alter the metabolism of antiseizure drugs (Table 6.3). Conversely, antiseizure drugs may increase or decrease the effects of concurrent but unrelated drug therapy. Consult a veterinary formulary or pharmacology textbook regarding specific potential for drug–liver interactions. Disease states, comorbidities, and age of the patient also play a role in either increasing or decreasing the metabolism of antiseizure medications. If hepatic metabolism is reduced, for example, in the neonate, the amount of drug may need to be reduced or the time between doses may need to be increased. The

Table 6.3 Drugs affecting hepatic metabolism (examples).

Inhibit	Ketoconazole (antifungal)
	Cimetidine (antihistamine [H_2] blocker)
	Chloramphenicol (and other antibiotics)
	Valproic acid
Induce	Barbiturates (e.g., phenobarbital) (anticonvulsants, anesthetics)
	Griseofulvin (antifungal)
	Phenytoin (anticonvulsant)
	Prednisolone/prednisone (glucocorticoid)
	Primidone (anticonvulsant)
	Quinidine (antiarrhythmic)
	Rifampin (antibiotic)

development of the cytochrome P450 enzyme system is near adult levels by 135 days of age in the young dog (Kawalek and el Said, 1990). The maturational development of drug-metabolizing enzymes in the cat is unknown. But it is well-known cats lack many of the glucuronidation enzymes commonly found in dogs, leading them to metabolize most drugs slower than dogs (Court 2013). Liver disease, kidney disease, and protein-losing states (reduced protein binding) may also affect the potency of antiseizure medications and their metabolism. Adjustments to medications need to be made for the individual and often reassessed during treatment. This is important to prevent premature "failure" of drugs due to toxic side effects. Often, a simple reduction in the dose or frequency of dosing can reduce the side effects and allow the continuation of a potentially helpful medication.

ELIMINATION

Elimination of antiseizure drugs, like most drug metabolites of the body, will be either through the kidneys or the feces, via the bile and enterohepatic recirculation. The elimination of an antiseizure medication is predictable for most of the canine and feline population; however, many complex variables may need to be considered when formulating treatment plans or adjusting medications. Some general rules to follow are:

- Enzyme *induction* leads to increased elimination.
- Enzyme *inhibition* leads to decreased elimination.
- Renal disease usually leads to decreased elimination.
- Liver disease usually leads to decreased elimination.
- Protein-losing states or hypoalbuminemia may affect potency (increased free drug) but can also affect the volume of distribution, usually leading to increased efficacy. This may be balanced by an increased elimination through glomerular filtration.
- Polypharmacy makes everything more complicated.
- Comorbidities can make treatment more complicated.
- Young animals (1–135 days) and old animals have reduced elimination compared to adult animals.
- Diet change may alter the elimination of medications (e.g., low salt diet reduces the elimination of bromide, potentially leading to a toxic state).

Renal excretion will be dependent on glomerular filtration, passive diffusion (through the tubular epithelium), and active tubular secretion or absorption. If a drug metabolite is small enough (<30,000–50,000 kDa), it will freely pass through glomerular capillaries (renal tubules) into the filtrate (Ruggiero *et al*., 2010). If bound to plasma albumin, it will be held back and need to be made more hydrophilic to be excreted through the urine. Active transport carrier systems will function to remove acidic and basic compounds. Carrier-medicated transport, via proximal tubular secretion, will deliver compounds bound to plasma albumin to the glomerular filtrate when they cannot undergo glomerular filtration. Most water contained in the glomerular filtrate will be reabsorbed into the plasma as it passes through the glomerular filtrate. If a metabolized compound is permeable to the tubular wall, it will be reabsorbed into the plasma and its excretion will be slowed. Highly polar (i.e., hydrophilic) substances will be impermeable and stay within the urine. Depending on the pH of the urine, a drug's ionization state can vary, making acidic drugs more likely to be excreted in basic urine and more likely to be reabsorbed in acidic urine. Therefore, the use of certain diets to dissolve urinary bladder stones or prevent their accumulation by altering urine pH may alter the elimination of antiseizure medications. Alkalization of the urine increases the elimination of phenobarbital, and acidification decreases its elimination (Fukunaga *et al*., 2008). Excessive chloride content in diet will enhance the elimination (and lower its efficacy) of bromide in dogs (Shaw *et al*., 1996). Conversely, a diet low in chloride (i.e., homemade diets, low in salt) will prevent the excretion of bromide, potentially leading to bromide toxicosis. If you are faced with a patient who has lost some seizure control with no change in the medications, always question owners on any recent diet changes. Homemade diets which are not properly analyzed and do not contain an added supplement can be problematic.

Drugs concentrated in the bile are delivered to the intestines. Once in the intestines, the conjugate moiety, which was created in the liver, is cleaved, usually by hydrolysis. This allows the free drug to once again be absorbed by the enterocytes and enter the plasma. This process is known as *enterohepatic recirculation* and is responsible for creating a "reservoir" of drug available to the body (Rang, 1995). Those drugs not reabsorbed will leave the body through the feces.

PHARMACOKINETICS

The pharmacokinetics of a drug are the actions of a drug in the body over time. It takes into consideration absorption, distribution, metabolism, and elimination, which are all happening simultaneously to characterize the drug's overall kinetic behavior in the body. This study allows for the determination of the *half-life* of a drug, which permits the determination of dosing schedules and many other important clinical considerations. A simple understanding of pharmacokinetics is helpful to understand the behavior of various drugs and combinations of drugs.

With *first-order kinetics*, the elimination of a drug is directly proportional to its plasma concentration (Figure 6.5a). In the case of *zero-order kinetics*, a metabolic process is the rate-limiting step which alters the elimination of the drug. Therefore, the drug reaches a saturation point whereby increased amounts of drug absorbed by the body are not eliminated at the same rate. The concentration of the drug in the plasma increases over time because of the rate-limiting step, and small increases in dose can significantly alter plasma concentration (Figure 6.5b). The rate of metabolism of the drug limits the dose of the drug, which can be given. If the dose is exceeded, the drug concentration will start to accumulate and toxicity may occur. Variations in steady state are more likely to occur with a drug exhibiting zero-order kinetics and are more *unpredictable*. The drug concentration in the body will gradually be reduced over time due to metabolism and elimination in either first-order or zero-order kinetics. Most antiseizure medications are eliminated via first-order kinetics. Phenytoin is an exception, whereby it is eliminated by zero-order kinetics. Small increases in phenytoin can significantly alter plasma concentration. It is not commonly used in veterinary patients due to the variability of plasma half-life. Its rapid excretion

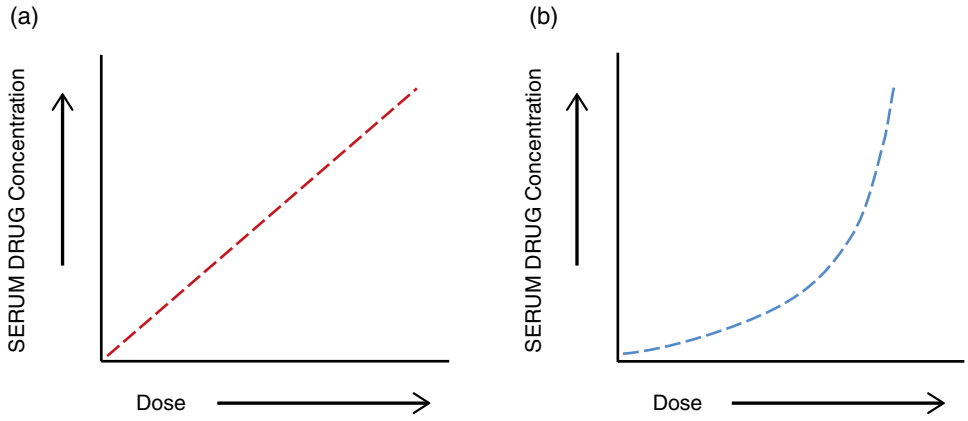


FIGURE 6.5 (a) With first-order kinetics, the elimination of the drug is directly proportional to its plasma concentration (i.e., the more drug, the more that is eliminated). (b) In the case of zero-order kinetics, a rate-limiting step of metabolism, such as saturation of the metabolizing enzyme, slows down elimination such that serum drug levels will increase exponentially with increases in dose. At some point, very small changes in the dose will lead to large increases in serum concentration.

in dogs makes dosing excessive to maintain steady state, and in cats, it accumulates in the body giving it a very narrow therapeutic index (see monograph in Chapter 7).

The *half-life* of the drug is the amount of time it takes to eliminate 50% of the total concentration of the drug at any one particular time (Figure 6.2). The half-life is constant over time and represents the *exponential* elimination of a drug from the body. The half-life of a drug is the most important factor used in determining dosing schedules for a particular antiseizure drug. The half-life can be influenced by:

- Enzyme induction
- Enzyme inhibition
- Distribution
- Metabolism
- Elimination

The half-life of a drug can be variable among individuals and species. If the anticipated effect of an antiseizure drug is not realized or expected, the half-life of the drug can be calculated through therapeutic monitoring (see Table 6.4 and Appendix 3).

The *steady state* is the time it takes for a drug to reach a concentration in the plasma whereby the amount being absorbed equals the amount being excreted. Since drugs are given in repeated dosages, the amount in the plasma will increase to a steady state, which is dependent on the total dose given but independent of the number of dosages given (Figure 6.1). The smaller and more frequent the dose given, the less variability in the swings of concentration within the plasma. The ultimate representation of an absence of swings of concentration would be a drug given as a continuous rate infusion (CRI) by the IV route. A *loading dose* is a larger dose of medication used to attain a more rapid steady state (Figure 6.6). The loading dose is the sum of all the daily doses which would have to be administered prior to steady state and consider the drug eliminated during the same amount of time (Boothe, 1998). It is effectively the amount of drug necessary to achieve the desired serum concentration, all at once. Its calculation is complex but fortunately, published loading doses are available for those where it is commonly used (e.g., phenobarbital and potassium bromide).

Table 6.4 Formula for calculation of plasma drug half-life.

Because we are dealing with first-order kinetics, the rate of elimination is directly proportional to the concentration in the plasma (C_p). A linear relationship exists between the rate of elimination and the plasma drug concentration. Even though the amount of drug eliminated in a first-order kinetic model changes with concentration, the *eliminated fraction* of the drug remains constant. Therefore, the elimination rate constant (K_{el}) represents the fraction of drug eliminated per unit of time. The value 0.693 is the ln 2, which is calculated from the slope of the concentration of drug in the plasma at time 1 and the concentration in the plasma one half-life later (time 2), which would be 50%:

$$\ln\left[\frac{C_p}{1}\times\frac{2}{C_p}\right]=\ln 2=0.693$$

The half-life can be calculated from the formula

$$t^{1/2}=\frac{0.693}{K_{el}}$$

K_{el} is the slope of drug concentration versus time line; therefore,

$$K_{el}=\frac{\ln[\text{concentration 1}/\text{concentration 2}]}{\text{time 2}-\text{time 1}}$$

You can work through this formula as in the example below or use the drug calculator website found in Appendix 3 or here: www-users.med.cornell.edu/~spon/picu/calc/halfcalc.htm

Example: Calculation of phenobarbital *t*½

Sample 1 at time 1 (6 h after dose = peak) = 30 μg/ml

Sample 2 at time 2 (12 h after dose = trough) = 20 μg/ml

$$K_{el}=\frac{\ln[30/20]}{12-6}=\frac{0.41}{6}=0.07$$

$$t^{1/2}=\frac{0.693}{0.07}=9.9\text{ h}$$

In this case, because the *t*½ of phenobarbital is <20 h, dosing every 8 h may result in better seizure control. See Appendix 3 for a more detailed explanation.

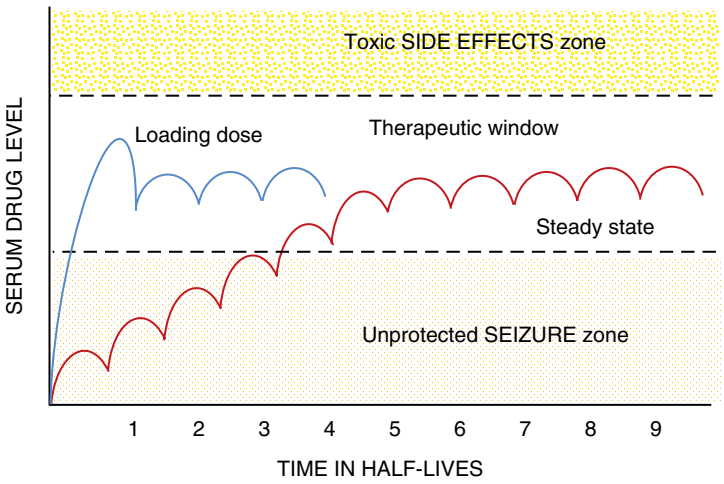


FIGURE 6.6 A loading dose of a "safe" drug can be given as a single administered dose used to achieve rapid serum concentration. The amount of the loading dose is determined by the volume of distribution of the drug, what the target tissue concentration is, and, if given orally, the bioavailability of the drug.

A simple model of pharmacokinetics known as the *single-compartment* model implies a volume (i.e., the body) consisting of one compartment. After absorption of the drug into the compartment, the drug is then metabolized and eliminated at various rates. The concentration of the drug in the compartment is dependent on the rate of elimination at any given time. At least 5 half-lives are required to reach steady state under conditions of first-order kinetics in a one-compartment model and in the absence of a loading dose (Tietz *et al*., 2006).

A more complicated model, employed to represent a biological system more accurately, is known as the *two-compartment* model. In this model, a second volume representing the tissues or peripheral space is included. The first volume represents the plasma compartment. Drug distribution into the tissue can only originate from the plasma compartment. The addition of a second compartment only affects the predicted time it would take to attain drug action and not the time to achieve steady state, which is the same as the one-compartment model.

CHOOSING A MEDICATION

Choosing a medication to attain antiseizure effects will depend on several variables (Table 6.5). All these factors will influence compliance, and compliance will influence the ability to achieve and maintain steady state. Without adequate steady state, seizure control cannot be expected.

Table 6.5 Factors influencing medication choice.

Patient-related factors	• The species being treated
	• The breed being treated
	• The size of the patient
	• The age of the patient
	• The presence of comorbidities
	• The physical state of the patient (i.e., pregnancy, lactating, etc.)
	• Individual idiosyncrasies
	• Individual tolerance to side effects
	• Concurrent drug therapy
	• The type of seizure being treated
	• Epileptic syndrome
Caretaker-related factors	• Owner's tolerance to side effects
	• Owner's preconceived notions of a medication
	• Dosing schedule
	• How easy the pet is to medicate
Medication-related factors	• The formulation of the medication (pill size, volume of liquid, pill vs. capsule, etc.)
	• The efficacy of the medication
	• The cost of the medication
	• The availability of the medication
	• Time to steady state
Prescriber-related factors	• Familiarity with the medication (prescriber)

Patient-Related Factors

Species: Antiseizure medication selection will be determined by the tolerance of a species to a certain medication. This may limit selections due to excessive metabolism in some cases or the development of toxic metabolites, reactions, or hypersensitivities in others. For example, as previously stated, phenytoin may be a poor choice for dogs due to the rapid half-life and the necessity to dose more frequently than other medications to achieve a therapeutic steady state. For cats, the half-life is significantly greater allowing for once-a-day dosing (although there is a narrow therapeutic window). Potassium bromide is a good antiseizure medication for dogs but produces potentially *fatal* side effects in cats and should not be used in the species. Cats also possess a significantly reduced ability for glucuronidation, which translates into a reduced dosage of medications, such as phenobarbital, compared to dogs. Other medications have a greater body of evidence surrounding their use for dogs when compared to cats. Many of the choices for cats are based on empirical evidence alone as opposed to proper experimentation. A lack of pharmacological data and efficacy and the development of potentially dangerous side effects may limit the selections to those medications where the drug disposition is known for the species.

Breed: While breed does not play a significant role in medication selection, there are a few considerations. Beagles, for instance, tend to rapidly metabolize phenobarbital, potentially leading to the necessity of higher and more frequent dosing to reach steady state. Even within a species or individual, variations of half-lives can be extreme (Cochrane *et al*., 1990; Boothe, 2001). Individual experiences with certain breeds known (anecdotally) to be "sensitive" to drugs (e.g., barbiturates) may alter drug selection.

Size: The size of the patient compared to the available pill sizes may affect medication selection. While most medications can be compounded to solutions or capsules containing an appropriate amount for the patient, the expense associated with compounding and availability of the preparations may be a limiting factor.

A medication available in multiple pill sizes may be easier for a client to manage and easier to add in medication by adding additional but differing pill sizes as the dose is titrated. The available pill sizes associated with certain preparations of medications, such as XR levetiracetam, may prevent their use in smaller patients, as the pills are unable to be broken. Breaking the pills would negate their XR properties. Therefore, XR levetiracetam at normal starting doses (30 mg/kg for the XR version) is not an option for dogs less than 15 kg. Early studies looking at the use of once-a-day dosing with the extended-release (XR) form for cats, are promising (see Chapter 7) (Heller *et al*., 2018).

Age: The age of the patient may significantly influence which medication to start with. This factor may also be considered with others, such as epileptic syndrome or the presence of comorbidities. Very young animals may not have fully developed hepatic clearance mechanisms. Older patients may have reduced hepatic or renal function, leading to disorders of metabolism and elimination. When considering the age of the pet and the potential for *lifelong* therapy, the consideration for a "safer" medication may be used or a medication which does not require routine blood work because of a wide therapeutic index.

Comorbidities: A comorbidity is an additional disease or disorder secondary to or in addition to the primary disease or disorder. The secondary comorbidity is discussed relative to the primary, in this case epileptic seizures and the possible underlying etiology of the seizures. The presence of a comorbidity should be considered when selecting drugs. A few (but not all-inclusive) examples are:

- Pancreatitis or GI issues: A history of any GI-related disease might limit or prevent the use of potassium bromide. The physical properties of the salt solution may create stomach mucosal irritation, nausea, vomiting, diarrhea, and reflux. Potassium bromide is known to cause pancreatitis; however, this may be prevented with dosing interval and preparation (i.e., every 12 h

[BID] dosing with a solution, given with food as opposed to once a day [SID] dose in capsule form on an empty stomach).

- Liver disease: A compromised liver or history of liver disease would make one seriously consider drugs which induce or inhibit hepatic microsomal enzymes or are primarily metabolized by the liver. The presence of portosystemic shunts or patients who have compromised hepatic function should be considered when choosing the dose of medication. Lower doses may be required as hepatic metabolism is reduced, leading to increased serum concentration when compared to a normally functioning liver.
- Protein-losing states or hypoalbuminemia: Considering many of the antiseizure drugs are heavily protein bound, reduced plasma protein, primarily albumin (and, to a lesser extent, β-globulin), may result in a greater "free" or active form of the drug, resulting in higher therapeutic levels. It is important when monitoring concentration of the drug to consider if the "bound" or "free" form of the drug is being measured as a true reflection of the amount reaching the brain. Although not commonly practiced, drug concentration in the cerebrospinal fluid would give a more accurate account of the actual free form of the drug delivered to the tissue.
- Acute disease: As opposed to a hypoalbuminemic state, a disease process which raises serum protein and therefore increases the potential binding of drug would reduce the available amount to the brain. Alpha-1-acid glycoprotein and other acute-phase proteins will increase with disease (Kremer *et al*., 1988). Because of this and other "stressors" with concurrent disease, epileptic seizure frequency or intensity may increase. Transient increases in medication dosage may need to be considered, or alternatively, the addition of a temporary ("bridge") medication, such as a benzodiazepine, should be considered until the patient's physical state normalizes (see next section under ***Strategies***).
- Renal disease: Decreased glomerular filtration will lower the rate and amount of elimination of certain antiseizure medications. Dosages should be adjusted accordingly.
- Diabetes mellitus, hyperadrenocorticism, and other endocrinopathies: Any disease that secondarily results in polydipsia and concurrent polyuria may alter therapeutic concentration, particularly when "self-diuresis" reduces the serum concentration of the medication. This is most relevant with potassium bromide. Also consider times when environmental changes may lead to increased water consumption, such as hot summer days, when active dogs are drinking a lot of water. I have personally treated a patient whose bromide level would decrease substantially in the hot summer months. Therapeutic serum concentrations could be maintained either by increasing the dose (temporarily) or keeping the dog in a cool environment. Never limit access to water.
- Structural brain disease: The presence of a brain tumor, granuloma, encephalitis, glial scarring, abscess, or other focal physical abnormalities of the brain should weigh heavily on medication selection. The clinician may choose a drug which attains steady state rapidly and is available in an injectable preparation. Many of these patients may undergo therapy (i.e., brain surgery), which could limit oral dosing of medication while they recover. The ability to switch to an injectable preparation (e.g., phenobarbital and levetiracetam) will allow the clinician to maintain serum therapeutic concentrations. Chronic rectal administration of medications such as potassium bromide or levetiracetam may also be considered.

Physical state: The physical state of the pet may change which medication to use or alter the choice of the medication temporarily. These changes in physical state may be pregnancy, the presence of a heat cycle, nursing animals, etc. Weight gain or weight loss, activity level, and lifestyle (e.g., the ability of the caregiver to dose when needed) may also dictate which medications are appropriate.

Individual idiosyncrasies: An idiosyncratic reaction to a class of medications or the predisposition to reactions may alter medication choice. Some patients may have a paradoxical reaction to the drug used to control seizures. These reactions are most common with the barbiturates and benzodiazepines. A paradoxical reaction can happen with any drug. These reactions typically manifest as an altered state of behavior consisting of anxiety, "panic," incessant pacing, and hyperactivity. Dogs having a history of allergic reactions to sulfa antibiotics may have a similar reaction to zonisamide, as the two substances are structurally similar (Neuman *et al*., 2008). Hypersensitivity reactions may be elicited from the drug itself or one of its metabolites. Most drugs are of such low molecular weight; they do not promote an immunological response. However, their metabolites, especially after being conjugated, can elicit a hypersensitivity reaction. *Type I hypersensitivity* reactions (anaphylactic shock) are rare but would be recognized by the sudden onset of a reaction within a time course very close to the doing of a drug. Tissue swelling, skin rash, urticarial reactions, bronchoconstriction, and hypotension are some of the more common clinical features of a type I hypersensitivity. Acute emergency treatment includes antihistamines, corticosteroids, and, in some cases, epinephrine. These are rarely associated with antiseizure medications. *Type II hypersensitivity* (antibody-dependent cytotoxic) results from an antibody binding to an antigen, resulting in a cell surface drug–macromolecule complex and a cell-directed immune response. For example, a conjugate formed with a drug metabolite. These reactions typically target any of the formed elements of the blood, such as red blood cells, leukocytes, and platelets, leading to cell lysis. Hemolytic anemia, agranulocytosis, and thrombocytopenia are examples whereby a single cell linage may be affected; however, aplastic anemia whereby all cell lines may be affected is also a potential. A *type III hypersensitivity* (complex-mediated) occurs when an antibody reacts with a soluble antigen. These antibody–antigen complexes then activate the complement cascade or attach to mast cells promoting the release of mediators, triggering an inflammatory response. A *type IV hypersensitivity* (delayed-type, cell-mediated immune response) is even more uncommonly associated with antiseizure drugs. Type I reactions are immediately associated with the dosage of a drug, whereas types II, III, and IV are delayed. In some cases, emergency treatment and supportive care must be instituted depending on the target organ(s). In all cases, the antiseizure medication should be withdrawn.

Occasionally, rapid drug withdrawal may result in *withdrawal seizures*. This typically occurs with barbiturates and benzodiazepines; however, in the case of benzodiazepines, chronic administration is not recommended due to the rapid development of *tolerance*.

The response to any chronic medication may result in tolerance. *Metabolic* tolerance would be related to increased elimination rates due to accelerated metabolism (e.g., induction of hepatic enzymes increasing the clearance of medications metabolized by the liver), whereas *functional tolerance* relates to alterations in the drug target site, such as adaptation of the central nervous system (CNS) to the effects of diazepam, or the degree to which a growing or changing substrate may induce seizures either through progression of disease or propagation of electrical and/or chemical changes in the brain, for which the antiseizure medication is not preventing. Metabolic tolerance may be overcome by the addition of a larger dose or dosage of medication, whereas functional tolerance (which may be a component of the *honeymoon effect*) can be more difficult to overcome. The term "honeymoon effect" is used in situations where the effectiveness of a medication tends to wear off over time in certain individuals compared to the general population. The effectiveness of the medication is usually measured in weeks or months as opposed to years and it may apply to multiple medications. One theory is seizures naturally *evolve* to find the most effective way to spread over time. We may even consider antiseizure medications artificially promote this evolution by creating selection processes much like antibiotic resistance.

Individual tolerance to side effects: Like idiosyncratic reactions (but regarded as less concerning) is the individual's tolerance to side effects of the medication. Polyphagia, polyuria, polydipsia, anorexia, sedation, ataxia, somnolence, etc. are all possible "annoying" side effects of an antiseizure medication. The degree of *affectedness* may limit the choice of medications.

For example, some dogs experience a dose-associated anorexia with zonisamide. Owners may complain the pet has become "picky" or it takes a little coaxing to eat, while other patients may refuse food altogether and have significant weight loss. Conversely, the polyphagia commonly associated with phenobarbital may be the annoyance of a "counter-surfer" or may result in patients who eat inappropriate objects, such as cat litter, dirt, gravel, and even drywall (yep, I've seen it). In these patients, extra care must be considered regarding accessibility to foreign objects and easily accessible "food" sources. Serious consequences may occur, including foreign body surgery, bloat, and even death. These complaints are not common (and very uncommon in cats) but should be taken seriously. To some degree, a moderate amount of polyphagia may be tolerable. However, significant weight gain may be a limiting factor in the choice of a medication, as well. Occasionally, a patient may have a classic (and often expected) reaction to a medication; however, the reaction occurs at a very low and usually unexpected dose. The ataxia associated with high serum levels of potassium bromide (usually greater than 3 mg/ml) may be observed in dogs "hypersensitive" to the medication. If epileptic seizures are controlled at a serum level below the reference range, the medication may be continued. If epileptic seizures are not controlled and an increase in the medication would either increase or result in negative side effects, either switching medications or the addition of another medication should be considered.

Concurrent medications: Certain drugs will significantly alter the serum concentration of antiseizure medications through various mechanisms, such as induction or hepatic microsomal enzymes, displacement of plasma proteins, and alteration of urine pH. The use of an antiseizure medication may also significantly alter other codependent medications. Phenobarbital, for example, has a varied effect on the metabolism of many drugs due to its hepatic microsomal induction (for a complete reference, see individual medication monographs in a veterinary formulary). It is important to catalog all medications, including supplements and holistic, naturopathic, herbal, etc. preparations. The appropriate medical professional and not a "well-versed" owner should closely supervise the use of nontraditional or integrative modalities directed at the treatment of epileptic seizures, comorbidities, or prevention of other conditions (supplements). Of note are drugs that alter coagulation, liver, renal, cardiac, and GI function. We need to remind our pet owners that nature is the first chemical factory and just because something is "natural" does not mean it is *safe*. Even something as innocuous as using agave syrup to mix with medications may be harmful (pet owners may do this on their own). Agave possesses potent *natural* anti-inflammatory chemicals (steroidal flavonoids, isoflavones, and coumarins, to name a few), and when used in combination with other anti-inflammatories (e.g., prednisone), caution should be used (Misra *et al.,* 2018).

Type of seizure (or "event"): Our aim of course is to affect all epileptic seizures in a positive way (through reduction or inhibition). In human medicine, the type of seizure is often a decision-making factor for the choice of antiseizure medication. In veterinary patients, because of limitations stated elsewhere (ability to practically characterize epileptic seizure type), our "sophistication" with specific treatment of individual seizure types is limited. However, the availability of low-cost EEG analysis and the ubiquity of smartphones allowing video recording of seizures are allowing the clinician to consider treatment of seizures based on identified or *suspected* seizure types, which were previously thought to not exist in veterinary patients. As mentioned before, seizure types commonly recognized in humans likely occur in animals but are poorly recognized. Careful consideration should be taken when choosing an anticonvulsant reported to "work" on a human. Drug disposition is an important consideration in animals, and any usage of an antiseizure medication for a pet, based on its use in humans (where we lack evidence supporting its use) must be weighed heavily. For example, absence seizures have long been regarded as not occurring in animals, and even if they do occur (and they do), the necessity of treatment is questioned if the episodes are mild and infrequent; however, certain drugs such as ethosuximide are used to specifically treat absence seizures in humans. Ethosuximide will reach stable serum concentrations in

dogs and therefore may be useful for the treatment of this type of seizure if identified (or suspected) and if considered debilitating or patterns show progression toward a more clinically concerning seizure type (Frey and Löscher, 1985). Certain focal seizures such as "spinning" or tail chasing may be more common in Bull Terriers (Dodman *et al*., 1996; Moon-Fanelli *et al*., 2011). These patients tend to be more responsive to potassium bromide (note: author's personal observations).

Epileptic syndrome: Being able to categorize an epileptic syndrome may help with antiseizure medication selection. Animals suspected of having genetic epilepsy are more likely to be younger and therefore need long-term treatment for their seizure disorder. This may give preference to a medication, which is well tolerated, with a few long-term side effects or unlikely to develop long-term side effects. The need for consistent therapeutic drug monitoring over the course of a patient's life may also influence which medications to avoid, as well as those which may lose their effect over time. Dogs with an underlying metabolic seizure disorder may require a medication which does not further compromise the already dysfunctional organ system (i.e., avoiding phenobarbital in patients with a portosystemic shunt). With most reactive seizures, once the offending source or substance is eliminated, the seizures may subside, meaning long-term medication is not necessary. A short-term medication may be a reasonable option. However, reactive seizures may create an epileptogenic site, necessitating long-term medication (unusual ...but possible). When considering dogs and cats with known structural brain disease, the clinician may be inclined to use an antiseizure medication with the highest degree of efficacy and rapidity of achieving a therapeutic serum concentration. Potassium bromide, for instance, may not be the best choice for a patient who has recently developed epileptic seizures and has a brain tumor. The clinician may want to choose a medication, which is available in an easy-to-get parenteral form.

Finally, we are occasionally faced with disorders that can be difficult to classify. This is especially true with the fuzzy line which may separate a behavior disorder from a true epileptic seizure. To add to that, we may have an outward observation of an "event(s)" which could be both. For example, dogs displaying *fly-biting* or *fly-catching* activity. In these cases, the outward semiology we see may be the reflection of either a behavior disorder or an epileptic seizure (Wrzosek *et al.,* 2015). The outward appearance is simply a reflection of a disturbance but not a definitive sign of the cause (i.e., much like a limp does not tell us the cause of the lameness). Structural diagnostic testing such as MRI and CSF, along with functional testing, such as EEG and brain auditory evoked response (BAER) testing, may identify the cause. Oftentimes, we resort to a *diagnosis by treatment*. If the disorder is epileptiform in origin, we would expect it to respond (most of the time) to an AED. So, in the case of fly-biting, if diagnostic testing is not a possibility or the results are inconclusive, it's reasonable to try phenobarbital, imepitoin, or levetiracetam and look for an effect. If there is no effect, consider fluoxetine. In the Wrzosek paper, 38% of the dogs exhibiting fly-catching had an abnormal EEG. When the patients were divided into treatment groups, 36% of the dogs in the phenobarbital treatment group responded, but 100% of the dogs in the fluoxetine group were classified as responders. But take caution with these results, often we need to increase AEDs to effect. In the Wrzosek paper, those subjects treated with phenobarbital had serum levels measured between 23 and 32 μg/ml. This level would be considered low to mid-range (normal range 20–40 μg/ml) for a dog being treated for seizures. Typically, we would increase the phenobarbital to an effect (i.e., satisfactory control), a negative side effect (i.e., excessive sedation), or when we reached the high end of the reference range.

Caretaker-Related Factors

Owner's tolerance of side effects: This category relates to the caretaker's ability to function with side effects of a medication not necessarily harmful to the pet but which are "annoying" to the pet owner. The veterinarian should not dismiss these complaints. The tolerance level of an individual

owner will certainly vary. *Intolerance* to negative side effects may result in reduced compliance, which could lead to a reduction in seizure control and the consequences that follow (e.g., damage to the patient, increased hospitalization, frustration of the owner, premature euthanasia, etc.). However, an owner who is too *compliant* with side effects can also unwillingly be doing potential harm to their pet. A dog who is ataxic on its bromide (but not having seizures) may be more prone to accidental injury, such as falling down stairs. A pet with severe polyphagia may shorten its life or seriously affect its quality of life by ingesting inappropriate objects. Watch for these clues and try to counsel your clients. As stated before, what might seem obvious to one individual may not to another.

Owner's preconceived notion of a medication: Quite often, pet owners will have done their own research and may be very versed in the (usually negative) consequences of a medication. Some owners will flat-out refuse the use of a medication such as phenobarbital by what they have read in their own research or heard from others who may have had a negative experience with a medication. The veterinarian can usually calm their fears or trepidation with the facts. However, it is best not to try to "sell" the medication if the owner is not convinced of its safety or efficacy. Conversely, some pet owners will insist on a medication or alternative therapy, which may be either contraindicated (e.g., potassium bromide, oral diazepam, etc. in cats or primidone in dogs or cats) or ineffective (i.e., certain "folk" remedies). It is important to strike a balance between dismissing the latter and relying on it. If used in conjunction with known effective medications and you are fairly certain it would not cause any harm, the clinician should support the owner's desire to find nontraditional alternatives for seizure control (see Chapter 9). The relationship you have with your client will depend on a willingness to discuss the disease and its potential treatment. If they trust you, they are probably more willing to listen to your advice and accept it (see Chapter 4).

Dosing schedules: Practically, dosing schedules can vary from every 24 h to every 8 h. In some patients, extensive and rapid elimination may necessitate every 8 h dosing for a typical 12 h dosed drug. Beagles may hyper-metabolize phenobarbital when compared to mixed-breed dogs (Frey and Löscher, 1985). Most clients will struggle with every 8 h dosing, making the use of certain medications less attractive (e.g., regular levetiracetam in dogs less than 15 kg or cats). Once-daily dosing is only applicable in the case of potassium bromide, assuming the dog tolerates it well and in certain felines with once-a-day phenobarbital or levetiracetam XR (Cochrane *et al.*, 1990; Heller *et al.*, 2018; Mojarradi *et al.*, 2023). They may be reasonable first choices when an owner can be certain they cannot medicate every 12 h. Potassium bromide, due to its long half-life, may also be an appropriate medication (for a dog) to start with if missed doses may be common. A missed dose of potassium bromide will not significantly alter serum concentrations. The vast majority of antiseizure medications are dosed every 12 h. Missing doses and extending doses beyond the recommended time course may result in breakthrough seizures; however, this effect is variable for the individual (depending on the therapeutic window). Some patients require very precise dosing schedules, whereas most may tolerate some variability.

Ease of medication: This does not tend to play a very important role since most medications are delivered by pills, solutions, or capsules, unless of course the client is attempting to medicate a cat. Special concern may be for the extremely old and *brittle* cats. Most medications can be compounded into flavored liquids, various sizes of capsules (to reduce the number of pills given), or flavored "treats." XR preparations cannot be compounded. In difficult-to-medicate patients, transdermal–topical preparations may be an option. Various drug absorption research models have been used for humans; however, there is very little research regarding the absorption characteristics of transdermal antiseizure medications in pets, with the exception of transdermal phenobarbital in cats. Most studies show an increased dose is necessary to achieve therapeutic concentrations via the transdermal route in cats (Finnerty *et al.,* 2014; Gasper *et al.,* 2015). The thick skin of animals may lead to erratic and variable absorption. If this route is employed, it is recommended to monitor serum concentrations very closely.

Medication-Related Factors

The specific drug you choose will determine dose planning. There are a few exceptions. Potassium bromide can be given once or twice a day depending on how the patient tolerates the medication (e.g., GI side effects). Chronic dosing of a medication will result in steady state. The goal is to achieve a level for the patient in the *therapeutic range*. We often focus on the *reference range*. The reference range is a statistical measure of effectiveness derived from a large population (Figure 6.1). It measures efficacy of 60–80% within a population. It should be considered in certain situations but not relied on. For instance, a patient who has their seizures controlled (or balanced) at a low steady state falling under the reference range would not need to have their dose changed to achieve a steady state in the reference range, and conversely, a patient who *needs* an amount of medication to control the seizures resulting in a level above the reference range does not necessarily need the dose dropped unless they are experiencing negative side effects (Figure 6.3). Of more importance for the individual is the *therapeutic range*. The therapeutic range is the serum concentration which results in a positive outcome for the individual. This "Goldilocks" zone resides somewhere between efficacy and intolerance.

Formulation: The available formulation of the medication may limit treatment options. Some medications are available in XR forms (levetiracetam and topiramate), and more may be available in the future. However, the size of the available pills in these forms may prevent the treatment of smaller patients due to the inability to divide XR preparations. Additionally, because the preparations are formulated for humans, the disposition in veterinary patients may not be known. Medications which come in a variety of pill sizes can be helpful in dosing small animals and providing more precision with titration. Most medications can be compounded into solutions, making more precise dose changes easier. Commercial formulations of potassium bromide are available, decreasing the reliance on compounding pharmacies. The availability of generic forms of medications may alter recommendations, and as more antiseizure drugs become available in generic formulations, diversity in treatment options will naturally increase. As stated previously, be aware of decreased seizure control or increased toxic side effects when switching formulations (solution vs. pill or capsule), having medications compounded, or using generic preparations (McConkey *et al*., 2012). Also, consider the potential difference in bioequivalence between different generic formulations (Krauss *et al*., 2011).

Efficacy: Not all antiseizure medications are equal. Certain medications, in practice, may be more efficacious than others. Research on commonly used medications is available, and personal experience will certainly help influence a decision (Podell *et al*., 2016). As newer antiseizure medications are formulated, those considered highly efficacious today may get bumped down the list. Research into more specific mechanisms of action of drugs and the pathophysiology of epilepsy will result in more efficacious medications with fewer side effects. The clinician may also strike a balance between efficacy and side effects. For example, side effects associated with gabapentin are very uncommon, making it very safe, although its ability to control epileptic seizures is considered suboptimal. Phenobarbital is considered one of the most efficacious antiseizure medications; however, the development and practical experience with newer medications, such as imepitoin, zonisamide, and levetiracetam, which tend to have fewer side effects, has given clinicians more options for a first choice AED. Phenobarbital (along with Imepitoin) is still considered a first tier AED for dogs and cats.

Cost and availability: The cost of a drug may be a significant factor in determining which one to start with. There tends to be a very dramatic difference in cost between proprietary and generic formulations. Consider the availability of the medication and its relationship to cost. Smaller pharmacies tend to have a higher markup on inventory less commonly dispensed and may not even stock certain antiseizure medications. Larger pharmacies with greater sales volume tend to have lower costs. The difference can be significant when price shopping. It is a good idea to have a

relative comparison of commonly used antiseizure medications the clinician may prescribe. The availability of a medication, whether kept in stock with the prescribing veterinarian or the local pharmacy, can influence the preference of treatment. Most clinicians and owners would prefer to have easily accessible medications. The preference to not have many controlled substances in the veterinary clinic may make accessibility to many commonly used medications limited (e.g., barbiturates and benzodiazepines).

Time to steady state: The time to steady state may influence which medication you choose. From a practical standpoint, if you were trying to achieve rapid control in a patient who is having frequent seizures, you would avoid a medication with a long time to steady state, such as potassium bromide. In these situations, a loading dose could be used assuming the patient tolerated the large dose of medication. A patient being treated on an outpatient basis with infrequent seizures may be a better candidate for potassium bromide.

Prescriber-Related Factors

Familiarity with a medication: An individual's familiarity or experience with a medication should weigh heavily on prescription choice. Many of the "older" antiseizure medications may not be considered *first choice*; however, if the clinician is more familiar with these medications and their efficacy and potential side effects, they should not be discounted. Also, consider accessibility to advice when prescribing an unfamiliar medication. The ability to call the manufacturer (and get an actual answer), a specialist or access information from colleagues may sway a decision toward or away from an unfamiliar (new to the prescriber) antiseizure medication. Negative or positive experiences with certain medications can also substantially influence a decision to prescribe a medication. Regardless of the choice, familiarity should not be dismissed. The clinician should be comfortable with the choice of medication or at the very least have accessibility to someone who is comfortable. This will naturally translate to better care for the patient and the client. Our empirical experience with a medication (despite what you may read in the literature) should be taken into consideration. For example, my personal experience and comfort with potassium bromide make it one of my first-line choices for the appropriate case.

Choosing an antiseizure medication is like picking an antibiotic when you do not know what the infection is. You aim to choose a broad-spectrum, safe, efficacious, and inexpensive medication. However, a certain degree of *trial and error* is to be expected. Clients should be warned of this and reminded that unlike an infection, we cannot perform a "culture and sensitivity" of a seizure for the most effective medication. Also, similar to an antibiotic, you should choose an appropriate dose. You would not under dose an antibiotic. Nor should you underdose an AED unless you have valid reason (e.g., compromised liver function).

TREATMENT STRATEGIES

Formulating an effective treatment strategy is as important as identification of the underlying cause of seizures and choosing the right antiseizure medication. However, the treatment of seizures should not be delayed due to lack of identification of the etiology. Treatment of epileptic seizures (with a conventional AED) will not affect any diagnostic testing apart from the EEG, which due to impracticalities is not commonly used in a clinical setting. This may change in the future as the identification of classes of seizures not commonly associated with or difficult to identify in dogs and cats (e.g., absence seizures) may lead to the use of drugs having more specific action on those types of seizures, as we see in human medicine. The use of corticosteroids to treat autoimmune causes of epileptic seizures is also an exception. For now, in veterinary medicine, we tend to use broad-spectrum antiseizure medications for all types of seizures, based primarily on tolerability of side effects, cost, frequency of dosing schedules, and familiarity with the drug.

Various treatment strategies may be used to attain better long-term seizure control, prevent breakthrough seizures, and lessen the chance of the development of status epilepticus. Furthermore, educating the pet's caregiver provides the clinician with another set of eyes to help with the early identification of possible toxic side effects and efficacious and inefficacious medications. The treatment strategies can be defined by:

- *Prophylactic–chronic treatment*: Chronic use of medication to achieve a baseline suppression of epileptic seizures.
- *Bridge therapy*: The temporary use of a medication to *cover the gap* while waiting for a prophylactic medication to reach steady state. May also be used during times of "stress" or clustering episodes (i.e., "cluster buster").
- *Pulse therapy*: Single-dose or short-term use of a medication during actual seizure events, at times of added stress when a seizure is more likely to occur, or when *predictable* seizures may occur. This also includes the use of medications to stop episodes of status epilepticus and clusters.

All strategies may be combined along with lifestyle or environmental changes and integrative medicine to help control epileptic seizures (Figure 6.7). These different layers will give the pet owner and veterinarian more options to prevent and control seizures in a manner traditional prophylactic therapy alone cannot account for in most cases. In general, we are referring to refractory epileptics. It is estimated that 70–80% of canine patients will have their epileptic seizures controlled with monotherapy (Fenner and Hass, 1989). However, another study demonstrated a 50% reduction in seizures in 30% of dogs treated with a placebo (Muñana *et al.*, 2010). We also need to remember various studies have shown only 15–24% of dogs with idiopathic epilepsy will go into remission when treated with an antiseizure drug (Berendt *et al.,* 2002; Hülsmeyer *et al.,* 2010; Gulløv *et al.,* 2012). So, it is important to clarify to owners what we mean by *seizure control* and realize despite what a study says, we are treating an *individual*. Therefore, the additional strategies may not be necessary in all cases but when needed may provide substantially better control of epileptic seizures and a distinctly identifiable improvement in quality of life both for the patient and the caregiver. When you consider all the variables which can play a part in seizure management (drugs, compliance, communication, strategies, etc.), it takes a significant amount of effort to fail. Failure becomes even more difficult when you have more "tools in the toolbox." Many pet owners may feel as though they are "held hostage" by their pet's seizures. They express significant anxiety at times when they know, through experience, their pet is more likely to have a seizure (e.g., visits to the veterinarian, groomer, family gatherings, etc.). Formulating strategies to help offset these concerns will allow for greater compliance and improved seizure control.

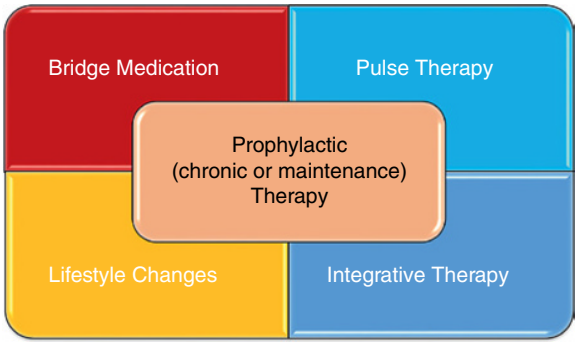


FIGURE 6.7 At the core of the strategies used to control seizures is *prophylactic* or *maintenance* medication. *Pulse* therapy, *bridge* therapy, lifestyle, and environmental changes along with integrative therapies may also be used to augment prophylactic therapy.

PROPHYLACTIC OR CHRONIC THERAPY

The single most common treatment strategy is the chronic application of a drug(s) to suppress seizure activity. These medications are given daily for an extended period (typically years or for the life of the pet) to achieve a steady-state concentration of drug, which is known to suppress seizure activity. No patient is the same; therefore, a "cookbook" approach should not be taken. Individual tolerance, metabolism, and seizure etiologies will necessitate every patient be critically evaluated for the appropriate effects of the medication(s).

It is essential pet owners do not expect 100% seizure control. They should have a relatively *realistic* expectation of success, which should be considered a 50% reduction in the frequency and/or intensity of the seizures. Of course, the *goal* of prophylactic treatment would be the complete elimination of seizures (why wouldn't it be?). To that end, with the development of new, more efficacious, and safer medications, the dose of many drugs may be increased to an effect (i.e., acceptable reduction in seizure events), to an intolerable but typically reversible side effect (e.g., sedation), or to a point where we may convince ourselves more of an ineffective medication will not be helpful.

WHAT MEDICATION SHOULD YOU CHOOSE?

As previously mentioned, picking an antiseizure medication is like picking an antibiotic to treat an infection *without the benefit of culture and sensitivity*. The choice is based on factors such as familiarity with the drug, the patient's individual health (e.g., comorbidities, such as liver disease), and availability of the medication, to name a few. Additional factors such as any preconceived judgments regarding the medication by the client, cost to the client, and dosing schedules are also considered. If a clinical syndrome has been identified, there are some general guidelines which may help in choosing a prophylactic medication. Some general rules to follow are:

- Avoid the use of any potentially hepatotoxic medications if hepatic function is in question (e.g., portosystemic shunts, elderly patients, or neonatal patients).
- Try to use a medication available in an injectable form if the patient has a propensity to be hospitalized (the need for IV administration).
- Try to use a newer-generation antiseizure medication in patients who are likely to be medicated for years or their lifetime. This lowers long-term costs associated with therapeutic monitoring and less risk of liver dysfunction.
- Follow recommendations based on safety and effectiveness in the literature but acknowledge that empirical evidence based on experience should not be discounted.

Seizure frequency and intensity may also help guide which medication to use. A patient who is having frequent, violent seizures (generalized) would benefit from a medication which achieves a rapid steady state such as imepitoin, zonisamide, or levetiracetam, whereas if a patient has infrequent seizures, which are short with a rapid recovery, a safe medication taking longer to achieve serum steady-state concentration would be acceptable such as potassium bromide (except for cats).

Choosing a starting dose should be based on known references or clinical experience. One of the most common mistakes in starting antiseizure medications is *under*dosing the medication. Another common mistake is failing to increase the dose when seizures are not adequately controlled but the patient's serum level is within the *reference* range. The reference range is only a guide. It should be used to help the clinician determine negative side effects, subtherapeutic dosing, and the point where a patient may be approaching serum levels more commonly associated with toxicity. It would be more important to work toward the patient's *therapeutic* range (Figures 4.6, 4.7, 6.1, and 6.9).

Example: A dog treated with phenobarbital, at 3 mg/kg every 12 h, whose serum concentration is 30 μg/ml (range 20–40 μg/ml) is still having seizures. Should you add in levetiracetam? No. It would be a mistake to fail phenobarbital in this dog because phenobarbital was in the reference range but still having seizures. It would be very acceptable to increase the phenobarbital dose until the point where seizures are *controlled*, blood work shows decreased liver function (increases in fasting and fed bile acids), or the serum concentration approaches 40 μg/ml, at which point a concern for potential liver toxicity may lead to the addition of another antiseizure medication (assuming seizures are not adequately controlled). We don't know what level of phenobarbital this dog needs to have his seizures controlled. It may be 35 or 42 μg/ml. The only way to know is to try. A simple algorithm may be followed when choosing to begin therapy or add-on medications to existing therapy (Figure 6.8).

When initiating polytherapy (i.e., the use of more than one drug), it is critical only one variable changes at a time. Increasing two drugs at once may create confusion as to which drug is having the greatest effect, causing toxicity, or resulting in negative side effects. The goal should be to always use as little and as few medications as possible; however, the clinician should also be careful when following the human model of *start low and go slow*. As previously mentioned, this approach tends to lead to frustrated owners and poorly controlled epileptic patients. Of course, it is also important to recognize when a patient is getting too much antiseizure medication. In the author's experience, most pet owners would rather have the seizures stopped (or significantly reduced) and then back down the medication to the minimal amount needed rather than gradually increase over a period of months. Again, it is important to take into consideration individual experience with the medication in question, as well as the patient's tolerance to the medication and the pet owner's concerns. A medication such as potassium bromide tends to have a very narrow therapeutic index or window of treatment efficacy. Small changes in dose may result in (*reversible*) side effects of sedation and ataxia with no reduction in seizure control. Conversely, medications such as imepitoin, zonisamide, or levetiracetam tend to have a large window of treatment efficacy (Figure 6.9). Newer-generation antiseizure medications have less of a concern for toxicity and generally provide a better quality of life for the pet (assuming they work) and the pet's owner through reduced need for routine therapeutic monitoring.

ANTISEIZURE MEDICATION CHOICES FOR DOGS

We have significantly more experience and evidence supporting medication choices for dogs, as opposed to cats. Studies of the available literature over the last decade have provided clinicians with recommendations which are evidence based both in the efficacy of the medications and safety. Even with these recommendation guides, there are still nuances to consider with any medication selection (Table 6.6). These may be out of your control, such as availability of a medication in your country or more subjective, such as a client's tolerance for the inconvenience and cost associated with routine blood work and monitoring. A 2014 study, looking at the available evidence and strength of that evidence, created antiseizure medication recommendations for dogs and followed up with antiseizure medication recommendations for cats in 2018 (Charalambous *et al.,* 2014, 2018). In 2015, The International Veterinary Epilepsy Task Force (IVETF) released its consensus proposal for the medical treatment of canine epilepsy in Europe (Bhatti *et al.,* 2015), which also includes helpful algorithms relating to specific medication protocols. In 2016, the ACVIM released a consensus statement on recommended antiseizure medications to use for dogs (Podell *et al.,* 2016). The consensus statement also provided guidelines for success and quality of life parameters. Of note, at the time of the ACVIM consensus statement, imepitoin, which has been universally found to be safe and effective (with efficacy equal to phenobarbital), was not available in the USA. At the time of this publication, imepitoin is approved in the USA for its use to treat noise phobias in dogs, not epilepsy. However, it may provide alternative treatment options when

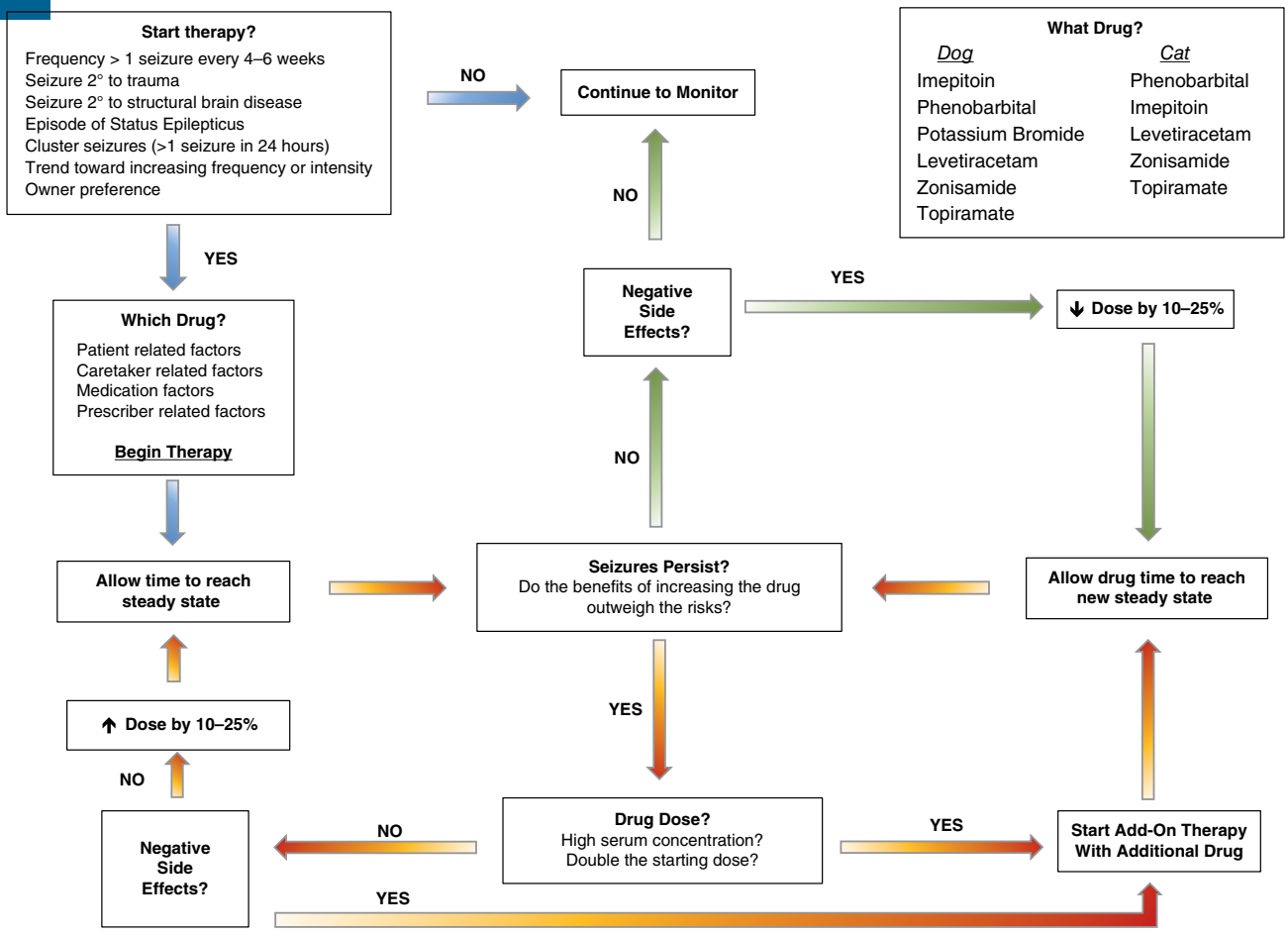


FIGURE 6.8 A simple algorithm can be used to help guide therapy choices.

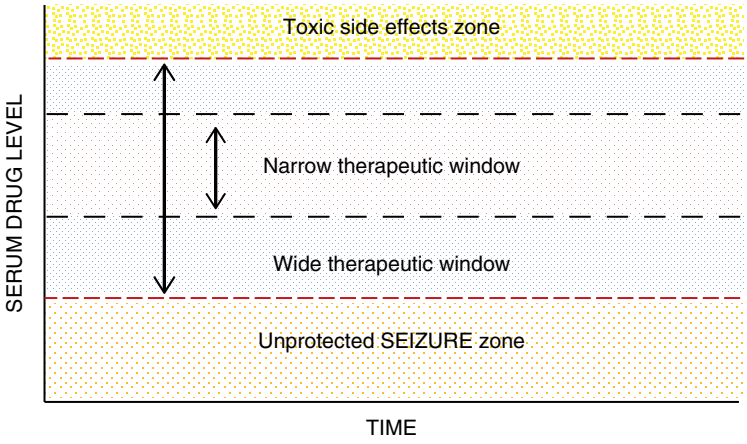


FIGURE 6.9 Any particular drug may have a wide therapeutic window (red dashed lines with blue stipple) or a narrow therapeutic window (black dashed lines with red stipple). Many of the newer antiseizure drugs have a wider therapeutic window when compared to the older drugs making them better choices for long-term therapy or for use in older or more debilitated patients. Remember, therapeutic window is determined for the individual.

used in an extralabel manner. It is still not available in the USA (mid 2025), as opposed to Europe and Australia where it is more widely available. It is also important to note that the weight of recommendations by organizations such as the IVETF and the ACVIM, as well as independent reviews lean heavily on the *available evidence*, as opposed to empirical evidence (which would be very difficult to assimilate). Other weighted measures in your decision-making process should include convenience of dosing, cost, and need for routine monitoring, as well as efficacy and safety (Figure 6.10).

Not surprisingly, phenobarbital is still at the top of all lists for recommended first-line therapy, at a starting dose of 2.5–3 mg/kg every 12 h. But phenobarbital also shares the spotlight along with imepitoin as a first-choice recommendation. Bromide follows up next with levetiracetam and zonisamide as third-level choices, primarily due to lack of appropriately designed, clinical trials, or being recommended based on expert opinion only. When it comes time to choose an antiseizure medication (whether for a dog or a cat), we have recommendations based on the literature, but if we look at *weighted* recommendations, which may vary from clinician to clinician, we group other factors into the decision-making process, such as cost and need for monitoring along with factors evaluated in the literature, such as safety and efficacy. When the literature does not provide us with the answers, it can be helpful to devise your own, internal recommendations based on your style of practice, demographics, experience, etc. Although this is a *pseudo-scientific* way of judgment, it is better than pure empirical therapy. For a summary, see Figures 6.10 and 6.11, where we can see the effect of a weighted hierarchy versus a unweighted hierarchy using implied science based on experience and opinion mixed with a little literature-backed science. It is only meant to be an *example*, but nonetheless, one you may find useful in following until someone really cracks the statistical mélange necessary to codify the results. Again, I emphasize, individual opinions *will* vary. Many, many veterinarians will initially reach for third level recommended AEDs based on individual experience and preference.

ANTISEIZURE MEDICATION CHOICES FOR CATS

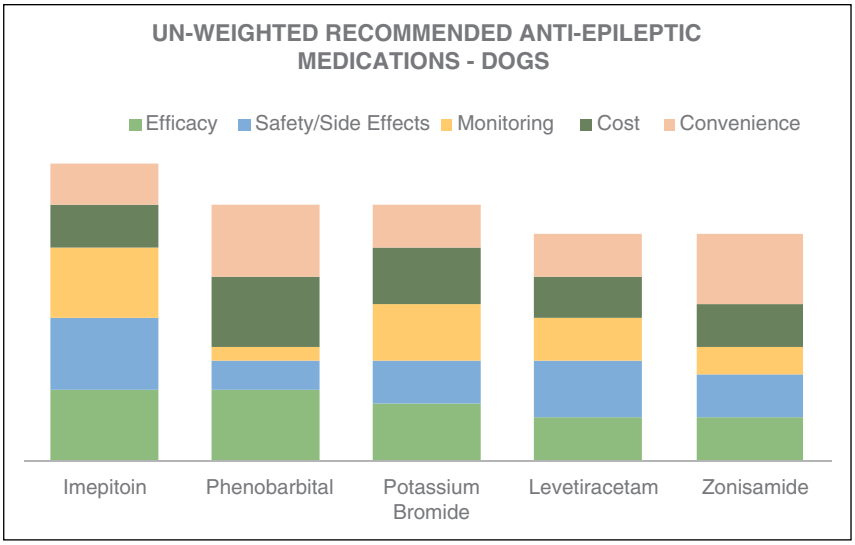
Recommendations for chronic medications in cats are based on limited literature review and personal experience (Table 6.7 and Figure 6.11) along with published recommendations. When

Table 6.6 Common drugs used as maintenance therapy for **dogs**.

Drug	Starting dose	Therapeutic levels	Time to steady state	Side effects	Monitoring (see Table 5.8)	Cost[a]
PB	2.5–3 mg/kg q 12 h Reduce dose by 25% if with LEV	20–40 μg/ml	~14 days (10–20)	Sedation, ataxia, polyuria, polydipsia, polyphagia, hepatotoxicity, blood dyscrasia, dermatologic disease	2 weeks, 6 weeks, 3, 6, 12 months, then q 6 months	$
KBr	30 mg/kg q 12 h 20 mg/kg q 12 h if with Pb	1–3 mg/ml	4–12 weeks. Reported up to 8 months	Sedation, ataxia, vomiting, diarrhea, polyuria, polydipsia, polyphagia, pancreatitis, pruritus	1 month after starting, then 4 months (steady state), and then routinely every 6 months	$
LEV	20 mg/kg q 8 h ⇑dose with Pb	5–45 μg/ml	2–3 days	Sedation	2 weeks, 4 weeks, then every 6 months	$$
LEV XR	30 mg/kg q 12 h ⇑ dose with Pb	5–45 μg/ml	2–3 days	Sedation	2 weeks, 4 weeks, then every 6 months	$$
ZON	5–10 mg/kg q 12 h	10–40 μg/ml	3–4 days	Sedation, ataxia, anorexia, hypersensitivity reaction	2 weeks, 4 weeks, then every 6 months	$$
IMP	10–30 mg/kg q 12 h	Not determined	1 day	Transient polyphagia, ataxia at higher doses	None	$$
TPM	2.5–10 mg/kg q 8–12 h	Not determined	1 day	GI distress, anorexia, anxiety/irritability, renal calculi	2 weeks, 4 weeks, then every 6 months, U/A	$
GBN	10 mg/kg q 8 h	4–16 μg/ml	1 day	Sedation, ataxia at high doses	None	$
PGN	4–10 mg/kg q 8–12 h	2–9 μg/ml	1–2 days	Sedation, ataxia at high doses	None	$$
FEL	20 mg/kg q 8 h	25–100 μg/ml	1–2 days	Blood dyscrasia, aplastic anemia, hepatotoxicity	2 weeks, 6 weeks, 3, 6, 12 months, then q 6 months	$$$
RUF	20 mg/kg q 12 h	10–45 μg/ml (extrapolated from humans)	2–4 days	Possible sedation	Routine blood work at 1 month, then q 6 months	$$$

[a] Relative cost to treat a 15 kg dog for 1 month (starting dose) compared to phenobarbital. Actual cost can vary considerably depending on pharmacy, generic, or proprietary formulation and availability. PB (phenobarbital), KBr (potassium bromide), LEV (levetiracetam), LEV XR (levetiracetam extended release), ZON (zonisamide), IMP (imepitoin), TPM (topiramate), GBN (gabapentin), PGN (pregabalin), FEL (felbamate), and RUF (rufinamide). Routine blood work is recommended with therapeutic monitoring.

(a)



(b)

	weight	Phenobarbital	Imepitoin	Potassium Bromide	Levetiracetam	Zonisamide
Efficacy	5	5	5	4	4	3
Safety	4	2	5	3	4	3
Monitoring	3	1	5	4	3	2
Cost	2	5	3	4	3	3
Convenience	1	5	3	3	3	5
Total un-weighted		18	21	18	16	16
Total weighted		51	69	55	54	44

(c)

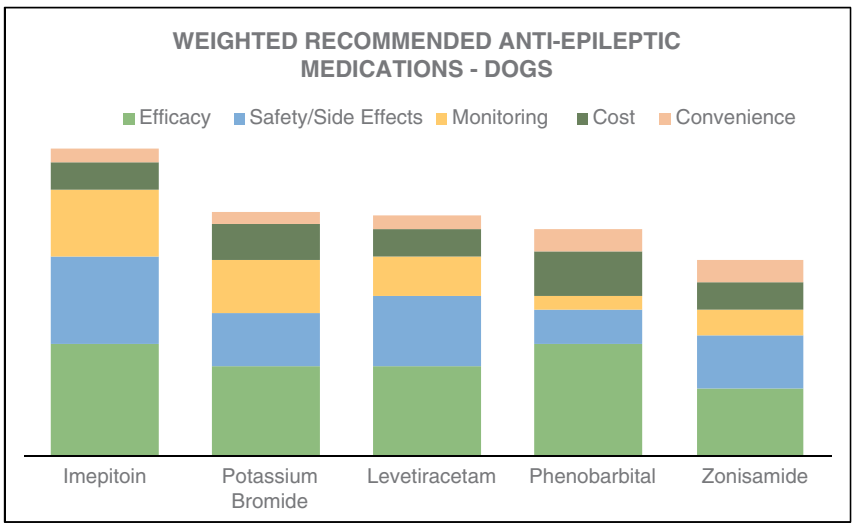
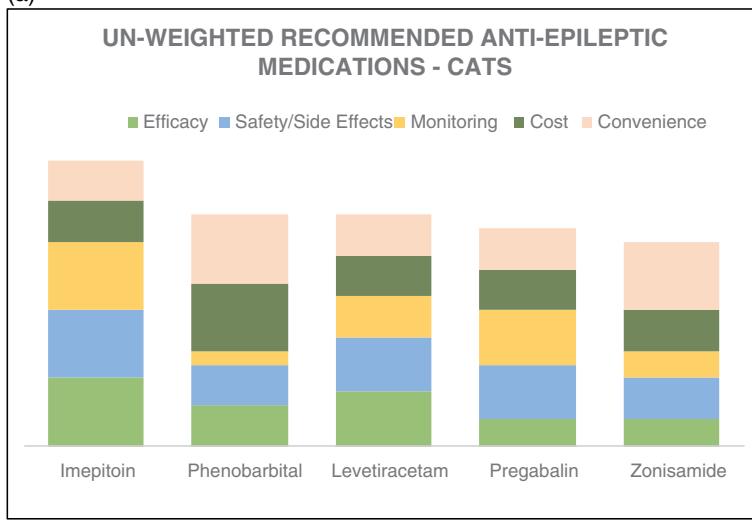


FIGURE 6.10 Based on current recommendations and a little pseudoscience, we can see what happens to recommendations for antiseizure medications for dogs when we apply various criteria (weights). (a) This graph shows recommendations based on consensus statements and the literature. The taller the bar, the more recommended the drug. (b) This is a simple heat map with various "weights" given to a medication based on what this author considered relevant (this may vary for each clinician). (c) The results of the "weighted chart" place potassium bromide ahead of phenobarbital and levetiracetam, *based on the author's experience*. The point of this chart is to emphasize that each clinician should consider various factors when choosing a medication. The individual score for a "weight" is what the author views as important. For example, convenience has the lowest possible weight.

(a)



(b)

	weight	Phenobarbital	Imepitoin	Pregabalin	Levetiracetam	Zonisamide
Efficacy	5	3	5	2	4	2
Safety	4	3	5	4	4	3
Monitoring	3	1	5	4	4	2
Cost	2	5	3	3	3	3
Convenience	1	5	3	3	3	5
Total un-weighted		17	21	16	17	15
Total weighted		45	75	47	54	39

(c)

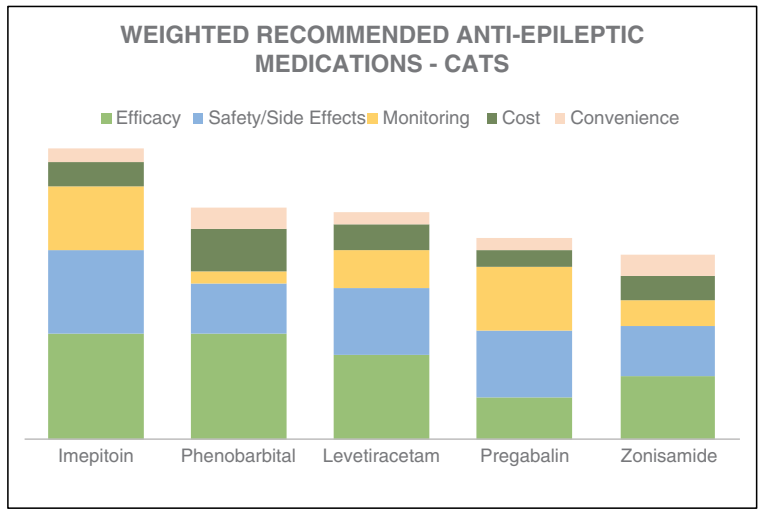


FIGURE 6.11 Here is a weighted graph for antiseizure medication recommendations for cats. Similar to Figure 6.10 for dogs. (a) We take the literature recommendations (unweighted) and apply personal "weights" to various factors scoring them based on how important we think they might be (again—stress this is an individual scoring system). (b) The heat map is generated, which scores the medications from most recommended (green) to least recommended (red). (c) In this case, the weighted graph does not differ from the unweighted graph (at least at this time). Most neurologists would place pregabalin in last place. It only retains its position due to minimal monitoring compared to levetiracetam and zonisamide. If this graph was created by a veterinarian in Japan, where zonisamide is a very common first-line medication, the assigned weights would be very different and zonisamide would probably be in the #1 spot.

Table 6.7 Common drugs used as maintenance therapy for cats.

Drug	Starting dose	Therapeutic levels	Time to steady state	Side effects	Monitoring	Cost[a]
PB	1–2.5 mg/kg q 12–24 h	10–30 µg/ml	10–14 days	Sedation, ataxia, polyuria, polydipsia, **polyphagia**, **blood dyscrasia**, **dermatologic disease**	Trough at steady state, 2 months, 3 months, and then routinely every 6 months	$
IMP	10–30 mg/kg q 12 h	Not determined	1 day	Intermittent vomit, sedation, ataxia, anorexia, hypersalivation, changes in H_2O consumption	None	$$
LEV	10–20 mg/kg q 8–12 h	10–50 µg/ml	1–2 days	Anorexia, lethargy, hypersalivation	1 week after start. Routine blood work q 6 months	$$
ZON	3–10 mg/kg q 12–24 h	10–40 µg/ml	7–10 days	Sedation, ataxia, anorexia, GI distress, renal calculi (poss.)	Routine blood work q 6 months, urinalysis	$$
TPM	12.5–25 mg (total dose) q 8–12 h	Not determined	1–2 days	Sedation, ataxia, anorexia, renal calculi	Routine blood work q 6 months, urinalysis	$
CZP	3.75–7.5 mg q 12–24 h (choose over DZP)	500–700 ng/ml (nordiazepam)	Unknown	Sedation, ataxia, polyphagia, *potential* for acute hepatic necrosis similar to DZP	Initial blood work q 2 weeks and then routine blood work q 6 months	$$
CLN	0.5 mg q 12–24 h (choose over DZP)	500–700 ng/ml (nordiazepam)	Unknown	Sedation, ataxia, polyphagia, *potential* for acute hepatic necrosis similar to DZP	Initial blood work q 2 weeks and then routine blood work q 6 months	$$
GBN	5–20 mg/kg q 8–12 h (sol. may cont. xylitol)	4–16 µg/ml	1 day	Sedation, ataxia at high doses	None	$
PGN	1–4 mg/kg q 12 h	2–9 µg/ml	1–2 days	Sedation, ataxia at high doses	None	$$

[a] Relative cost to treat a cat for 1 month (starting dose) compared to phenobarbital. Actual cost can vary considerably depending on pharmacy, generic, or proprietary formulation; need for compounding; and availability. Common maintenance antiseizure drugs used for cats. Drug order is listed as safest and most used; however, individual circumstances may dictate the choice. **Oral diazepam (DZP) and potassium bromide are *not* recommended**. PB (phenobarbital), IMP (imepitoin), LEV (levetiracetam), ZON (zonisamide), TPM (topiramate), CZP (clorazepate), CLN (clonazepam), GBN (gabapentin), and PGN (pregabalin).

contemplating first-line treatment for cats, phenobarbital is considered the initial drug of choice (Charalambous *et al.,* 2018). As opposed to dogs, tolerance in cats does not readily develop due to lack of microsomal hepatic enzyme induction. Cats eliminate the drug more slowly than dogs and are more susceptible to the sedative effects of the drug. Therefore, a lower starting dose is usually used. Serum levels of phenobarbital in the reference range have been associated with once-a-day dosing; however, there is potential variability among serum levels at consistent doses both within the species and within an individual cat (Cochrane *et al*., 1990). Alternatives to phenobarbital for monotherapy are levetiracetam and imepitoin (Charalambous *et al*., 2018). However, zonisamide is becoming more commonly used as first-line therapy in cats and may be dosed once a day due to its long half-life (Hasegawa *et al*., 2008). If add-on therapy is needed, one would naturally reach

to one of the monotherapy medications which has not been used and zonisamide would be a very reasonable choice (Djani, *et al*., 2024). Only imepitoin has been evaluated with a strong level of evidence concerning its safety profile in cats (Engel *et al*., 2017). A single study evaluating the use of XR topiramate in a small number of cats found the development of subclinical anemia (Graham *et al*., 2023). The author has not experienced any negative side effects in feline patients treated with any of these secondary choices; however, GI toxicity (reversible) has been associated with the use of zonisamide in a small number of cats (Yoshida *et al.,* 2023). A single case of suspected zonisamide-related generalized lymphadenopathy, hyperglobulinemia, and cytopenia (neutropenia and lymphopenia) has been reported with resolution of clinical signs following zonisamide withdrawal (Collinet and Sammut, 2017). Further add-on therapy may consist of clonazepam or clorazepate for cats, considering they are less likely to develop idiosyncratic hepatic failure (associated with diazepam), although with a larger variety of potentially less risky medications available, any benzodiazepine given orally in cats should be carefully considered. Finally, we may consider the use of corticosteroids to augment seizure treatment in cases of *autoimmune limbic encephalitis* in cats (Glantschnigg-Eisl, *et al.,* 2023).

PROBLEMS WITH PROPHYLACTIC THERAPY

Approximately one-third of dogs treated for epileptic seizures will be pharmacoresistant. This means they have failed at least two standard medications given at appropriate doses for an appropriate amount of time (time enough to reach steady state and evaluate for an effect). We may often either need to add on a medication(s) or try to work through a case where a patient is receiving multiple medications (both for dogs and cats). Untangling a polypharmacy situation can be time-consuming and frustrating (both for the veterinarian and the pet owner). It is important to avoid *pseudoresistance* a situation where a medication or medications have been inappropriately failed or an add-on medication was used to "leap-frog" another, which had not been given an adequate chance to work. Here are a few real-world examples:

Example 1: A patient started taking phenobarbital and experienced a 50% reduction in seizure frequency (i.e., success). However, the patient was still having an epileptic seizure every 2 weeks and had reached the comfortable, maximum reference range of phenobarbital (e.g., 38 μg/ml). Potassium bromide was then added and gradually increased to a level where the patient had developed mild ataxia and was still experiencing one seizure every 2 weeks (i.e., presumably no effect). A third antiseizure medication is added (e.g., zonisamide), and the seizures were again reduced by 50% in frequency. The question now becomes, which one of the polypharmacies should be reduced or eliminated? With good record keeping, it would be apparent phenobarbital and zonisamide had an effect where potassium bromide did not. This may seem to be an obvious example; however, most are not, and decisions regarding which medications to keep and which to reduce can be greatly influenced by a pet owner's record keeping. Always remember to max out a medication before adding on another.

Example 2: A patient was having one seizure a week. Phenobarbital was prescribed (3 mg/kg BID) and after one month, there was no change in seizure frequency. Levetiracetam XR (30 mg/kg BID) was added and after another month there was no change in seizure frequency. Potassium bromide was then added (30 mg/kg BID) and after two months, the dog was slightly ataxic but seizures were reduced by 25% (three per month). What should be done now?

a. Add in a fourth AED (zonisamide, imepitoin, or topiramate).

b. Reduce the potassium bromide, then add a fourth.

c. Increase the potassium bromide and D/C the others.

d. Increase levetiracetam.

e. Increase phenobarbital.

What went wrong in this case was not evaluating the phenobarbital serum concentration early on in the treatment. Prior to adding levetiracetam, phenobarbital should have been failed. That means increasing the phenobarbital until the seizures are reduced to an acceptable level or the serum concentration is >35 μg/ml. If you increase the phenobarbital dose by 25% every three weeks, you will either have an effect or no effect. If you measure the serum concentration and hit near 35 μg/ml with no effect, then it would be appropriate to add in the levetiracetam (or any other second-tier choice). Second mistake, not increasing the levetiracetam to a max dose. This would be 60 mg/kg BID of the XR. If you hit double the starting dose (this also applies to zonisamide, imepitoin, and topiramate) and still do not see an effect (presumably with no side effects), then more of what is not working will not work any better.

The correct answer is c. However, we cannot "fail" phenobarbital or levetiracetam yet because we did not give them a chance to work. We may need them in the future. In this case, we would increase the potassium bromide (because we know it had an effect ...stick with what is working) and warn the owners they may see a temporary increase in ataxia. Also, make sure the owners have not changed the dog's diet (i.e., low salt in the diet can decrease the elimination of bromide—very common with homemade diets). Over the next 6 weeks, we would taper the phenobarbital (25% reduction every 2 weeks). At the end of the sixth week (phenobarbital at 25% of the original dose), we would stop it completely and then wait another 2 weeks. If seizures got worse during the taper, we would go back to the last highest dose in the phenobarbital taper and hold. If the ataxia resolved, we would increase the potassium bromide by another 25%. If the seizures did not get worse after stopping the phenobarbital, then we would start weaning off of the levetiracetam and follow the same rules. As we remove the phenobarbital and levetiracetam, there is a good chance the ataxia will resolve. If seizures continue, we then focus on maxing out the potassium bromide. If we max out the bromide and the seizure control is still not adequate, then we would add in a second AED (phenobarbital, imepitoin, or levetiracetam) and work with that medication. We have not failed phenobarbital or levetiracetam (in this case) so we can lean on them in the future. Untangling these complex cases of polypharmacy can be a time-consuming challenge for which your compensation will be nowhere near what it should be for the amount of time it takes to unravel. You may spend a significant amount of time interrogating records to create a linear seizure log (which is why it is nice to have clients do it as they go through their pet's epilepsy journey) (Figure 6.12). The problem should not happen in the first place, however, coming to a solution and getting seizures under control can be very satisfying. You may be the last book on the shelf for the pet owner and all that stands between a happy dog/cat—family and frustration euthanasia.

BRIDGE THERAPY

The idea of a *bridge* therapy is to provide temporary suppression of epileptic seizure activity during times of potential added stress. Bridge therapy may be considered in several situations:

- While waiting for a chronic medication to reach steady state
- To use at times of added stress where circumstances may lead to increased epileptic seizure activity (i.e., holiday gatherings of family)
- To use when a predictable (and unavoidable) event may induce epileptic seizures (i.e., trip to veterinarian, groomer, trainer, etc.)
- To use following a single seizure when a cluster event is predicted to occur or during an episode of cluster seizures

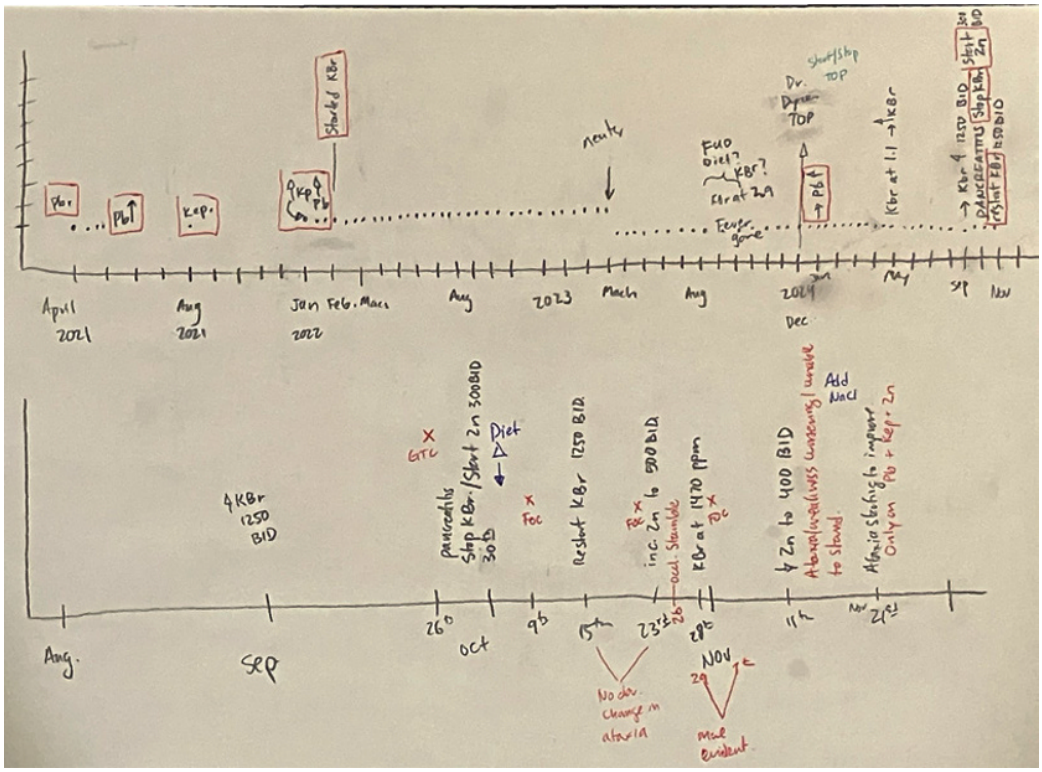


FIGURE 6.12 Example of a linear seizure log created by the author for a particularly complicated case. The log condenses 3.5 years and several gigabytes of medical records into a "30,000-foot view." I was one of the five neurologists (and one resident) at three different hospitals, in two separate states working on the case. Ideally, the client should stay the course with one clinician to avoid a "too many cooks in the kitchen" situation. This patient had been treated with six prophylactic AEDs (up to four at one time), bridge medications (clorazepate and clonazepam), pulse medications (midazolam and lorazepam), and cutaneous vagal nerve stimulation. She experienced two episodes of pancreatitis, a fever of unknown origin and significant ataxia while on bromide. The owners were willing to do anything for the dog. The owners had also switched to a homemade diet after the second episode of pancreatitis a few weeks before the dog developed severe ataxia (was on KBr). Only one medication out of the 6 was "failed"; topiramate due to a very negative reaction at a low dose. The upper graph is in years, and the lower graph is the last 5 months. Seizures were eventually controlled with a combination of Phenobarbital and Zonisamide (both at max doses/levels).

The general idea of bridge therapy is to provide temporary protection using medications that achieve therapeutic serum levels rapidly and are very efficacious and considered very safe. The long-acting benzodiazepines clorazepate and clonazepam work well in this situation. However, because tolerance rapidly develops in dogs and cats may be susceptible to possible liver damage with benzodiazepines, their use as a *chronic* antiseizure medication is not recommended. It is best to try to avoid using these medications any longer than 2 weeks in dogs and with attention to the liver in cats. One week or less is ideal along with blood work to monitor for elevations in liver-specific enzymes in cats. They should be withdrawn slowly if used longer than 1 week or there is a greater risk of withdrawal seizures. Withdrawal seizures are a *reactive* type of seizure and not necessarily related to the underlying epileptic condition. *Withdrawal seizures* are due to γ-aminobutyric acid A ($GABA_A$) receptor downregulation and alterations in neurotransmitter ratios (Bidlack and Morris, 2009). With chronic treatment, protein expression of the $GABA_A$ receptor is reduced, as well as the GABA transporter and glutamic acid decarboxylase, the enzyme associated with GABA

synthesis (Raol *et al.,* 2005). This protein downregulation is also related to the development of *tolerance*. A normal (i.e., no history of epileptic seizures) patient treated with chronic antiseizure medication may have seizures if the medication is ceased too quickly.

Bridge therapy gives pet owners an extra tool to get through the added times of stress when seizure threshold may be lower and can significantly improve quality of life and shorten hospital stays. Additionally, it allows pet owners to feel more comfortable with leaving their pets unattended for extended periods of time, in certain situations.

Waiting for Steady State

In this situation, a patient may have just started an antiseizure medication, or add-on therapy may have just been initiated. The long-acting benzodiazepines can be temporarily used to provide short-term seizure control while waiting for the new drug to reach steady state. For example, if zonisamide is started, one would generally expect it to take 4–6 days (a conservative estimate) to reach steady state. At the same time, clorazepate can be dosed every 8–12 h for 1 week to provide "coverage," while the zonisamide builds up in the body. Of course, the longer the half-life, the longer one must wait to reach steady state (Figure 6.13). Bridge therapy would not be practical if potassium bromide was the primary antiseizure medication as tolerance to the long-acting benzodiazepine would potentially be reached prior to potassium bromide reaching steady state. In this situation, a *loading dose* of potassium bromide (or levetiracetam, imepitoin, or phenobarbital if those are being used) combined with clorazepate may make more sense. However, the sedative effects of a loading dose on a patient may be profound and usually a bridge medication is not necessary. The clinician and pet caregiver must be vigilant for the development of excessive sedation when combining medications. This strategy is generally very well tolerated and if sedation is encountered, the dose of the bridge medication can be reduced or it may be eliminated. If dosed chronically (longer than 1 week), it is recommended to taper the medication gradually over a few days to avoid withdrawal seizures. In general, the longer the bridge therapy is used, the longer the taper. A practical rule would be to reduce the medication by 25% every 3–5 days (for a bridge medication—chronic medications need a longer taper period).

During Times of Added Stress

Think of a seizure as "falling off a cliff." Some patients walk closer to the edge of the cliff and others further away. Those who are closer to the edge are more likely to be pushed over during times of stress. Certain circumstances may produce stress in a pet's life, which when combined with an already predisposition to have epileptic seizures may result in breakthrough seizures. Stressful events such as travel, a trip to the veterinarian or groomer, guests or other transient pets staying at the house, etc. may be enough to trigger breakthrough seizures in a pet at otherwise adequate control. In these situations, since the "stressor" is temporary, we would rather avoid increasing the primary (chronic or prophylactic) antiseizure medication. The bridge therapy would be given as long as the stressor is present. Once the stressor is eliminated, the medication can be discontinued. The time period may only be a few hours (such as fireworks or a trip to the groomer) or may last several days (such as guests visiting for the holidays). Don't forget added times of metabolic stress, such as pregnancy or sickness.

Predictable Seizure-Inducing Events

Similar to a stressor, a caregiver may be able to *predict* the occurrence of a seizure. Some patients have seizures so routinely, they can be plotted on a calendar and predicted with decent accuracy. This highlights the importance of a seizure diary (Figure 4.3 and Appendix 2). If a dog is known to have a seizure every 5 weeks, a caregiver can go to the calendar, note when the predicted event is

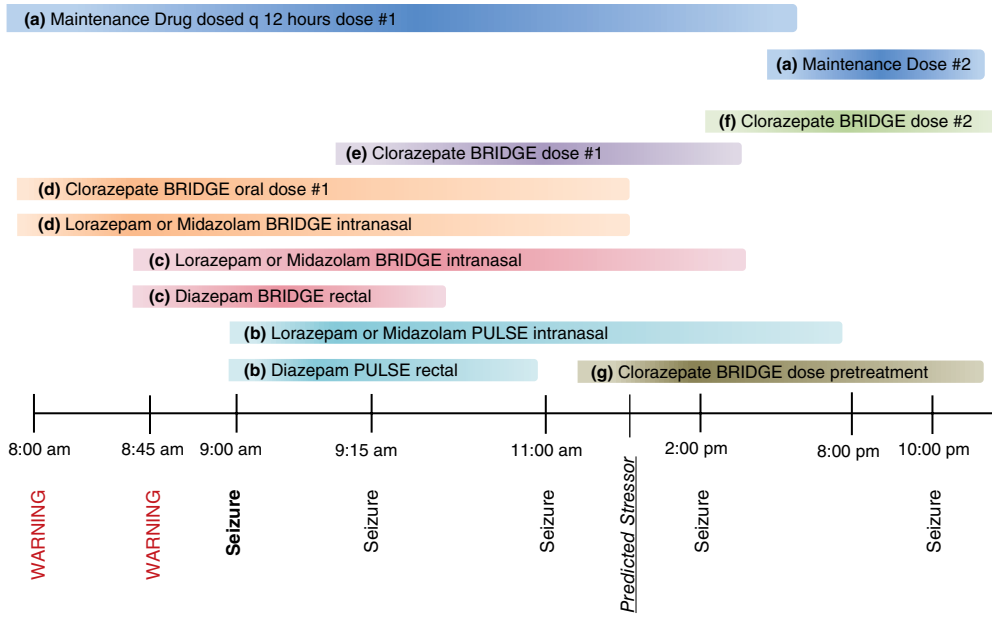


FIGURE 6.13 A hypothetical day to describe treatment strategies. (a) The maintenance (chronic or prophylactic) drug (e.g., phenobarbital, KBr, levetiracetam XR, zonisamide, etc.) is given every 12 h to suppress seizures. (b) A seizure occurs without warning at 9:00 a.m. Pulse therapy is used, either giving rectal valium (onset in 10 min) or intranasal lorazepam or midazolam (onset in 5 min) during the event. The valium will lose its effect by 2 h post-dose. The lorazepam will have an effect for 4–6 h, midazolam, slightly less, potentially preventing the seizure at 11:00 a.m. and 2:00 p.m., which may occur (if a patient *typically* has clusters). (c) The pet "warns" the owner it is going to have a seizure (i.e., a typical preictal behavior for that pet). If the warning is typically less than 15 min, the owner can *pretreat* with rectal diazepam or intranasal lorazepam to try to prevent the 9:00 seizure from occurring. (d) If the warning is greater than 30 min, the pet owner can pretreat with intranasal lorazepam (which has a longer effect than diazepam) or oral clorazepate (which will need ~45 min post oral dose to begin to have an effect but work for about 4–6 h). (e) Following the seizure at 9:00, once the pet can take a pill, the owner gives oral clorazepate to bridge the potential seizures later in the day (if that is the historical pattern). (f) A second dose of clorazepate is given to continue the bridge throughout the day and night if necessary. (g) If a predicted event will cause "stress" (e.g., trip to veterinarian, fireworks, thunderstorms, etc.) and potentially induce a seizure at the time of the event or later in the day, oral clorazepate can be given at least 1 h prior to the event to provide temporary seizure suppression (i.e., a "bridge").

"scheduled" to occur, and then pretreat with a long-acting benzodiazepine or levetiracetam for a few days, prior to and after the predicted event. The treatment would continue until the pet is outside the *window of opportunity* of the seizure. In general, this is usually a few days (1–2 days before the event and 1–2 days after the event should have happened). If seizures are highly predictable in this manner, take a closer look at the potential for a *provoked cause* of the seizures. Have the pet owner really take a close look at any environmental factors or lifestyle events, which may correlate with the predictable seizures. The author had a patient who would have seizures every 6 weeks in an extremely predictable manner. After evaluating the seizure diary, the pet owner noticed the seizures corresponded to delivery dates for their home business. Taking the dog for a walk prior to the arrival of the delivery truck (and driver he was very excited to see) eliminated these events. Although shown not to be a factor in either the frequency or intensity of a seizure, some caregivers are convinced (and their diaries occasionally support their claims) that a full moon will bring along seizures. For these patients, a few days of clorazepate before and after the

full moon may put the pet caregiver at ease or at least provide peace of mind. Occasionally, a client may report activity of the pet, which may signal an oncoming seizure, such as being excessively "clingy" or hiding for a period preceding the seizure. Depending on the amount of time the "warning" gives the pet owner, various bridge therapies may be used (Figure 6.13). Usefulness, notwithstanding, it is important for the clinician to maintain a good working relationship with the client and pet. The abuse of benzodiazepines is common with humans, and the veterinarian should always keep this in mind when filling prescriptions.

Following a Single Seizure (Avoiding a Cluster)

Like *pulse* therapy in the following text (see next section), a long-acting benzodiazepine may be useful in cases where known clusters of seizures tend to occur. In these situations, the long-acting benzodiazepine is given following the first seizure as soon as the pet can adequately take an oral medication. This strategy should not be used to stop a seizure but as a preventative to temporarily increase the seizure threshold (move the patient away from the cliff). The clinician should remember that a long-acting oral benzodiazepine will take up to 1 h to reach peak concentration in the central nervous system and then be available for approximately 4–8 h of "coverage" (i.e., clorazepate or clonazepam). Repeated dosing throughout the day may help prevent other seizures, which commonly are known to occur following the first event. These secondary and tertiary seizures may occur minutes to hours after the first seizure. Obviously, if the second seizure occurs prior to the ability of the long-acting benzodiazepine to reach therapeutic levels in the central nervous system, an alternative must be used. The long-acting benzodiazepine would then be repeatedly dosed if there is a *potential* for other seizures to occur. Usually, this is a 24–48 h period following the first event.

Example: A dog has a history of having cluster seizures. Within a few hours following the first seizure, she will *tend* to have another seizure and maybe two or three more throughout the day. Following the first seizure, once she can take an oral medication, clorazepate is given and then continued every 8 h for the rest of the day, thus *bridging* the cluster episodes by providing temporary coverage.

PULSE THERAPY

The goal of pulse therapy is to stop an ongoing seizure and/or prevent the occurrence of a secondary seizure within 1–4 h of the first. The rapidly absorbed benzodiazepines (diazepam, lorazepam, midazolam) are used in this manner and can be dosed in a variety of ways both for in-hospital use and at-home use (Table 6.8). Historically, the most common application of this strategy was the use of rectal diazepam to stop an active seizure and prevent clustering. This strategy has been shown to reduce ER costs and reduce stress associated with caring for an epileptic pet (Podell, 1995). In this case, diazepam is dispensed to pet owners in prefilled single-dose glass vials to prevent the absorption of diazepam to plastic surfaces (e.g., syringe) (MacKichan *et al*., 1979). Diazepam dispensed in glass containers is stable for up to 210 days if kept refrigerated and 30 days at room temperature (Table 6.9) (Gottwald *et al*., 1999). The owner is sent home with several vials of the injectable form of diazepam, usually dispensed into red-top blood collection tubes. Additionally, the client is sent home with a syringe with a red rubber feeding tube which has been shortened and attached to the tip of the syringe for the client (Figure 6.14). The client is instructed, in the event of a seizure, which is not following a normal pattern or lasting longer than 5 min, to withdraw the entire contents of the vial into the syringe and then insert the red rubber tube in the rectum approximately 2–6 inches (depending on the size of patient) and inject the contents while slowly withdrawing the syringe. This lessens the chance of intra-feces injection and provides a greater mucosal surface area for the diazepam to be absorbed. My advice to clients is to use this strategy when the epileptic seizure is not following a normal pattern of cessation or for any dog or cat which typically has seizures lasting longer than 5 min. Additionally, it can be used if a patient is prone to the development of clustering or a prolonged postictal time, typically resulting in hospitalization.

Table 6.8 Drugs used for pulse therapy and treatment of status epilepticus (dogs and cats).

Drug	Starting dose	Route of administration
Diazepam	0.5 mg/kg IV, 1.0 mg/kg rectal	IV, CRI, rectal, nasal
Lorazepam	0.1–0.2 mg/kg q 6–8 h	IV, IM, oral, nasal
Midazolam	0.1–0.2 mg/kg q 6–8 h	IV, IM, oral, nasal
Propofol	1–6 mg/kg bolus to effect IV. 0.1–0.6 mg/kg/min CRI	IV, CRI
Levetiracetam	30–60 mg/kg over 10 min (CRI). 40 mg/kg suspension or injectable) if rectal use	IV (for status epilepticus), IM, or rectal if PO unable

Table 6.9 Stability of home-dispensed benzodiazepines.

Drug	Room temperature (15–30°C)	Refrigeration (4–10°C)
Lorazepam undiluted glass[a]	150 days	210 days
Lorazepam diluted polypropylene (PP) syringe[b]	7 days	2 days
Midazolam undiluted glass[c]	60 days (at least)	60 days (at least)
Midazolam diluted PP syringe[d]	90 days	365 days
Midazolam diluted (orange syrup) glass[e]	102 days	102 days
Diazepam undiluted glass[a]	30 days	210 days

[a] Gottwald et al. (1999).
[b] Colsoul et al. (2020).
[c] McMullan et al. (2013).
[d] Gilliot et al. (2020).
[e] Walker et al. (1997).
Solutions considered "stable" if they retained 90% of their original concentration.

In the case of cluster events, the rectal diazepam can be given as a seizure is happening or immediately after; once the caregiver has access to the patient's rectum. This confers two advantages:

- To help in the cessation of the immediate event
- To provide "coverage" for the next 45–60 min until the pet can take a long-acting benzodiazepine orally
- Less chance of getting bit

In addition to the rectal route, *IN* administration has also been shown to achieve concentrations similar to serum levels (Platt *et al*., 2000). The major *disadvantages* to this route are the volume of diazepam, which must be given intranasally and the concern for possible aspiration pneumonia.

To help prevent the possibility of aspiration pneumonia, IN lorazepam and midazolam may also be used and when compared to diazepam, they are both given at a significantly reduced volume (Mariani *et al*., 2003; Eagleson *et al*., 2012). A lorazepam or midazolam kit may be prepared in a similar fashion to diazepam; however, the drug can be dispensed in syringes with a nasal atomizer to aid in the distribution of the medication. The viscosity of the medications prevents them from being atomized; however, when injected through the "atomizer," they (either lorazepam or midazolam) leave the device in a solid stream rather than dropping out without an attached atomizer. This allows for better mucosal coverage (Figure 6.15). The rapid oral absorption of lorazepam and midazolam, presumably through the oral mucosa and not the GI tract, also



FIGURE 6.14 Example of a take-home diazepam kit. (a) The kit is packaged in a large pill vial and stored in a cool dark place. (b) Each dose of diazepam is dispensed in a red top tube. A red rubber feeding tube (usually 10Fr or larger) is cut to length of an appropriate size for the dog, and the owner is instructed on how to withdraw the contents of the vial into the syringe with feeding tube attached. (c) The tip of the feeding tube is gently melted. (d) A correctly prepared tip will have a smooth rounded end to prevent trauma to the anus and rectum. Podell *et al.* (1998) / John Wiley & Sons.

supports its use in this manner. Unlike the rectal use of diazepam, rectal absorption of midazolam and lorazepam is erratic (Court and Greenblatt, 1992; Eagleson *et al*., 2012). Lorazepam does not stay stable once *diluted* and stored, for more than 2 days (Colsoul *et al*., 2020). However, *undiluted* lorazepam injectable, kept in glass syringes, is stable for up to 210 days when kept refrigerated and 150 days at room temperature making it an ideal at-home therapy for IN use (Gottwald *et al.,* 1999). Lorazepam may also be given orally (the injectable preparation); however, since many patients have excessive salivation during a seizure and may bite, using it in this manner is

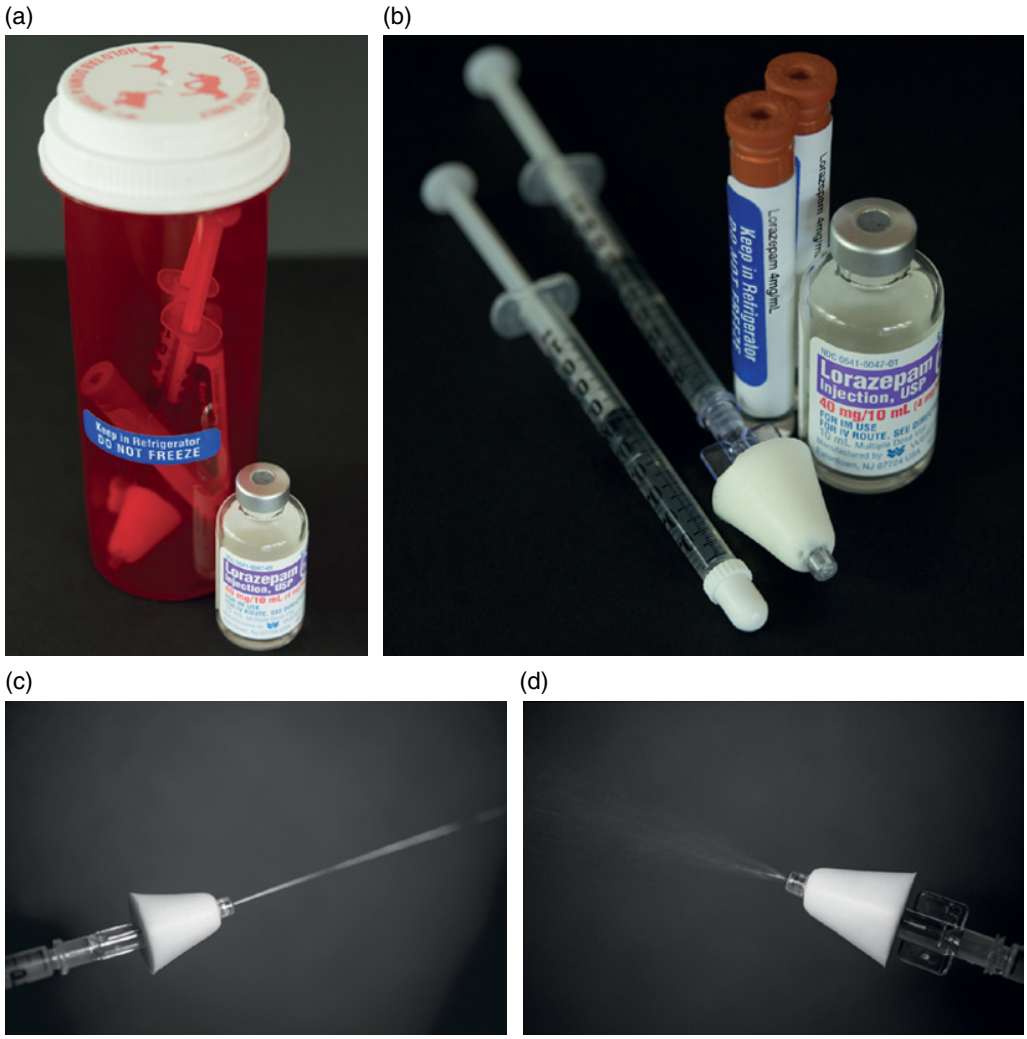


FIGURE 6.15 Example of a take-home lorazepam kit (note: midazolam can be prepared in the same way). (a) The kit is packaged in a large pill vial with instructions to store in a refrigerator. (b) Individual doses are packaged in syringes with caps and a reusable nasal atomizer (must be washed between uses). (c) When lorazepam is injected through the atomizer (because of its viscosity), it is ejected as a jet-like stream, allowing it to reach far back into the nasal cavity. (d) An aqueous solution ejected from an atomizer is made into a "mist." The atomizer may be reused between dosages if it is rinsed and allowed to dry.

discouraged. Undiluted midazolam is self-stable for 60 days at room temperature in a glass container (McMullan *et al.,* 2013). The shelf life of the injectable midazolam formulation, when mixed with a vehicle, is reported to be up to 102 days (Steedman *et al*., 1992; Walker *et al.,* 1997). Midazolam has been shown to be shelf-stable for up to 90 days in a diluted form stored in a polypropylene syringe at room temperature and up to 1 year when refrigerated (Gilliot *et al.,* 2020) (Table 6.9). Midazolam is commonly used as an oral syrup, prepared from the injectable form, for pediatric sedation. Midazolam also achieves rapid distribution when given intramuscularly (Court and Greenblatt, 1992). In summary, the rapidly absorbed benzodiazepines may be used in multiple routes for at-home and hospital *pulse* therapy (Table 6.8).

Table 6.10 Therapeutic drug monitoring recommendations.

- After starting a drug, once steady state is achieved
- After any adjustment in medication (up or down), once a new steady state has been achieved
- If seizures are not adequately controlled prior to increase in the dose
- If side effects are present, prior to lowering the dose
- Every 6–8 months routinely to watch for trends, often coupled with routine blood work to screen for possible liver toxicity and decreased renal function
- After completion of a loading dose, halfway to normal steady state (i.e., 1 week for phenobarbital and 6 weeks for bromide) and at typical time to steady state. Allows for adjustments to maintenance levels
- If half-life of the drug is greater than three times the dosing interval, peak and trough sample *do not* need to be taken
- Serum separator tubes should not be used

The above are recommended for phenobarbital, potassium bromide, and any other drug which has a narrow therapeutic window.

DRUG MONITORING

Specific recommendations for drug monitoring can be found under the individual drug's monograph in the next chapter. Because epilepsy is a chronic condition, often requiring lifelong therapy, particular attention should be made to the overall patient's health, the development of new disease processes, the addition of other drugs (either to treat seizures or comorbidities), weight loss or gain, the development of suspected tolerance to the drug (e.g., phenobarbital or the benzodiazepines), and any other factor that may affect the metabolism or elimination of particular drugs (e.g., diet, supplements, etc.). Certain drugs will have more stringent recommendations due to a narrow therapeutic window (e.g., phenobarbital and potassium bromide), while others are considered fairly safe and may have mild and reversible side effects (e.g., levetiracetam, imepitoin, and zonisamide), making routine monitoring less strict. The goal of therapy is to achieve maximum seizure control with the minimum amount of side effects of the medication while at the same time lessening the chance for the development of potential long-term organ damage (e.g., phenobarbital). Specific recommendations for serum monitoring are listed in Table 6.10.

DISCONTINUATION OF MEDICATION

Most owners should be counseled to expect lifelong therapy. However, occasionally, it may be reported there has been a complete cessation or remission of seizures. In these instances, one must balance the benefits of stopping therapy against the possible risks. Stopping a medication if seizures are controlled should only be considered if there have been no seizures for more than 1 year. Serious consideration should be given to simply maintaining the medication, if it is well tolerated and not causing any significant hardship to the pet (i.e., side effects or stress of dosing) or the client (e.g., financial or time commitment). Caution all owners who consider stopping the medication of the possibility for seizures to return and potentially be more difficult to get back under control. If the underlying etiology of the seizures is determined to be metabolic, reactive, or provoked (i.e., toxin or transient disease state), more consideration can be given to stopping the antiseizure medication if the underlying cause has been eliminated (i.e., not waiting for a 1 year seizure free interval). If the etiology of the seizures is either genetic, unknown, or structural brain disease (nonprogressive), more serious consideration should be given as to whether or not stopping the medication is a good idea. If the medication has a wide therapeutic window with little chance of long-term side effects, it may be more reasonable to continue even if seizures have not occurred in over a year. Conversely, if there is a greater potential for long-term side effects (e.g., phenobarbital), more weight may be given to the advantages of stopping the medication. If the cause of the epileptic seizures is structural brain

Table 6.11 Recommendations for tapering antiseizure medications.

Phenobarbital

- Decrease the dose by 25% every 3 weeks
- If in liver failure, decrease dose by 50% every week; consider bridge medication and potassium bromide (loading dose)

Potassium bromide

- Due to its long half-life, it can be stopped all at once and will take weeks to gradually leave

Imepitoin

- Decrease the dose by 25% every 2 weeks

Levetiracetam

- Decrease the dose by 25% every 2 weeks

Zonisamide

- Decrease the dose by 25% every 2 weeks

Gabapentin/pregabalin

- Decrease the dose by 25% every 1 week

Felbamate

- Decrease the dose by 25% every 1 week

Clorazepate/clonazepam

- Decrease the dose by subtracting one dose interval every 3–5 days depending on how long the treatment originally was. For example, if taking every 8 h for 3 days, reduce to twice a day for 3 days and then once a day for 3 days and then stop

If unsure, it is generally safe to reduce the dose by 25% every 2 weeks. Decrease to the point where it becomes impractical to make smaller pill sizes or the dose is 25% of the original starting dose and then stop.

disease, *which is progressive*—you likely will not be having this conversation. Nevertheless, antiseizure medication should not be discontinued unless it is replaced by a functional equivalent. Regardless of the medication, if it is to be stopped, it should be withdrawn gradually (this is especially true for barbiturates and benzodiazepines). If the patient has polypharmacy, wean off one medication at a time and give a significant amount of time before starting to wean subsequent medications to make sure seizures do not return. Recommendations for tapering medications are listed in Table 6.11.

CONCLUSION

No two patients will be the same. The first hurdle to get over is the notion that using medications to prevent seizures can be approached in a "cookbook" fashion. However, there are general guidelines (a recipe of sorts). Several factors will help determine when to start medications and which medications to use. Ultimately, these different variables will balance each other so the clinician can pick the medication, which will have the greatest chance of success, with the fewest side effects, and at the same time allow for the best chance for owner compliance. The client ultimately determines compliance. However, factors such as dosing schedule, dose route, side effects, and cost will significantly affect owner compliance. An understanding of basic pharmacological principles is necessary to understand potential reasons for a lack of efficacy, the development of toxic side effects, what to do when a comorbidity develops, and the potential for multidrug interactions. Having a wide selection of drugs to choose from aids in treatment success. Certain drugs will come in and out of preference especially as new drugs are developed which hold promise to be safer and more efficacious. Knowledge of different treatment strategies will give the clinician and the pet

owner a variety of options to help treat seizures when they arise in different situations. Chronic, maintenance, or prophylactic therapy forms the foundation for successful antiseizure management. The dose of the chronic therapy should be increased until the desired effect is achieved, a negative side effect is encountered, or, for those drugs with a wide therapeutic index (e.g., imepitoin, zonisamide and levetiracetam), double the starting dose is achieved. If seizures are still not adequately controlled past these points, add-on therapy should be considered. Bridge therapy can be effective to protect the patient while waiting for therapeutic concentrations to be achieved and provide the pet's owner with another strategy for home seizure control. Bridge therapy and pulse therapy can prevent seizures, stop status epilepticus, reduce trips to the emergency hospital, and improve the pet and pet owner's quality of life. Many of the newer-generation antiseizure medications have such a wide therapeutic window that routine serum concentration of the antiseizure drug is not necessary. However, for drugs with a narrow therapeutic window, routine monitoring along with regular evaluation of renal and liver function (and sometimes blood gases and urine) is necessary to prevent long-term toxic effects and help the clinician adjust medications. Always be aware of possible idiosyncratic reactions, even to "safe" AEDs. Ultimately, with experience, time, and working within certain guidelines, the clinician should gain confidence in making medication recommendations and being a long-term source of advice for the client.

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Antiseizure Medications CHAPTER 7

KEY TAKEAWAYS

Different benzodiazepines have different potency.

Know the variety of medications you can use to treat patients.

Follow consensus protocols (Chapter 6) but do not be afraid to step out of the box when they fail.

Fail a drug: Avoid the tangled knot of polypharmacy. Before moving to another antiseizure drug, make sure you fail the one the patient is currently using. Failure means reaching a max dose with no effect or an intolerable side effect. Caution as you approach the high end of reference range (phenobarbital) but don't necessary pre-emptively "fail." This creates *pseudo resistance*.

QUICK JUMP

Comparison of the benzodiazepines:	Figure 7.1 (dogs) and Figure 7.2 (cats)
Corticosteroids:	p. 257
Phenobarbital drug interactions:	Table 7.1
New drug dose formula:	Table 7.2
Potassium bromide dosing ex:	Table 7.3
Zonisamide abnormalities:	Table 7.4

Introduction 256

Corticosteroids 257

Standard Common Drugs 259

- **Clonazepam**: Bridge therapy, PO, *most* potent benzodiazepine 259
- **Clorazepate**: Bridge therapy, PO, *least* potent benzodiazepine 261
- **Diazepam**: Status epilepticus, IV, rectal 262
- **Gabapentin**: Chronic prophylactic, weak 267
- **Imepitoin**: Chronic prophylactic, strong 269
- **Levetiracetam**: Chronic prophylactic, bridge, pulse, PO, IV, rectal, medium 272
- **Lorazepam**: Status epilepticus, IV, IM, nasal, PO 276
- **Midazolam**: Status epilepticus, IV, IM, nasal, PO 279
- **Phenobarbital**: Chronic prophylactic, status epilepticus, IV, PO, strong 282

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Companion website: www.wiley.com/go/sanders/seizures2e

Potassium Bromide: Chronic prophylactic, PO, rectal, strong 292
Topiramate: Chronic prophylactic, IV, PO, medium 297
Zonisamide: Chronic prophylactic, PO, medium 300
Newer or Less Common Drugs 304
Felbamate 304
Ketamine 306
Lacosamide 308
Pregabalin 309
Propofol 311
Rufinamide 313
Rarely Used Drugs 314
Carbamazepine 314
Ethosuximide 316
Phenytoin 317
Primidone 318
Valproic Acid 318
Antiseizure Medications Not Used in Dogs and Cats 322
Antiseizure Drugs Under Development 324
Brivaracetam 325
Carbenoxolone 325
Fluorofelbamate 325
Ganaxolone 326
Losigamone 326
Perampanel 326
Tonabersat 327
Retigabine (Ezogabine) 327
2-Deoxy-D-glucose 327
Summary 328

Myelominutia: Levetiracetam and *Botulinum* toxin bind to the same protein—SV2A

INTRODUCTION

Human neurologists have literally dozens of anti-seizure drugs to choose from, Yet, it is estimated as many as 30% of humans do not have adequate seizure control, despite being treated with adequate antiepileptic drug therapy, which is similar to dogs (a little less so for cats) (Farnbach, 1984a; Schwartz-Porsche *et al*., 1985; Podell and Fenner, 1993; Walker and Williams, 2013; Löscher *et al*., 2020). Our primary source of seizure control at this time is medications, from which veterinarians are significantly limited compared to our human counterparts. Antiseizure medications do not alter the disease itself, rather they simply act to prevent the occurrence of seizures (note: in the strictest sense, corticosteroids used as an antiseizure drug can alter the underlying disease). There will never be one single treatment available to reverse or modify the cause of epilepsy, just as there will never be one single treatment available to reverse or modify *lameness*. Seizures, like lameness, are a symptom of a disease, not a pathological entity. As our understanding of the causes of epilepsies develops, specific treatments, such as gene therapy and molecules used to target specific cellular signaling, will be available to correct the cause of epilepsy. Animals have always been experimental models of many human diseases, and treatment of those diseases invariably has involved experimentation on dogs and cats to determine the rational efficacy and toxicity of the medications intended for human use. Many of the medications used to treat human epilepsy can also be used for animals, but certainly not all of them, and conversely, some of the medications we use for dogs and cats cannot be used for humans.

The oldest purposefully utilized antiseizure medication, potassium bromide, is still used today. Its efficacy and safety make it a good choice either as a primary or an add-on antiseizure medication for dogs. The use of potassium bromide was first described in 1857. The use of antiseizure medications has paralleled that in humans, although dogs and cats certainly are not considered equals when applying treatment options. The rapid metabolism of many medications

by dogs and cats prevents meaningful therapeutic levels from being attained in many circumstances. Over 55 years passed from the first use of potassium bromide to the application of phenobarbital to treat epileptic seizures in 1912. The use of phenobarbital to treat seizures was the beginning of a more rapid advancement in the development of antiseizure medications, as modern practices in chemistry and understanding disease processes provided a synergy for the genesis of modern medicine.

There are five basic mechanisms through which antiseizure drugs work (Sills and Rogawski, 2020). The goal is to suppress abnormal hyperexcitability that would lead to hypersynchronous activity in brain circuits and seizures. Essentially, we are either taking our foot off the gas pedal (less excitation) or applying more brakes (more inhibition). These mechanisms are:

- Modulation of voltage-gated ion channels
- Increase GABA-mediated neurotransmission (inhibition)
- Inhibition of glutamate-mediated excitatory neurotransmission
- Modulate neurotransmitter release through a presynaptic action
- Mechanism targeted therapy—on/off signaling switches

The following medication monographs are not meant to be an exhaustive description of antiseizure medications. It is meant to be more of a general guide. We still have limited understanding of how some medications work even after several decades of study and use and many compounds appear to have multiple mechanisms through which they act. For a complete reference, the reader is recommended to utilize a veterinary pharmacy formulary such as *Plumb's Veterinary Drug Handbook* and specific peer-reviewed journal articles regarding the medication they are interested in. This text will include medications not present in most veterinary formularies. Both the American College of Veterinary Internal Medicine (ACVIM) and the International Veterinary Epilepsy Task Force (IVETF) have published consensus statements regarding the organizations' recommendations for the use and evaluation of antiseizure medications in dogs and cats (Bhatti *et al.*, 2015; Potschka *et al.,* 2015; Podell *et al.*, 2016; Charalambous *et al.,* 2024). Finally, the clinician and pet care provider need to remember the treatment of epileptic seizures is not "cookbook"; each case must be evaluated and considered individually.

CORTICOSTEROIDS

Before we dive into antiseizure drugs from the standard approach, it is reasonable to consider the use of corticosteroids for the prevention of epileptic seizures. In a strict sense, corticosteroids do not directly stop seizures but they may prevent them from occurring. Steroids may be frowned upon for the treatment of neurological disease and certainly, neurologists will have their preferences based on individual years of clinical experience. But let's look at various cases for the practical use of steroids, in either treating the direct underlying substrate causing the epileptic seizures or the secondary effects of the cause of epileptic seizures. Where would it be *reasonable* to try corticosteroids—either empirically or with definitive evidence for their use?

- Cases of confirmed or suspected *encephalitis* (collectively—meningoencephalomyelitis of unknown origin—*MUO*) based on CSF analysis (or highly suspicious based on signalment and imaging). Usually combined with a traditional AED. Doses tend to be in the anti-immune range and may be combined with other immunomodulators (i.e., cytarabine, cyclosporine, etc.).
- Cases where *vasogenic* edema may be present secondary to a mass effect in the brain. Brain tumors and other possible structural causes of cerebral compression, grow and exist in a confined space. This creates secondary damage to surrounding tissue. We can see this on MRI examination primarily as a hyperintense signal within the white matter on T2-weighted and

Fluid-attenuated inversion recovery (FLAIR) images (Figure 5.4). The cautious use of anti-inflammatory doses of corticosteroids may help reduce some of the detrimental effects of vasogenic edema associated with brain tumors (Gomes *et al*., 2005; Hudak *et al*., 2014).

- To treat conditions where there are confirmed (or suspected) autoantibodies against *neural intracellular or surface antigens*. For example, autoantibodies against the $GABA_A$ receptor have been reported in people and in a dog (Huenerfauth *et al*., 2022). In this extremely cool case report, a young dog with drug-resistant epilepsy and declining clinical status had a *normal MRI exam and CSF analysis*. After 5 days of continuing declining status at an ER, it was treated with dexamethasone at 0.5 mg/kg IV followed by 0.2 mg/kg IV. The dog gradually improved over 3 days. Autoantibodies against the $GABA_A$ receptor were identified (serum 1:320 and CSF 1:2). The dog continued treatment with prednisone at 1 mg/kg/day, as well as, AEDs. The dog was neurologically normal 4 weeks after discharge and serum antibodies to $GABA_A$ receptor were measured at 1:20 and CSF was negative. The dog was eventually weaned off steroids over a 7-month time course with no return of seizures. Autoantibodies have also been reported against the *N*-methyl-D-aspartate receptor 1 (NMDAR1) in dogs, detected in CSF (Stafford *et al*., 2019). The three dogs in this study with anti-NMDAR1 antibodies responded to treatment for MUO. Autoantibodies directed at the voltage-gated potassium channel complexes/leucine-rich glioma inactivated protein 1 (VGKC/LGI1) have been reported in cats with successful treatment using corticosteroids (Pakozdy *et al*., 2013, 2015).
- The drug-resistant epileptic. You've tried everything and nothing seems to work. You are on the fifth AED and reasonably certain all previous medications have been trialed appropriately (see Chapter 6). Would it be reasonable to at least try a short course or corticosteroids? Probably. We know the more drugs we add to a protocol, the less compliance we get and over time, the closer the patient comes to euthanasia due to reduced quality of life of both the pet and the caretaker (Fredsø *et al*., 2014; Wessmann *et al*., 2014). A corticosteroid trial would be a reasonable consideration, if not for the possible 1/100 chance the patient may be responsive. Most clinicians will not have the time or resources to perform a research-level investigation for these patients (see bullet above). If we know it was beneficial for one patient, there is a reasonable chance it could be for another.

It is well-accepted, that corticosteroids, particularly high doses of methylprednisolone sodium succinate, should not be used in cases of traumatic brain injury (TBI) (Edwards *et al*., 2005; Brain Trauma Foundation *et al*., 2007). This general rule also extends to cases of cytotoxic (i.e., *cellular* edema, Figure 5.1) such as that associated with cerebral ischemia (e.g., stroke). However, the algorithm is not that clear-cut. For example, in cases of TBI, we often see a mixture of cytotoxic *and* vasogenic edema. Many clinicians have used lower anti-inflammatory doses of either prednisone or dexamethasone in cases of TBI with the assumption they might be helping the vasogenic edema and certainly not hurting the case, especially where traditional management of increased intracranial pressure may fail (see Chapter 8). In cases of TBI, both forms of edema are typically present and therefore it may be reasonable to consider the cautious use of corticosteroids to treat the vasogenic component of TBI. A study using diffusion tensor imaging MRI (DT-MRI) looked at the effect of dexamethasone for the treatment of peri-contusion vasogenic edema in humans with TBI and found those humans who received dexamethasone had a median *reduction* of intracranial vasogenic edema from 22 to 19 ml, whereas those patients who did not receive dexamethasone had a median *increase* of vasogenic edema from 11 to 15 ml (Moll *et al*., 2020). The dose of dexamethasone used was considered low (for humans) and gradually tapered over 10 days in a manner following common neuro-oncology dose protocols (Reynolds, 1996). A similar, modified, protocol is often used by the author and many, many veterinary neurologists (author's personal observation). Of course, the utmost caution should be used when considering corticosteroid use in compromised

veterinary patients, especially cats (cover your ears my internal medicine friends) but when facing a patient in declining clinical status, you may find the possible benefits of corticosteroid use outweigh the risks (...even in cats).

STANDARD COMMON DRUGS

CLONAZEPAM (CLN) (KLOE-NA-ZUH-PAM)

Clonazepam is a longer-acting benzodiazepine, which may also be used much in the same way as clorazepate. It is over 10 times more potent than diazepam and considered the most potent oral benzodiazepine (Figure 7.1) (Frey, 1989). It is more frequently used for anxiety. In the USA, it is marketed under the trade name *Klonopin*® and is also available in generic forms.

Mechanism of Action

Clonazepam will interact with the $GABA_A$–chloride ionophore membrane complex. It directly binds to the γ-aminobutyric acid (GABA) receptor, similar to other benzodiazepines, and *enhances the affinity* of GABA for its binding site, which potentiates the flow of chloride ions across the ion channel, thereby hyperpolarizing the plasma membrane and lowering the seizure threshold. Only the barbiturates, at high concentrations, will directly open the chloride ion channel (Rho *et al*., 1996). The benzodiazepines and barbiturates also differ functionally with the barbiturates increasing the *duration* of opening of the chloride channel relative to the presence of GABA and the benzodiazepines increasing the *frequency* of channel opening (Twyman *et al*., 1989). Tolerance will develop in days rather than months, compared to clorazepate if used chronically.

Drug	Relative potency	Dose	t ½	Time to tolerance	Route	Use
Clorazepate	1	0.5–1.5 mg/kg q 8–12 h	4–6 h	Weeks to months	PO	Bridge, pulse
Diazepam	5×	0.5–2.0 mg/kg IV,IN 1–2 mg/kg Rectal 0.1–0.5 mg/kg CRI[a]	2–4 h	Days to 1 week	PO, IV, Rectal	SE, bridge, pulse
Midazolam	10–30×[b]	0.1–0.2 mg/kg IV, IN, IM, sublingual 0.1–0.2 mg/kg/h CRI	1 h	N/A (no oral form)	PO, IV, IM, IN	SE, bridge, pulse
Lorazepam	50×	0.2 mg/kg IV, IN, IM, sublingual	1 h	Hours to days	PO, IV, IM, IN	SE, bridge, pulse
Clonazepam	75×	0.5–2.0 mg/kg q8–12 h	2–4 h[c]	Days	PO,IV[d]	Bridge, pulse (IV)

[a]Total calculated dose diluted in D5W and delivered at calculated maintenance rate of fluids/hour
[b]References range from 2× to 6× compared to diazepam
[c]Dose dependent. Increased dose = increase half-life
[d]IV formulation not available in US



FIGURE 7.1 Comparison of common benzodiazepines for dogs.

Pharmacokinetics

After being given orally in dogs, clonazepam has a bioavailability of approximately 33%. Protein binding accounts for 82% of the drug, and like other benzodiazepines, it is rapidly metabolized. It has a similarly large volume of distribution (Vd) of 2 l/kg. Its half-life is approximately 2 h at a dose of 0.5 mg/kg in dogs (Frey, 1989). Serum therapeutic concentrations can be maintained at a dose of 0.5 mg/kg every 8–12 h in dogs.

Toxicity, Side Effects, and Interactions

Like other benzodiazepines, the primary side effects of clonazepam are sedation and ataxia. Tolerance to the medication usually develops in *days*. Aggression has been noted as a possible complication likely due to social disinhibition. Signs of drug withdrawal are more likely to occur with dogs having the medication discontinued after chronic use. In these patients, at a dose of 0.5 mg/kg every 12 h for 7 weeks, after cessation of the medication, physical signs of dependence were noted including listlessness, "wet dog shakes," tremor, increased body temperature, weight loss, and withdrawal tonic–clonic seizures. The signs resolved within 1 week of the cessation of the drug (Scherkl and Frey, 1986).

Clonazepam may also increase the effects of other potentially sedating drugs, especially barbiturates, antihistamines, tricyclic antidepressants, phenothiazines, and analgesics. Withdrawal of the medication should be gradual to prevent the development of withdrawal seizures. Clonazepam should be used cautiously in patients with compromised liver function and in cats (only due to diazepam's potential toxicity in cats—and the fact clonazepam is also a benzodiazepine).

Indications for Use

The use of clonazepam would be similar to clorazepate as a "bridge" medication in order to gain control of epileptic seizures while waiting for serum concentrations of a chronic antiseizure medication to reach therapeutic levels. It can also be used during times of breakthrough seizures or episodes of clustering (Figure 6.13). In this manner, if a known seizure event is predictable, clonazepam may be given 1 h prior to the predicted event and then every 8 h while there is still potential for a seizure to develop. In the event of clusters, the medication is given after the first seizure as soon as the patient can safely take a pill and then every 8–12 h while there is still a risk of more seizures. It should not be used longer than a few days to avoid the development of tolerance. In humans, clonazepam is used as a first-line medication for myoclonic seizures and a second-line medication for absence seizures (Engel, 2013). In Europe, clonazepam (*Rivotril*®) is used to treat status epilepticus (SE); however, an injectable form is not available in the USA.

Dose

The oral dose for dogs varies from 0.5 to 2.0 mg/kg PO every 8–12 h and should be adjusted for effect or to side effects (usually excessive sedation). In cats, a dose of 0.02–0.5 mg/kg PO every 12 h is recommended, but again, the question is its use in cats due to the potential to develop acute hepatic necrosis (not reported—only by association as a benzodiazepine).

Clonazepam is available as oral tablets in 0.5, 1.0, and 2.0 mg sizes. It is also available as an oral, rapidly disintegrating tablet in 0.125, 0.25, 0.5, 1.0, and 2.0 mg sizes. The oral disintegrating tablets **may contain xylitol**.

Monitoring

Clonazepam levels can be monitored; however, all metabolites of the drug must be measured. Monitoring is not considered necessary owing to the safety of the medication and because it should not be relied on for chronic seizure control. Due to its safety, only routine monitoring of liver

function is necessary in dogs—but only if used chronically. Cats should have their liver values assessed similarly to that described for diazepam. If therapeutic monitoring of benzodiazepine levels is indicated, do not use serum separator tubes. Serum separator tubes result in a time and drug-dependent decrease in concentration much like that of phenobarbital (Boothe *et al.*, 1996).

CLORAZEPATE (CZP) (KLOR-AZ-AH-PATE)

Clorazepate is a low potency benzodiazepine (75 times less potent than clonazepam, see Figure 7.1) often used for long-term control of seizures and intermittently for control of cluster episodes. Its primary use is as a "bridge" medication (see section "Indications for Use"). In the USA, it is marketed under the trade name *Tranxene*® and is also available in generic forms.

Pharmacokinetics

After oral administration, clorazepate is rapidly hydrolyzed in the stomach to *N*-desmethyldiazepam (nordiazepam) (Forrester *et al.*, 1990). Nordiazepam is the active metabolite of clorazepate. Serum levels between 500 and 1900 ng/ml are associated with improved seizure control in humans. However, as with most antiseizure medications, the goal, regardless of reference concentration in the serum (assuming a wide range of safety), is to treat to effect or side effects. Furthermore, it has been suggested the serum concentration necessary to control seizures in dogs is greater than in humans (Papich and Alcorn, 1995). The disposition of nordiazepam after oral dosing with clorazepate is like that of nordiazepam after oral dosing with diazepam (Löscher and Frey, 1981). However, the half-life is 4–6 h in dogs (as opposed to 2–4 h for diazepam), and dogs do not develop tolerance to this drug as readily as they do to diazepam (Figure 7.1).

Mechanism of Action

The mechanism of action of clorazepate is suspected to be identical to diazepam. Clorazepate interacts with the $GABA_A$–chloride ionophore membrane complex. It directly binds to the GABA receptor and enhances the affinity of GABA for its binding site, which potentiates the flow of chloride ions across the ion channel, thereby hyperpolarizing the plasma membrane and lowering the seizure threshold. However, owing to its longer half-life and slower development of tolerance compared to diazepam and clonazepam, it is generally considered more efficacious when used as an oral, longer-term antiseizure medication. Additionally, the active metabolite of both diazepam and clorazepate, *nordiazepam*, is produced at higher concentrations and over a longer period from clorazepate when compared to diazepam (Brown and Forrester, 1991).

Toxicity, Side Effects, and Interactions

Clorazepate has similar side effects to the other benzodiazepines including sedation and ataxia. While hepatic necrosis has not been reported in cats, it is recommended to use the same caution as expressed under the section for diazepam relating to the use of clorazepate in cats. Clorazepate may *increase* phenobarbital concentrations in the serum within 1–2 months of its use. It is recommended to check phenobarbital levels and usually requires lowering the dose of phenobarbital to compensate for its serum concentration increases. However, if clorazepate is withdrawn, reduced, or used chronically, the serum phenobarbital concentrations will eventually lower. Clorazepate use may result in decreased (but still within the normal reference range) serum albumin and blood urea nitrogen (Forrester *et al.*, 1990). Clorazepate may also increase the effects of other potentially sedating drugs, especially barbiturates, antihistamines, tricyclic antidepressants, phenothiazines, and analgesics. Withdrawal of the medication should be gradual to prevent the development of withdrawal seizures.

Indications for Use

Clorazepate may be used as a temporary "bridge" therapy to control epileptic activity while waiting for serum concentrations of chronic antiseizure medications to reach therapeutic levels. This drug may also be used in patients who have routine episodes of cluster seizures despite being otherwise controlled with another anticonvulsant. These "breakthrough" episodes are controlled with clorazepate on an as-needed basis (see section "Bridge Therapy" under Strategies for Seizure Control, Chapter 6 and Figure 6.13). The drug is only given in the few days before and after the usual time or expected onset of the cluster episodes. This requires diligent monitoring of seizure activity on the owner's part and particular attention to cluster patterns, which may develop with time.

The use of clorazepate for the *chronic* control of seizures is hampered for several reasons. Due to its short half-life, a missed dose may result in a breakthrough seizure. Clorazepate serum concentrations may reduce over time with no concurrent decrease in dose (i.e., the development of tolerance) (Boothe, 1998).

Dose

When used with phenobarbital, the recommended dose is 1 mg/kg every 8–12 h. The dose used to treat intermittent episodes of cluster seizures is 0.5–1.5 mg/kg every 8–12 h. For cats, the recommended dose 3.75–7.5 mg (total dose per cat) is divided and given every 12–24 h (Podell, 2008). It should be stressed again this is only used in the few days preceding the predicted clusters and discontinued a few days after the episodes are expected to pass. While dogs are less likely to develop tolerance to the medication as rapidly as diazepam, it is not recommended to use it longer than 2 weeks at a time. Individual responses may vary. The sustained-release form of clorazepate offers no benefit to dogs (Brown and Forrester, 1991). If a patient has a compromised liver (e.g., portosystemic shunt), start with 25% of the calculated dose. Use caution when considering the use of this medication in cats.

Clorazepate is available in 3.75, 7.5, and 15 mg oral tablets.

Monitoring

Clorazepate levels can be monitored; however, all metabolites of the drug must be measured. Monitoring is not considered necessary owning to the safety of the medication and because it should not be relied on for chronic seizure control. Due to its safety, only routine monitoring of liver function is necessary in dogs. Cats should have their liver values assessed similarly to that described for diazepam. If therapeutic monitoring of benzodiazepine levels is indicated, do not use serum separator tubes. Serum separator tubes result in a time- and drug-dependent decrease in concentration much like that of phenobarbital (Boothe *et al*., 1996).

DIAZEPAM (DZP) (DYE-AHZ-AH-PAM)

Diazepam is considered one of the most effective antiseizure drugs. While it is considered a first choice for the treatment of status epilepticus, midazolam or lorazepam is more potent. It is a benzodiazepine and may also be used for anxiety, as an appetite stimulant and as a muscle relaxant. It has a very wide safety margin and very few side effects when used within published guidelines. Its use in veterinary and human patients for the control of epileptic seizures is primarily in the parenteral form for the treatment of acute epileptic seizures and SE. Owing to a very short half-life in dogs, rapid first-pass metabolism when given orally, and development of tolerance, *it is not a good chronic, oral antiseizure medication* for dogs. It may be more beneficial for use as a chronic antiseizure medication in cats, although fatal hepatotoxicity has been reported with the use of oral diazepam in cats (Center *et al*., 1996). In the USA, it is marketed under the trade name *Valium*® and is also available in generic forms.

Mechanism of Action

In general, benzodiazepines are suspected to exert their primary antiseizure effect through interaction with the $GABA_A$–chloride ionophore membrane complex. Diazepam and other benzodiazepines directly bind to the GABA receptor (a separate site from phenobarbital and other barbiturates), enhance the affinity of GABA for its binding site, and potentiate the flow of chloride ions across the ion channel, thereby hyperpolarizing the plasma membrane and lowering the seizure threshold. However, the interaction of benzodiazepines with the $GABA_A$ receptor is likely not the only mechanism of action for its antiseizure effects (Engel, 2013). At high doses (those unattainable by oral administration), there is suppression of repetitive firing in partially depolarized spinal cord neurons. This is due to a dose and use-dependent reduction in sodium conductance. These effects may be observed when diazepam is given intravenously (Frey, 1989). It acts to block arousal in the central nervous system (CNS) and centrally depresses spinal reflexes (Boothe, 1998).

Pharmacokinetics

Following oral administration, diazepam has a very rapid first-pass metabolism resulting in demethylation of diazepam to *N*-desmethyldiazepam (nordiazepam). Other metabolites include temazepam and oxazepam (Frey, 1989). All three metabolites possess antiseizure activity, although not as potent as diazepam. However, the primary antiseizure effect of diazepam *in vivo* is due to its active metabolites (Frey and Löscher, 1985). The oral bioavailability of unchanged diazepam in dogs is 1–3%, whereas its less active metabolites of *N*-desmethyldiazepam and oxazepam have a much higher oral bioavailability (76–90% and 8–23%, respectively) (Löscher and Frey, 1981). Diazepam has a half-life of 2–4 h in dogs resulting in an inability to maintain therapeutic concentrations with repeated doses (Figure 7.1). The rapid half-life along with the development of tolerance within a few days to weeks makes it unsuitable for oral use in dogs for the control of epileptic seizures (Frey *et al.*, 1984). The half-life in cats is considerably longer (15–20 h) (Frey, 1989) (Figure 7.2). Because of its extended half-life, cats can maintain therapeutic concentration in the

Drug	Relative potency	Dose	t ½	Time to tolerance	Route	Use
Clorazepate (caution)	1	3.75–7.5 mg *total dose*, divided q 12–24 h	4–6 h	Weeks to months	PO	Bridge, pulse
Diazepam (caution)	5×	0.25–0.5 mg/kg IV, IN 1–2 mg/kg Rectal 0.1–0.5 mg/kg CRI[a]	2–4 h	Days to 1 week	IV, Rectal	SE, bridge, pulse
Midazolam	10–30×[b]	0.1–0.2 mg/kg IV, IN, IM, sublingual 0.1–0.2 mg/kg/h CRI	1 h	N/A (no oral form)	PO, IV, IM, IN	SE, bridge, pulse
Lorazepam	50×	0.1 mg/kg IV 0.2 mg/kg IN, IM, sublingual	1 h	Hours to days	PO, IV, IM, IN	SE, bridge, pulse
Clonazepam (caution)	75×	0.5 mg (total dose) q8–12 h	2–4 h[c]	Days	PO,IV[d]	Bridge, pulse (IV)

[a]Total calculated dose diluted in D5W and delivered at calculated maintenance rate of fluids/hour
[b]References range from 2× to 6× compared to diazepam
[c]Dose dependent. Increased dose = increase half-life
[d]IV formulation not available in US



FIGURE 7.2 Comparison of common benzodiazepines for cats.

serum and do not develop tolerance to the drug. The pharmacokinetics of diazepam in cats are similar to humans (Colter *et al*., 1984). However, oral use in cats may result in acute fulminant hepatic necrosis; therefore, its oral use is not recommended for chronic therapy in cats (Center *et al*., 1996). Caution should be used if diazepam is employed for seizure control in hepatic-compromised animals. Overdose may be successfully treated with a titrated continuous infusion of flumazenil (Costa *et al*., 2023).

Diazepam is 94–96% protein bound and has a very large Vd. It is highly lipid soluble and reaches the brain at maximal concentrations within 1 min of IV injection (Ramsay *et al*., 1979; Löscher, 1981). However, because it is so highly protein bound, only a small fraction of the original dose (1–2%) crosses the blood–brain barrier to reach the CNS. Following IV administration at 1 mg/kg, the plasma levels of diazepam decline rapidly within 30 min in dogs (Schwartz *et al*., 1965). In dogs, following oral administration, maximum serum concentrations of diazepam are reached within 45–60 min; however, they are very low compared to the less active metabolites (Löscher and Frey, 1981). If diazepam appears to be effective in treating seizures with oral administration, the mechanism of seizure control is likely due to its metabolites rather than the diazepam itself. In these cases, clorazepate may be warranted because of its longer half-life (Boothe, 1998).

Diazepam is erratically absorbed after intramuscular (IM) injection (Parent, 1988). Its use in this manner is not recommended.

Diazepam will reach serum therapeutic concentrations (i.e., 150 ng/ml) within 8–14 min of rectal administration (Mealey and Boothe, 1995; Wagner *et al*., 1998). The bioavailability of diazepam and its metabolites following rectal administration averaged at approximately 40–65% (Mealey and Boothe, 1995; Papich and Alcorn, 1995; Wagner *et al*., 1998). Because a fraction of venous blood returns from the rectum, via the caudal rectal veins, and bypasses the liver, there is a significantly greater bioavailability of rectally administered diazepam when compared to orally administered diazepam (Podell, 1995).

The bioavailability of diazepam and its active metabolites when given intranasally (IN) (either through nasal drop method or atomization) at a dose of 0.5 mg/kg in dogs was estimated at 40% with a time to peak plasma concentration (>300 ng/ml) of less than 5 min (Platt *et al*., 2000; Musulin *et al*., 2011). While the atomized method of delivering the diazepam IN was easy to administer, it did not have any other benefit compared to the nasal drop method. Crushing diazepam pills in water and giving the solution rectally is not recommended. Only the parenteral form should be used for rectal administration. Additionally, human *suppository* preparations (designed for epileptic children) may have erratic rectal absorption and are not recommended for use in veterinary patients (Probst *et al*., 2013).

The metabolites of diazepam are conjugated with glucuronide in the liver and excreted in the urine (~60%). Diazepam is also excreted in the feces (~34%) of the dog (Schwartz *et al*., 1965).

Toxicity, Side Effects, and Interactions

Complications secondary to diazepam therapy are very rare in dogs. They may include sedation, a tolerance to the medication within days, aggression (presumably due to disinhibition), increased appetite, and an increase in the effects of other sedatives, particularly barbiturates. These commonly occur when serum concentrations are greater than 500 ng/ml (Boothe, 1998). For cats, similar side effects occur as in dogs; however, there is the *possibility* of cats developing acute fulminant and often fatal hepatic necrosis, when dosed orally (Center *et al*., 1996). The reaction in cats is idiosyncratic and not related to dose or time. This can occur as early as 5–11 days after oral administration and occurred in cats receiving doses from 1 mg once a day to 2.5 mg every 12 h. It is recommended liver enzymes be monitored at 5–7 days after starting therapy and then evaluated every 6 months if using oral diazepam in cats (Platt, 2001). The first clinical signs recognized in cats developing hepatic necrosis were excessive sedation followed by anorexia, vomiting, dehydration,

lethargy, hypothermia, and jaundice. If these signs are recognized and hepatic necrosis is suspected, the diazepam should be discontinued and aggressive treatment with fluids, nasogastric tube feeding, ampicillin, and vitamin K should be instituted. Even with aggressive treatment, the prognosis is poor although successful treatment has been reported (Park, 2012).

Chronic use of the injectable form of diazepam is not recommended in cats. The injectable form of diazepam contains propylene glycol, a buffering agent and a preservative, which is a known toxin to cats and may cause Heinz body anemia. Long-term use of diazepam may also lead to it being less effective in treating SE. Diazepam is also less effective when given to dogs treated chronically with phenobarbital (Wagner *et al.*, 1998).

Rectal perforation has been reported in one dog when diazepam was administered per rectum using a teat cannula (Podell *et al.*, 1998a). The author advises a red rubber tube with a softened tip (Figure 6.14). The volume of diazepam needed to deliver therapeutic concentrations via the intranasal route in larger dogs may pose a risk for aspiration pneumonia. A more concentrated formulation in low molecular-weight glycol may circumvent this potential risk (Platt *et al.*, 2000). An alternative would be lorazepam or midazolam which allows for smaller volumes to be used intranasally.

Because diazepam reacts with light, solutions prepared for administration longer than 2 h should be protected from light (Parent and Quesnel, 1996). Additionally, because diazepam may bind to certain plastics, diazepam should be run through the IV administration line prior to its use in the constant rate infusion (CRI) and should not be dispensed in plastic syringes for take-home use (MacKichan *et al.*, 1979). To avoid this complication, diazepam can be dispensed in red top blood collection tubes along with a red rubber feeding tube attached to a syringe (Figure 6.14). The client is advised on how to withdraw the contents of the diazepam from the vial and administer the medication rectally. In the case of intranasal administration, the red rubber feeding tube may be omitted. A nasal atomizer attached to the syringe will create a "stream" of liquid, which has a better ability to reach the nasal mucosal surface. Diazepam has an "oily" consistency which may cause red rubber tubes or atomizers to dislodge during injection. Diazepam may also increase the effects of other potentially sedating drugs, especially barbiturates, antihistamines, tricyclic antidepressants, phenothiazines, and analgesics. Discontinuing the medication should be gradual to prevent the development of withdrawal seizures.

Indications for Use

Diazepam is one of the first-line drugs of choice (along with midazolam and lorazepam) for the treatment of SE and acute seizures either in the hospital setting (IV use) or through rectal and intranasal use at home or where venous access is not possible. Diazepam should not be used in the oral form for the treatment of epileptic seizures in either dogs or cats, although it can be used as a last resort in cats (assuming the failure of safer medications) with appropriate monitoring and caution.

In most cases, diazepam adequately stops a seizure or SE event; however, if the effect is short-lived, diazepam can be given as a CRI either by syringe pump or mixed in 5% D5W (Boothe, 1998). If given via syringe pump in its unaltered form, a central line should be used and care should be taken to avoid extravasation. The amount of diazepam necessary to stop the initial seizure event is given over 1 h as a CRI or at a dose of approximately 0.1–0.5 mg/kg/h along with maintenance fluids.

There are significant benefits to the use of diazepam given per rectum. Hitting a vein in a dog presenting for generalized tonic–clonic seizures is challenging at best. Along with intranasal midazolam or lorazepam, rectal administration of diazepam can be effective in the acute control of SE. It is absorbed very rapidly (within 10 min) when given rectally. Because a portion of the venous blood from the rectum (the caudal rectal vein) bypasses the portal circulation, diazepam will reach

therapeutic levels in the CNS before its rapid first-pass metabolism (Podell, 1995). Diazepam may be sent home with clients to be given rectally in the event of a seizure (Figure 6.14). Because many dogs treated with a single anticonvulsant will become refractory to that anticonvulsant (20–52%), there is a good chance home use of diazepam will be necessary (Farnbach, 1984a; Schwartz-Porsche *et al.*, 1985). The use of rectal diazepam may result in a significant decrease in the number of cluster seizure events in a 24 h period, a decrease in the total number of seizure events, a decrease in the total cost of emergency care, and a decrease in the amount of owner anxiety when diazepam is dispensed for home use (Podell, 1995). Witnessing a seizure in a pet can be extremely stressful for a pet owner. The use of at-home diazepam (for the pet) alleviates some of the helplessness owners feel when their dogs (and cats) have seizures. This most likely also decreases the number of patients who are euthanized due to frustration for the owner and increased severity or frequency of seizure events along with the associated expense of their treatment.

The author dispenses diazepam in single-dose vials. Red top blood collection tubes are used. The diazepam should be stored at room temperature out of the light in an upright position. The owners are carefully explained how to withdraw the diazepam and inject the solution rectally. Extreme importance is given to the instructions, which are also carefully written out on a separate administration instruction sheet. The use of a red rubber tube to withdraw the diazepam from the blood collection vial is safer than a needle. Emphasis is placed on making sure the owner knows to insert the tube in the rectum and not simply spray the diazepam on the perianal area (yes..., it has happened). In addition, it is recommended that diazepam be given even if the seizure has stopped by the time the owner gets to the patient. This may prevent clusters from developing or the progression of a single seizure to SE. Rectal diazepam can also be used in cases of focal seizures to prevent possible secondary generalization. Because diazepam binds to plastic, it should never be dispensed in syringes. A potential complication of rectal administration is rectal perforation and subsequent abscess or fistula development (Podell *et al.*, 1998a). For this reason, the tip of the red rubber tube is not cut but left blunt or if cut is slightly melted to create a smooth surface (Figure 6.14c and d).

Dose

Diazepam is very effective at blocking seizure activity in the pentylenetetrazole (PTZ) seizure threshold test, as well as the maximal electroshock (MES) model of seizures. A dose of 0.5–1.0 mg/kg was effective at treating seizures in 50% of the tested canine population (ED50) (Frey, 1989). The dose range for acute control of seizures is extremely variable. A calculated dose of 0.5–1 mg/kg in the dog should be sufficient; however, the effects can be variable within the species. A dose of 0.5–2 mg/kg IV is recommended for SE (Papich and Alcorn, 1995; Boothe, 1998). In cats, a dose of 0.25–0.5 mg/kg IV is recommended. Intravenous doses should be administered slowly to prevent hypotension. Avoid extravasation of diazepam.

When treating an ongoing seizure, an easy rule of thumb is to initially give 1 ml (5 mg) IV for small dogs and cats (5–10 kg), 2 ml (10 mg) IV for medium dogs (10–20 kg), and 3 ml (15 mg) IV for large dogs (>20 kg). If there is no effect within 5 min, the dose is repeated. If there is still no effect by 10 min, the dose is repeated again. Because of the high safety margin of the drug, the dose can be repeated several times. Subtherapeutic dosing is the most common reason diazepam fails to control seizures. If a patient is known or suspected to have liver dysfunction (e.g., portosystemic shunt) or has been chronically dosed with phenobarbital or other anticonvulsants metabolized by the liver (primidone, phenytoin, etc.) and presents with SE, then 25% of the calculated dose of diazepam should be used. If given to patients with liver failure, diazepam may put them into a "diazepam coma," which may last for several hours to days. Flumazenil may be helpful in these cases (Costa *et al.*, 2023). Diazepam should be injected slowly IV. Its bioavailability is very unpredictable and slow when given IM and is therefore not recommended to be dosed in this route.

An intranasal dose of 0.5 mg/kg should reach serum therapeutic concentrations within 5 min (Musulin *et al*., 2011). This dose is ½ of the recommended rectal dose by some investigators and has been shown to reach therapeutic concentrations in the CNS more rapidly than rectal delivery (Platt *et al*., 2000) and oral delivery (Lui *et al*., 1991).

A rectal dose of 1 mg/kg should be used in dogs and cats. If being treated with chronic phenobarbital therapy, the rectal dose should be increased to 1–2 mg/kg. The dose range can be variable. The author tends to go on the high side of the rectal dose. A dose of 1 mg/kg is an initial starting point increasing up to 2 mg/kg for dogs.

As a CRI, a dose of 0.1–0.5 mg/kg diluted in 5% D5W and administered at normal maintenance fluid rates per hour should be given. This dose can be increased as high as 2 mg/kg. Once the seizures have been stopped, it is recommended to gradually reduce the diazepam CRI through a 25% reduction every 2–4 h.

Diazepam is available in 2, 5, and 10 mg oral tablets. It is also available as an oral solution at a concentration of 1 mg/ml and a concentrated oral solution of 5 mg/ml. A rectal gel is available in 2.5, 10, and 20 mg sizes. The IV injectable form comes in a concentration of 5 mg/ml and can also be used for rectal and intranasal administration. If used rectally, the suppository form of diazepam should not be used. The *suppository* forms (rectal gel) do not provide the targeted serum concentration of diazepam and nordiazepam between 150 and 300 ng/ml associated with the treatment of seizures (Probst *et al*., 2013).

Monitoring

Therapeutic monitoring is not necessary unless being used as a chronic antiseizure drug in cats (which should be avoided). In these cases, serum levels of diazepam and its active metabolites can be evaluated (Boothe, 1998). If therapeutic monitoring of benzodiazepine levels is indicated, do not use serum separator tubes. Serum separator tubes result in a time- and drug-dependent decrease in concentration much like that of phenobarbital (Boothe *et al*., 1996).

GABAPENTIN (GBP) (GAB-AH-PEN-TIN)

Gabapentin was designed and synthesized as a structural lipophilic analogue to the inhibitory neurotransmitter gamma-amino-butyric-acid (GABA) which could cross the blood–brain barrier. It is available in generic oral forms. Its proprietary name is *Neurontin*®. It was approved for use in humans as an antiseizure medication in 1993. It is used primarily as an add-on medication in humans and veterinary patients, combined with more effective medications for the control of focal and generalized seizures. Although structurally similar to (GABA), it does not behave as a GABA agonist nor affect the binding, reuptake, or degradation of GABA. Its mechanism of action is for the most part unknown, however, *in vitro* studies have shown it binds with high affinity to the presynaptic α2δ-1 subunit of P, Q, and N-type voltage-gated calcium channels, resulting in their inactivation and subsequent inhibition of the release of excitatory neurotransmitters such as glutamate, substance P, and norepinephrine (Varadi, 2024).

Gabapentin has gained more popularity and use in veterinary medicine (as well as human medicine) for its ability to help control chronic pain, as a pre-emptive medication for postoperative surgical pain and as an anxietolytic (i.e., “chill pill”).

Mechanism of Action

Contrary to the premise behind its design, gabapentin does not appear to alter GABA concentrations in the nervous system, enhance the release, or promote the binding of GABA to its receptor. It does not interact with the $GABA_A$ or $GABA_B$ receptors (Jensen *et al*., 2002). It is not converted to a GABA agonist or GABA. Gabapentin does not alter or inhibit the GABA-metabolizing enzyme,

GABA transaminase (Gee *et al*., 1996). It may have a lesser effect on increasing the synthesis of GABA. Its primary effect is thought to be mediated through its binding to the α2δ-1 subunit of the voltage-gated calcium channel (P, Q, and N), which *was* thought to play a primary role in the control of neuronal excitability by inhibiting the release of excitatory neurotransmitters at the presynaptic nerve terminal (Gee *et al*., 1996). However, experimental evidence of this effect is not supportive as the gabapentinoids (gabapentin and pregabalin) do not appear to alter calcium channel currents and knockouts of the α2δ-1 subunit also do not affect calcium currents (Sills and Rogawski, 2020). The interaction of gabapentin with *N*-methyl-D-aspartate (NMDA) receptors, and their inhibition may also contribute to its anticonvulsant activity but it is not thought this is the primary mechanism of action (Chen *et al*., 2018).

Pharmacokinetics

Gabapentin has an oral bioavailability of approximately 80% in the dog with peak plasma levels being reached about 1 h after oral dosing (50 mg/kg) (Radulovic *et al*., 1995). At a dose of 10–20 mg/kg, peak plasma concentrations were reached at 1.5 and 1.75 h, respectively (KuKanich and Cohen, 2011). In the cat, the bioavailability is about 90% with peak plasma concentrations reached within 100 min of oral dosing at 10 mg/kg (Siao *et al*., 2010). The half-life in both dogs and cats is about 3 h (2–4 h). It reaches a steady-state concentration in about 1 day. Gabapentin is minimally protein bound and CNS concentrations are much less than serum. Contrary to humans, where no hepatic metabolism of gabapentin exists, in dogs, gabapentin is partially metabolized by the liver to *N*-methyl-gabapentin (30–40%), and the remainder is unmetabolized and excreted almost exclusively in the urine. The therapeutic range is 4–16 μg/ml (Bazil, 2002; Dewey, 2006).

Toxicity, Side Effects, and Interactions

Gabapentin is well tolerated in dogs and cats with typically only mild and reversible side effects of ataxia and sedation at high doses. Side effects typically either resolve spontaneously or with a reduction in gabapentin or adjunctive medications (i.e., phenobarbital or potassium bromide). Although partially metabolized by the liver, there are no increases in serum hepatic enzymes in dogs (Dewey, 2006). Antacids may reduce the absorption of gabapentin and are recommended to be given at least 2 h before or after gabapentin. Morphine and hydrocodone, when either is administered with gabapentin, may result in increased efficacy of gabapentin or increased side effects of gabapentin. Gabapentin may reduce the effectiveness of hydrocodone when given concurrently (Plumb, 2011). In people, mild dizziness, vomiting, and nausea have been reported (Boothe, 1998).

Indications for Use

Gabapentin should not be used as a first-line antiseizure medication unless all other choices have failed. It may be used as an add-on or adjunctive antiseizure medication; however, its use should be considered after more clinically efficacious combinations have been used. When combined with phenobarbital or potassium bromide, gabapentin improves seizure control in dogs (Govendir *et al*., 2005). Due to the limited data regarding cats and newer antiseizure medications, gabapentin may be considered a second-line antiseizure medication for cats.

Dose

In humans, a dose of 1800 mg of gabapentin per day has an analgesic effect. Serum concentrations greater than 2 μg/ml are associated with a reduction in the frequency of epileptic seizures in humans. Based on those results, an extrapolated dose of 3 mg/kg administered orally every 6 h would achieve a serum concentration of 2 μg/ml in cats (Siao *et al*., 2010). In dogs, a dose of 10–20 mg/kg every 8 h would maintain at least 2 μg/ml plasma concentration (KuKanich and Cohen, 2011). For cats, most clinicians will begin with a dose of 10 mg/kg every 8 h and titrate to effect or side effect.

In dogs, a similar approach is taken where the dose varies from 10 to 60 mg/kg every 8–12 h. In a study looking at the efficacy of gabapentin in dogs with the genetic (idiopathic) form of epilepsy, when combined with either phenobarbital or potassium bromide at serum concentrations that did not result in any side effects, the addition of gabapentin at 10 mg/kg every 8 h resulted in a reduction of seizure frequency of at least 50% in 6 out of 11 dogs (Platt *et al.*, 2006). In another similar study in dogs, some patients stopped having epileptic seizures completely, and others had an increase in the interictal period along with a reduction in the time to recover from epileptic seizures (Govendir *et al.*, 2005). It is recommended to give the medication at least 7–10 days to evaluate its effect before making dose adjustments. Gabapentin is available in oral capsules and tablets at 100, 300, 400, 600, and 800 mg sizes. The commercially available oral solution of gabapentin at a concentration of 50 mg/ml contains **xylitol**, and its use *should be avoided* in dogs and cats. An extended-release formulation is available; however, no pharmacokinetic studies have been performed in dogs or cats.

Monitoring

It appears to be so safe in dogs, cats, and humans that therapeutic monitoring is not necessary. Rather, the medication is titrated to effect or side effect. Monitoring is primarily based on clinical and home observation of the patient for efficacy and the development of adverse side effects.

IMEPITOIN

Imepitoin is approved in the European Union (EU), the UK, Australia, New Zealand, and Japan for the treatment of epileptic seizures in dogs and is marketed under the trade name *Pexion*™. In the EU, the UK, and the USA, it is approved for use in dogs to treat noise aversion (Engel *et al.*, 2019; Perdew *et al.*, 2021; Muñoz Amezcua *et al.*, 2024). Imepitoin is a low-affinity, partial agonist for the $GABA_A$ receptor, binding to the same location as the benzodiazepines. Additionally, it blocks voltage-activated calcium channels in a dose-dependent manner (Rieck *et al.*, 2006). The development of imepitoin for the treatment of human epilepsy was suspended due to metabolic differences between human smokers and nonsmokers (Löscher *et al.*, 2013). Although there are contrasting studies evaluating its effectiveness as an anti-epileptic it is considered a *first-tier* choice for the treatment of epilepsy (level IA evidence) and as an add-on medication for epilepsy (level IIIC) and generally regarded to be as effective as phenobarbital and significantly safer (Charalambous *et al.*, 2014; Podell *et al.*, 2016).

As far as efficacy, there is near unanimous consent in the literature as to imepitoin's ability to suppress seizure activity. In a PTZ model of epilepsy in dogs, imepitoin was found to significantly increase the PTZ seizure threshold when dogs were treated at a dose of 5 mg/kg BID for 5 weeks (Löscher *et al.*, 2004). In an observational, prospective, cohort study comparing imepitoin to phenobarbital for the treatment of generalized, tonic–clonic seizures in dogs with idiopathic epilepsy, dogs treated with imepitoin were more likely to develop cluster seizures long-term, discontinue the medication due to unacceptable side effects (aggression) and the overall reduction in seizure frequency was less than phenobarbital (Stabile *et al.*, 2019). In contrast, another study (blinded, parallel-group design) found imepitoin to be comparable to phenobarbital as far as seizure control and with fewer side effects (Tipold *et al.*, 2015). A long-term study of the efficacy of imepitoin in dogs found it to significantly (54%) reduce seizure frequency with only mild and transient side effects (Gallucci *et al.*, 2017). This study also found dogs >3 years old at the start of therapy, were more likely to be responders. In another study, Imepitoin was as effective as phenobarbital or primidone in reducing seizures in newly diagnosed epileptics with minimal side effects at a dose range of 20 mg/kg or less every 12 h (Rieck *et al.*, 2006). In dogs treated with imepitoin in an experimental model of epilepsy (40 mg/kg BID), tolerance did not develop, as is often the case of benzodiazepine receptor agonists (Löscher *et al.*, 2004). In dogs where phenobarbital or potassium bromide were used as add-on medications to patients who

were at their max imepitoin dosage and had their seizures well controlled, withdrawal of imepitoin over a 3-month time, did not lead to an increase in seizure frequency (i.e., no development of withdrawal seizures) (Stee *et al.*, 2017). In an online survey of owners of dogs with idiopathic epilepsy, who were being treated with imepitoin for fear and anxiety-related behavior (dose range 10–35.7 mg/kg BID), there was a median reduction of seizure frequency by 45% (Packer *et al.*, 2017). Side effects only affected a few patients, and were mild and short-lived, consisting mainly of polyphagia and polydipsia. In a long-term, randomized, controlled clinical trial of imepitoin, 37.5–46.8% of dogs achieved seizure freedom when treated with a dose of 30 mg/kg BID (% represents different phases of the long-term study) (Rundfeldt *et al.*, 2015). In summary, dogs do not develop tolerance to imepitoin or withdrawal seizures. It is safe and six out of seven studies (of various forms) found it to be efficacious.

A tolerability study and single-arm, open-label, uncontrolled, clinical trial of imepitoin found it to be well tolerated in a small number of *cats* up to 80 mg/kg BID for 30 days with only mild, reversible side effects of emesis (Engel *et al.*, 2017). Out of the eight cats involved in the efficacy trial, 50% achieved seizure freedom during the 8 weeks of the trial.

Imepitoin is available in 100 and 400 mg tablets. As of the date of this publication, although approved by the FDA in the USA for canine noise phobia, it is not commercially available. The author has had success in having it shipped from Australia.

Mechanism of Action

Imepitoin is a low-affinity, partial agonist at the benzodiazepine binding site of the $GABA_A$ receptor. Because it is a partial agonist, it produces less adverse effects and a lack of tolerance or dependence (not that we need to worry about that in veterinary patients) compared to full agonists such as benzodiazepines (Löscher *et al.*, 2013). Imepitoin also weakly inhibits neuronal calcium channels in a dose-dependent manner, an effect that may contribute to its antiseizure effects (Rieck *et al.*, 2006).

Pharmacokinetics

Imepitoin is well absorbed after oral administration reaching a C_{max} of 14.9–17.2 µg/ml after 2–3 h in dogs (dose of 30 mg/kg) (Rundfeldt *et al.*, 2014). Dosing with food does not alter its absorption and the absorption time correlated well with the average small intestine transit time of dogs. It is recommended the dosing correlation with or without food be kept consistent to achieve a consistent trough plasma level. The plasma protein binding was only 55% and there were no effects due to test subject sex or metabolic tolerance of the test dogs. Imepitoin is primarily excreted via the feces with no induction of cytochrome P450 family of liver enzymes (*in vitro*). It was concluded protein binding and metabolism resultant, drug–drug interactions were unlikely to occur.

Toxicity, Side Effects, and Interactions

Imepitoin is considered very safe with side effects like those of benzodiazepines, even though structurally, it is more like phenytoin (an imidazolone). Common, reversible side effects include lethargy, ataxia, increased appetite, polydipsia, vomiting, and hyperactivity. It is also known to lead to disinhibition of fear-based behavior, which could lead to aggression. There is no data on its disposition in animals less than 5 months old or weighing less than 2 kg.

There is a single case report of a cutaneous adverse drug reaction associated with long-term use of imepitoin (Royaux *et al.*, 2016). The clinical signs developed 3 days after a dose increase from 20 to 30 mg/kg BID. A histologically confirmed, lupoid drug reaction, consisting of erythema and exfoliation at the mucocutaneous junctions, ears, axillae, and abdomen was identified. Clinical signs resolved within 4 weeks after cessation of imepitoin and low-dose prednisone therapy.



FIGURE 7.3 (a) A 5-year-old, male, neutered lab mix who is a drug-resistant idiopathic epileptic (Tier II diagnosis) developed bilateral prolapse of the third eyelid after increasing his dose of imepitoin from 10 mg/kg every 12 hours to 15 mg/kg every 12 hours. The dog's owner said he could not open his eyes and suspected he may be having difficulty with vision even at the 10 mg/kg dose. (b) The same dog ten days after dose reduction. When the dose was lowered (and eventually discontinued) the clinical signs resolved. The patient was concurrently being treated with phenobarbital, levetiracetam and zonisamide. Prolapse of the third eyelid and eyelid closure is a rarely reported (<1/10,000) side effect of imepitoin and in this dog was reversible.

A very rare (<1 out of 10,000) side effect of elevated nictitating membrane is reported by the manufacturer and in clinical studies along with possible eyelid closure at very high doses (30, 50, or 150 mg/kg BID) (Tipold *et al.*, 2015). Although the author has limited experience with the medication in the USA, it was observed to occur in one patient bilaterally along with eyelid closure when the dose was increased from 10 to 15 mg/kg BID. The dog was unable to open its eyes and even at the 10 mg/kg BID dose, and his owners thought his vision was altered. The side effect resolved once the dose was reduced back to 10 mg/kg BID (Figure 7.3).

Imepitoin does not alter serum concentrations of total thyroxine, triiodothyronine, free thyroxine, thyroglobulin antibodies, thyroid stimulating hormone, cholesterol, or triglycerides—in healthy beagle dogs (Bossens *et al.*, 2016).

Imepitoin should be used with caution in patients who may have hepatic impairment or cardiovascular or renal disease. Withdrawal should be performed slowly over several months.

Indications for Use

While imepitoin is only approved in the USA to treat fear-based anxiety, it may be used in an extra-label manner to treat canine and feline epilepsy. It should be considered as a first-line treatment for treating epilepsy in dogs and cats. Although there are no studies evaluating its efficacy and safety as an add-on, it would be reasonable, given its efficacy and safety profile in other studies to cautiously use it as an add-on anticonvulsant as well.

Imepitoin should not be used rectally in dogs (Martlé *et al.*, 2020).

Dose

For dogs and cats, start with a dose of 10 mg/kg BID and gradually increase to 30 mg/kg BID if needed. Give the medication at least 10 days between dose increases to see an effective reduction in seizure frequency.

Monitoring

A baseline minimal database consisting of vital signs, CBC, biochemical profile, and urinalysis is recommended. If used long-term, consider repeating every 6 months. Monitor closely for effectiveness and adverse effects. There is no therapeutic drug monitoring necessary.

LEVETIRACETAM (LEV) (LEV-ET-EAR-AS-EHH-TAM)

Levetiracetam was discovered in 1974 while being investigated as a possible anti-narcoleptic drug, which did not quite pan out. It belonged to a class of drugs that were being investigated as possible "cognitive enhancers." Through a random screening, it was discovered to have anti-epileptic properties. Levetiracetam was approved for use to treat epileptic seizures in the USA in 1999 and is marketed under the proprietary name of *Keppra*®. It is also available as a generic and an extended-release form. Levetiracetam is available as a parenteral form for IV injection (which may also be used for rectal administration) (Peters *et al*., 2014). A levetiracetam suspension made by mixing pure powdered drug with sterile saline at a concentration of 200 mg/ml and administered rectally has also been shown to be effective in treating status epilepticus and cluster seizures (Cagnotti *et al*., 2018, 2019). Levetiracetam is an analogue of the nootropic (cognition enhancer) piracetam. Piracetam is used in the treatment of Alzheimer's disease and may have some antiseizure effects (Engel, 2013). Levetiracetam is becoming more popular among veterinary clinicians as a first-line therapy for a broad spectrum of seizure types in dogs, although still considered a Tier III anticonvulsant drug for dogs (Podell *et al*., 2016 and Charalambous *et al*., 2014, 2018). Its use in cats is also considered third tier, due to the inconvenience of every 8-h dosing, however, early studies looking at the use of once-a-day dosing with the extended-release (XR) form for cats, are promising (Heller *et al*., 2018). It is considered very safe but is less effective than typical first-line medications, such as phenobarbital, imepitoin, and potassium bromide (Charalambous *et al*., 2014, 2018; Podell *et al*., 2016). Compared to phenobarbital and zonisamide for the treatment of idiopathic epilepsy, as a monotherapy, levetiracetam had the lowest treatment failure rate, although phenobarbital had a greater reported seizure suppression rate (Gristina *et al*., 2023). Due to its short half-life in dogs, in the original form, it must be dosed every 8 h, making compliance difficult. It is available in an extended-release preparation; however, the patient must be at least 15 kg in order to take the smallest available pill at the recommended dose (pills cannot be cut or you would lose the "extended"-release feature). Concerns have been raised about pills showing up in the feces of dogs when dosed in the extended-release form. These "ghost" pills are the remnants of the outer casing of the pill and are indigestible. Ghost pills were not noted in the feces of cats in a study looking at once-a-day dosing of the XR form of the drug (Heller *et al*., 2018).

Mechanism of Action

Levetiracetam and its analogue brivaracetam were licensed with no clear indication of their mechanism of action. Levetiracetam inhibits hypersynchronization of epileptiform neuronal burst firing by affecting neurotransmitter release while not reducing neuronal excitability (hence the lack of common antiseizure medication side effects) (Margineanu and Klitgaard, 2000). The mechanism of action is unknown; however, its primary target is the *synaptic vesicle protein 2a* (*SV2a*), which is involved in membrane transport functions, and interestingly is also the binding target for *botulinum* neurotoxin, although, at different sites on the protein (Yamagata *et al*., 2024). Brivaracetam is more potent and specific compared to levetiracetam (Gillard *et al*., 2011). The exact physiological role of the SV2a protein is still unclear, however, since the protein is necessary for the release of neurotransmitters contained within vesicles (or co-factors necessary for an action potential to be generated), it is hypothesized that inhibition of vesicle release plays an important role in its mechanism of action (Lynch *et al*., 2004). In experimental models of epileptic seizures, levetiracetam has a broad-spectrum ability to suppress many different epileptogenic initiators such as amygdala-kindled seizures and models of mesial temporal lobe epilepsy induced by pilocarpine

and kainic acid. Levetiracetam will suppress the spread of an epileptic seizure at the point of epileptogenesis (Löscher *et al*., 2000). It binds to an allosteric site of the GABA/glycine receptor and modulates its function by inhibiting other allosteric inhibitors (disinhibition) (Rigo *et al*., 2002). Levetiracetam does not affect sodium or T-type calcium channels but *does* partially inhibit the N-type, voltage-gated calcium channel (Lukyanetz *et al*., 2002). Levetiracetam also specifically affects calcium signaling in the hippocampus via inhibition of ryanodine receptor and inositol 1,4,5-triphosphate mediated calcium release (Nagarkatti *et al*., 2008). Both mechanisms are factors necessary for the release of intracellular calcium in the hippocampus, which is thought to play an important role in epileptogenesis.

Pharmacokinetics

Levetiracetam is well absorbed following oral administration (~20 mg/kg every 8 h) and reaches peak concentration in plasma within 45 min in dogs. When a commercially available oral suspension (20 mg/kg) was given to cats, serum therapeutic concentrations were achieved within 10 min of administration and maintained in the range for at least 9 h in 7/10 cats (Carnes *et al*., 2011). The half-life is calculated at between 3 and 4 h and stable after multiple days of administration in both dogs and cats (Benedetti *et al*., 2004; Bailey *et al*., 2008; Moore *et al*., 2010). After a single IV dose of 60 mg/kg administered over 2 min in dogs, the drug was well tolerated and achieved serum therapeutic concentrations (recognized for humans) for at least 8 h (Dewey *et al*., 2008). In cats, an IV dose (20 mg/kg diluted in 5 ml of 0.9% sodium chloride and given over 5 min in the jugular vein) achieved serum therapeutic concentrations within 10 min and stayed within the therapeutic range for 9 h in 7/10 cats (Carnes *et al*., 2011). When administered rectally to dogs at a dose of 40 mg/kg, concentrations of levetiracetam, within the therapeutic range (5–40 μg/ml) are attained within 10 min (Peters *et al*., 2014). A rectal suspension, administered to dogs also achieved a therapeutic range (extrapolated from humans), however, minimum therapeutic concentration was not achieved until 30 min after rectal dosing (Cagnotti *et al*. 2018). It is important to note in the last study that the first time point to measure levetiracetam in the blood was 30 min after dosing. These results show levetiracetam can be effective in not only stopping but also suppressing episodes of status epilepticus and cluster seizures when used rectally. The pharmacokinetics of levetiracetam are independent of the chronicity of dosing and the route of dosing. In dogs and cats given an oral dose of 20 mg/kg every 8 h, serum concentrations will fall within the therapeutic range established for humans (Bailey *et al*., 2008; Moore *et al*., 2010). After a single oral dose of the drug, serum concentrations are less than the therapeutic range within 8 h, explaining the need for every 8 h dosing consistent with the short half-life in dogs. In the study by Moore *et al*., an unexpected diurnal difference in peak and trough concentrations was observed with morning trough concentrations being significantly higher compared to afternoon trough concentrations. This is hypothesized to be due to diurnal variations in glomerular filtration rate and may be an underlying reason for breakthrough seizures.

When given IM at 20 mg/kg to dogs, peak serum concentrations (with the proposed therapeutic range) were achieved within 40 min and the bioavailability was calculated at 100% (Patterson *et al*., 2008). Early investigation into the use of intranasal levetiracetam in a rat model of epilepsy suggests it would be effective, however, if extrapolated to a canine or feline, the volume necessary to give intranasally would be large (12 ml of the 100 mg/ml injectable preparation for a 20 kg dog at a 60 mg/kg dose) (Zhao *et al*., 2023). Concern for aspiration would warrant using an alternative such as midazolam (0.8 ml for a 20 kg dog if using the 5 mg/ml preparation) or lorazepam (1.0 ml for a 20 kg dog if using the 4 mg/ml preparation). Levetiracetam reaches a steady state within 48–72 h (dogs).

Levetiracetam appears to undergo very minimal hepatic metabolism and is excreted 50% unchanged (~90% total clearance) primarily in the urine of dogs (Isoherranen *et al*., 2001; Benedetti *et al*., 2004). It undergoes extensive metabolism via hydrolysis and oxidation to an acid derivative via an enzymatic process having wide tissue distribution. However, this may be even

more extensive within the liver of the dog and impacted through the induction of cytochrome P450 inducers such as phenobarbital (Benedetti *et al*., 2004; Moore *et al*., 2010, 2011, Muñana *et al*., 2015, 2018). Adjustments to the dose of levetiracetam (both regular and extended release) may need to be made if used concurrently with phenobarbital.

Because of its short half-life in dogs, every 8 h dosing is needed to maintain serum therapeutic concentrations of levetiracetam. When dogs were dosed with the extended-release form (30 mg/kg every 12 h) of the medication approved for humans (*Keppra XR®*), serum levetiracetam reached therapeutic levels by 200 min and stayed within the therapeutic range for an average of ~20 h (Beasley and Boothe, 2012, 2015). The bioavailability of the extended-release form and the time to peak serum concentration was significantly higher if the medication was given *with* food but did not affect the half-life of the drug. This suggests every 12–24 h dosing would be possible in dogs at a dose of 30 mg/kg. However, because commercially available extended-release pill sizes are no smaller than 500 mg, the extended-release form is only useful for those animals weighing more than 15 kg, although a single day dose of the XR form may be useful for cats (Heller *et al.,* 2018).

Levetiracetam, compounded as a transdermal preparation (400 mg/ml) and applied to the pinna of cats at a dose of 60 mg/kg, will achieve therapeutic concentrations (extrapolated from human values), although the range of C_{max} varied significantly from the small number of healthy cats in the study (Smith *et al*., 2019). This gives great options for owners of cats who have seizures are difficult to pill and may not tolerate phenobarbital.

Another option for cats may be to use a single 500 mg extended-release capsule given once a day (Heller *et al*., 2018). In this study, the median dose was ~95 mg/kg and the mean C_{max} was 102.5 µg/ml (reference range 5–45 µg/ml). Cats were dosed continuously for 11 days and experienced only mild, reversible side effects such as ataxia, sedation, and vomiting or regurgitation in small numbers. Side effects resolved without a dose adjustment or any additional treatment. This would certainly be an option for a single-dose trial in a cat with seizures. In this study, it was noted all cats consumed the pills whole. The mean T_{max} was 6 h. I would be fairly concerned about the possibility of a cat biting the capsule and negating the "extended release" feature of the capsule. This would effectively give the cat a 500 mg immediate dose. Owners should be warned of this possibility if this means of delivery is chosen.

Toxicity, Side Effects, and Interactions

Levetiracetam appears to be very safe with minimal (type A—dose dependent and predictable) drug interactions, side effects, and toxicity in dogs and cats. In dogs, the most common side effect reported is vomiting and sedation. Other reported side effects such as ataxia, hyperactivity, anorexia, polyphagia, and polydipsia are considered reversible (Packer *et al*., 2015; Charalambous *et al*., 2016). In cats, it is hypersalivation, sedation, and anorexia (Charalambous *et al*., 2018). In humans, it has been associated with psychotic disturbances and *toxic epidermal necrolysis* (Stevens–Johnson syndrome) (Gómez-Zorrilla *et al*., 2012). In dogs receiving levetiracetam in conjunction with phenobarbital, the elimination half-life of levetiracetam was increased by 50%, and serum concentration was significantly reduced compared to those receiving levetiracetam alone. Additionally, clearance of levetiracetam was dramatically increased, which suggests dose alterations should be considered when the two medications are used concurrently in dogs (Moore *et al*., 2010). Similar effects are noted when looking at the interactions of phenobarbital with extended-release levetiracetam, with a significant reduction in the maximum concentration (C_{max}) of serum levetiracetam in those dogs concurrently receiving phenobarbital (Muñana *et al*., 2018). In patients with impaired renal function, dose adjustments may need to be made and caretakers should be cautioned to use close observation for side effects (primarily sedation and ataxia). Levetiracetam is known to cause both positive and negative or intensification of pre-existing behavioral changes when given to dogs and pet owners should be cautioned about this potential side effect (Erath *et al*., 2020). Positive behavior changes may include calmer behavior, increased activity, and increased energy, whereas negative behaviors such as aggres-

siveness and hyperactivity were noted, however, the incidence of the negative behavior changes is similar to other anticonvulsant drugs (Heynold *et al*., 1997; Chang *et al*., 2006; Boothe *et al*., 2012; Fredsø *et al*., 2016). No tissue damage is reported to occur when levetiracetam is given outside of a blood vessel (extravasation) (Patterson *et al*., 2008).

When used intravenously in humans, it is recommended levetiracetam be diluted in either 5% dextrose, lactated ringer's or 0.9% sodium chloride to a maximum concentration of 15 mg/ml (~6 ml diluent for every 1 ml of concentrated solution) and injected slowly over several minutes. However, rapid IV infusion of levetiracetam in humans is considered safe and tolerable (Haller *et al*., 2021; Jense *et al*., 2022). In a randomized, double-masked, placebo-controlled trial for the treatment of status epilepticus (or acute repetitive seizures), IV administration of undiluted levetiracetam, given over 5 min was well tolerated and more effective than placebo or diazepam alone (Hardy *et al*., 2012). Rapid injection of undiluted levetiracetam resulted in the death of a Chihuahua dog (Biddick *et al*., 2018). It would be prudent to use caution in administering undiluted levetiracetam rapidly in small dogs, although anaphylaxis in any patient is a possible consequence.

Indications for Use

In dogs and cats, levetiracetam may be used as a first-line prophylactic antiseizure medication and an add-on medication for pharmacoresistant patients with a wide variety of seizure types (Platt *et al*., 2007; Bailey *et al*., 2008; Volk *et al*., 2008, Lowrie *et al*., 2017, Linder *et al*., 2024). Levetiracetam is not as effective in controlling seizures as phenobarbital, imepitoin, or potassium bromide in dogs or phenobarbital and imepitoin in cats but its safety margin and reduced necessity of monitoring compared to phenobarbital make it a common choice as a first-line therapy for both species (Charalambous *et al*., 2014; Podell *et al*., 2016). However, levetiracetam was more effective in controlling *myoclonic seizures* in cats with feline audiogenic reflex seizures with fewer side effects than phenobarbital (Lowrie *et al*., 2017). Most neurologists and emergency/critical care specialists will choose *phenobarbital* over *levetiracetam* but as discussed in Chapter 6, many factors go into any anticonvulsant medication choice (Meland *et al*., 2019). Its successful short-term use in treating reactive seizures at an initial dose of 60 mg/kg IV followed by 20 mg/kg TID in dogs has been reported (Stabile and De Risio, 2021). Levetiracetam (~27 mg/kg TID) has been successfully used to treat paroxysmal exertional dyskinesia in a Welsh Terrier (Green and Olby, 2021). Levetiracetam has been shown to decrease the incidence of postoperative epileptic seizures after the treatment of congenital portosystemic shunt in dogs (Fryer *et al*., 2011). However, several other studies have shown no protective effect of levetiracetam when used to help manage post-attenuation seizures in dogs who underwent portosystemic shunt surgery (Brunson *et al*., 2016; Strickland *et al*., 2018; Mullins *et al*., 2019). Still, because of its affordability and safety, it has been recommended to pre-emptively treat patients (dogs and cats) undergoing surgical treatment for congenital portosystemic shunts, with levetiracetam (Mastrocco *et al*., 2024). Because it is excreted almost exclusively by the kidneys, dose adjustments may need to be considered in renal-compromised patients, as well as monitoring for side effects (Gim *et al*., 2021). At a dose of 20 mg/kg every 8 h in dogs, epileptic seizure frequency was reduced by at least 50% in 9 out of 14 dogs (Volk *et al*., 2008). In another open-label observational study, there was a 54% reduction in the number of seizures in 15 dogs being dosed between 7 and 24 mg/kg every 8 h (Steinberg and Faissler, 2004). In a retrospective case series, levetiracetam was found to be effective in treating seizures and cluster seizures associated with structural brain disease in dogs (Kelly *et al*., 2017). Contrary to the above-mentioned reports, in a randomized, placebo-controlled, crossover study design, the ability of levetiracetam to reduce seizure frequency in refractory epileptic dogs at a dose of 20 mg/kg every 8 h was no greater than placebo (Muñana *et al*., 2012). In another study, levetiracetam at a max dose of ~22.5 mg/kg TID was found to be not effective as a monotherapy in dogs (Fredsø *et al*., 2016). It is important to note in both previously mentioned studies, levetiracetam was dosed at what most clinicians would consider a *starting dose* of 20 mg/kg TID or less. Many patients will need their dose titrated to effect or failure. Failure would be considered and increase to double the starting dose or ~40 mg/kg TID for the

intermediate release form and 60 mg/kg BID (starting dose of 30 mg/kg BID) for the extended-release form, with no beneficial reduction in seizure frequency or intensity. In a retrospective evaluation of dogs treated chronically at ~20 mg/kg TID, levetiracetam resulted in 69% of the dogs having a 50% or greater reduction of seizure frequency (Packer *et al*., 2015). In another study, dogs with *drug-resistant epilepsy* were treated with either add-on of *pregabalin* or an increase in the existing add-on drug, *levetiracetam*. Both medications were found to be minimally effective (3X extension of the longest baseline interseizure interval) (Kriechbaumer *et al*., 2022). However, it is important to note, in this study, 2 of the 14 dogs (2/14; 14.3%) who received pregabalin and 1 of the 12 dogs (1/12; 8.3%) did achieve early treatment success. These results emphasize that when we treat pharmacoresistant epilepsy, our success rates will naturally be low (because they are ...pharmacoresistant) and despite the poor *group* results, a few of the dogs did benefit (at least short term). We treat the patient, not the group. The literature is full of conflicting results which only reinforces the notion that picking an anticonvulsant is like picking an antibiotic—what may work for one etiology may not work for another.

When given as an IV dose at either 30 or 60 mg/kg to treat SE or acute repetitive seizures, dogs treated with levetiracetam were better controlled than those receiving placebo (Hardy *et al*., 2012). Furthermore, IV levetiracetam was well tolerated with minimal side effects.

Levetiracetam was shown to be effective in 7 of 10 cats in reducing the total number of epileptic seizures when dosed at 20 mg/kg every 8 h (Bailey *et al*., 2008). Levetiracetam may be used through IV, IM, rectal, and oral routes.

Dose

The recommended dose for dogs and cats is 20 mg/kg every 8 h (40 mg/kg if given rectally). The extended-release form may be dosed at 30 mg/kg every 12 h in dogs greater than 15 kg (due to availability of pill size). The extended-release preparation may also be trialed in cats at a single day dosing (warn owners of the potential effects of a cat biting into the extended-release capsule). The dose can be safely increased gradually to effect, side effect, or twice the starting dose, whereby more will likely not confer any additional benefit, and the possibility of adverse side effects is increased. Due to its wide safety margin, the dose can be increased by ~25% every 1–2 weeks until a desired effect is achieved, sedation or ataxia is encountered, or double the starting dose is attained, at which point an alternative drug should be considered.

Levetiracetam at a dose of 20 mg/kg every 8 h, beginning 24 h prior to surgery, was shown to be helpful at reducing the incidence of postoperative epileptic seizures in dogs being treated for congenital portosystemic shunt (Fryer *et al*., 2011). However, several other studies did not show any beneficial effect of the use of levetiracetam to control postoperative seizures in dogs undergoing shunt surgery (Brunson *et al*., 2016, Strickland *et al*., 2018 and Mullins *et al*., 2019). It is interesting to note that all studies used what would be considered a low starting dose (20 mg/kg TID), although some also pretreated with a 60 mg/kg IV dose.

Monitoring

The effective therapeutic range in humans has been established at 12–46 µg/ml (Engel, 2013). In dogs and cats, a range of 5–45 µg/ml has been used. Due to the safety profile of levetiracetam, therapeutic monitoring is mainly recommended to monitor levels for dose adjustments. Patients should be monitored by observation for both effects of the medication and the development of side effects.

LORAZEPAM (LOR) (LOR-AYZ-EH-PAM)

Lorazepam is a longer-acting benzodiazepine compared to diazepam and is available in oral and injectable forms. In the USA, it is marketed under the trade name *Ativan*® and is also available in generic forms. It is primarily used in treating SE and hospitalized patients having breakthrough

seizures, and may also be dispensed for home use (Figure 6.15). Lorazepam has become the first-line treatment of SE in human patients with epileptic seizures (Engel, 2013). However, in a randomized clinical trial of its use compared to diazepam for the treatment of SE in pediatric human patients, there was no difference between the two medications, other than the lorazepam patients were more likely to be sedated (Chamberlain *et al*., 2014). Lorazepam is gaining more widespread use in veterinary medicine emergency rooms as an alternative to diazepam for the treatment of SE and breakthrough seizures due to its ease of use and multiple dosing options (along with midazolam). The binding affinity of the benzodiazepines for the $GABA_A$ receptor has been studied in humans but not dogs and cats. Lorazepam binds to the $GABA_A$ receptor with an affinity 2–5 times greater than midazolam and 10 times greater than diazepam (in rats) (Reves *et al*., 1985 and Arendt *et al*., 1987) (Figure 7.1).

Mechanism of Action

The benzodiazepines are suspected to exert their primary antiseizure effect through interaction with the $GABA_A$–chloride ionophore membrane complex. Lorazepam and other benzodiazepines directly bind to the $GABA_A$ receptor, enhance the affinity of GABA for its binding site, and potentiate the flow of chloride ions across the ion channel, thereby hyperpolarizing the plasma membrane and lowering the seizure threshold. However, the interaction of benzodiazepines with the $GABA_A$ receptor is likely not the only mechanism of action for their antiseizure effects (Engel, 2013). Multiple, high-affinity benzodiazepine binding sites are recognized in several tissues (MacDonald, 2002). Compared to diazepam, lorazepam possesses increased binding to the high-affinity benzodiazepine receptors and is more effective at controlling SE (Leppik *et al*., 1983). In addition, concentrations of lorazepam in the CNS remain elevated even after serum concentrations have started to decline (Walton and Treiman, 1990). Serum concentrations necessary to stop SE are reported to be 30 ng/ml in adult humans (Podell *et al*., 1998b). At high intravenous doses (those unattainable by oral administration), there is suppression of repetitive firing in partially depolarized spinal cord neurons. This is due to a dose and use-dependent reduction in sodium conductance. These effects may be observed when benzodiazepines are given intravenously (Frey, 1989). Benzodiazepines act to block arousal in the CNS and centrally depress spinal reflexes (Boothe, 1998).

Pharmacokinetics

Following IV administration at a dose of 0.2 mg/kg, lorazepam peak levels reached 165 ng/ml and were maintained at greater than 30 ng/ml (the level recognized in humans to stop an episode of SE) for up to 60 min (Mariani *et al*., 2003). In another study, at the same dose given IV, peak plasma concentrations were reached within 5 min after the IV dose and remained above 190 ng/ml for 20 min in two dogs and above 30 ng/ml in all dogs for up to 90 min (Podell *et al*., 1998b). Following *intranasal* administration, peak levels of 106 ng/ml were achieved and remained above 30 ng/ml in 3 of 6 dogs (Mariani *et al*., 2003). After intranasal administration, antiepileptic levels were reached in 3–9 min. Lorazepam is absorbed 3× faster through nasal administration compared to oral (when the injectable was given IN or PO) (Mariani *et al*., 2003).

In dogs, approximately 80% of lorazepam is metabolized by the liver through glucuronidation, and the liver acts as a reservoir for continued distribution (Gerkens *et al*., 1981). The liver is also responsible for the majority of lorazepam metabolism in the cat (Ruelius, 1978). Contrary to other benzodiazepines, the major metabolite of lorazepam, *lorazepam glucuronide*, does not possess any antiseizure activity (Podell *et al*., 1998b). The half-life of lorazepam is approximately 1 h in the dog; however, brain concentrations of the drug persist longer than plasma concentration (Plumb, 2011). An extensive amount of lorazepam metabolism occurs outside of the dog liver, which makes it a potentially safer drug to use in liver-compromised patients (Gerkens *et al*., 1981).

Most of the excretion is through the urine in dogs, while in cats, approximately 50% of the metabolite is excreted through the urine and 50% through the feces (Schillings *et al.*, 1975). When given rectally in the dog, at doses up to 1 mg/kg, plasma concentration was less than 5 ng/ml (the lower limit of detection). However, following hydrolysis of lorazepam, plasma concentrations up to 1000 ng/ml were achieved at all doses (0.5, 0.75, and 1 mg/kg), displaying a profound first-pass effect with rectal administration, making this route of administration *unacceptable* for dogs (Podell *et al.*, 1998b). In humans, lorazepam is absorbed faster when given sublingually compared to oral absorption. Lorazepam is rapidly and completely absorbed when given by IM injection in humans. Its pharmacokinetics via oral, sublingual, or IM routes have not been evaluated in dogs or cats.

Toxicity, Side Effects, and Interactions

Lorazepam has been shown to be one of the safest drugs used to treat SE in humans. Veterinary experience parallels human medicine (Podell *et al.*, 1998b). Like other benzodiazepines, the primary side effects of lorazepam are sedation and ataxia. However, lorazepam shows less respiratory depression than diazepam when used IV to control SE in children (Appleton *et al.*, 1995). Tolerance to the medication usually develops in days and potentially hours making additional treatment options necessary if breakthrough seizures occur and multiple doses are given even over a short period of time. For this reason, following the initial cessation of seizures, prophylactic medication (e.g., imepitoin, phenobarbital, levetiracetam, etc.) should be initiated. Withdrawal signs are not a concern, as the medication is not used chronically to control epileptic seizures.

Lorazepam may also increase the effects of other potentially sedating drugs, especially barbiturates, antihistamines, tricyclic antidepressants, phenothiazines, and analgesics. Concurrent use of theophylline may reduce the effects of lorazepam.

As a significant amount of lorazepam metabolism occurs outside of the liver in dogs, it may be one of the safer benzodiazepines to use in patients with compromised liver function; however, the initial dose given should be titrated to effect (start low and go slow) (Gerkens *et al.*, 1981).

Lorazepam should not be given through the intra-arterial route as it may cause arterial vasospasm and subsequent necrosis (Plumb, 2011).

Indications for Use

Lorazepam is used to treat SE and breakthrough seizures in a hospital setting. Additionally, it may be used at home via the *intranasal* route to stop an epileptic seizure event. Lorazepam is not stable once diluted and stored, for more than 2 days (Colsoul *et al.*, 2020). However, the *undiluted injectable* form of lorazepam, stored in a glass vial (syringe in the study) is stable for up to 150 days at room temperature, and up to 210 days when kept refrigerated, which makes it an excellent choice for home dispensing (Gottwald *et al.*, 1999). Lorazepam does not achieve effective levels when given rectally (as opposed to humans). Lorazepam may have antiseizure activity when given sublingually and potentially may avoid some of the rapid first-pass metabolism. Lorazepam may be given by IM injection for the control of epileptic seizures and SE if venous access is not available, although IV and nasal routes are preferred.

Dose

For dogs, a dose of 0.2 mg/kg is given IV once for SE. If the patient is still having an epileptic seizure after 5 min, the dose may be repeated. A dose of 0.1 mg/kg may be used in cats, although no published data is available regarding its efficacy.

A dose of 0.2 mg/kg may also be used IM or IN in dogs and cats. A dose of 0.2 mg/kg (of the injectable form) may be given sublingually; although this route has not been effectively evaluated in dogs or cats, however, it is effective in humans. The sublingual route should be avoided in

patients actively having a seizure, as hypersalivation and foaming at the mouth will likely result in little drug being absorbed.

Lorazepam is available in an injectable form at the concentrations of 2 and 4 mg/ml. It is also available as an oral solution at a concentration of 2 mg/ml. Lorazepam is available in oral tablets at 0.5, 1, and 2 mg tablet strengths. The oral pills are reported to be tasteless and rapidly disintegrating in saliva (Plumb, 2011).

Monitoring

No serum therapeutic monitoring is necessary for lorazepam. Patients should be monitored for clinical efficacy and adverse side effects.

MIDAZOLAM (MDZ) (MID-AZZ-ZOE-LAM)

Midazolam is a shorter-acting but more potent benzodiazepine compared to diazepam and is available in an oral solution and injectable forms. In the USA, it is marketed under the trade name *Versed*® and is also available in generic forms. Its primary use in veterinary medicine is as a combination of premedication for anesthesia. It is also used in the IN route and as an IV and IM injection for the control of SE when first-line (prophylactic) medications have failed (Figure 7.1). When given IV to dogs (0.2 mg/kg) in an experimentally induced model of seizures, midazolam was more effective than diazepam in controlling epileptic seizures at identical doses (Horikawa *et al*., 1990). In children, midazolam was also found to be more effective and better tolerated in controlling SE compared to pentobarbital (Holmes and Riviello, 1999). It may also have effective use when used in the sublingual route in humans (Scott *et al*., 1998).

Mechanism of Action

Like the other benzodiazepines, midazolam's primary antiseizure effect is suspected to be through interaction with the $GABA_A$–chloride ionophore membrane complex. Midazolam and other benzodiazepines directly bind to the GABA receptor, enhance the affinity of GABA for its binding site, and potentiate the flow of chloride ions across the ion channel, thereby hyperpolarizing the plasma membrane and lowering the seizure threshold. However, the interaction of benzodiazepines with the $GABA_A$ receptor is likely not the only mechanism of action for their antiseizure effects (Engel, 2013). Multiple, high-affinity benzodiazepine binding sites are recognized in multiple tissues (MacDonald, 2002). Compared to diazepam, midazolam possesses double the binding to the high-affinity benzodiazepine receptors and is nearly 3 times more potent (Reves *et al*., 1985). In another study, midazolam was found to be 5–6 times more potent than diazepam (Horikawa *et al*., 1990; Charalambous *et al*., 2021). Additionally, midazolam has a faster onset of action compared to diazepam but a shorter duration of action (Plumb, 2011). Benzodiazepines act to block arousal in the CNS and centrally depress spinal reflexes (Boothe, 1998).

Pharmacokinetics

The concentration of midazolam needed to stop an epileptic seizure in dogs and cats is unknown. Midazolam achieves very rapid CNS concentration following IV injection, owing to its lipophilic nature. In the dog, it has a Vd of 3 l/kg (Court and Greenblatt, 1992). In dogs, when given at a dose of 0.2 mg/kg, it took a significantly larger amount of lidocaine to induce seizure activity in an experimental model compared to diazepam, supporting the notion midazolam is more effective at controlling epileptic seizures than diazepam (Horikawa *et al*., 1990). The time to attain peak serum concentration in the dog, when given IV at a dose of 0.2 mg/kg, was less than 3 min (Eagleson *et al*., 2012). The imidazole moiety of midazolam makes it more water-soluble and allows it to be more rapidly metabolized when compared to other benzodiazepines (Holmes and Riviello, 1999).

This also allows an injectable formulation without the need for propylene glycol, which can be a vascular irritant if given IV or IM. Once injected into the body, the physiologic pH of the patient will make it more lipophilic, which results in rapid distribution to the brain (Reves *et al.*, 1985). Midazolam is highly protein bound (~97%); therefore, its use must be carefully evaluated in patients with reduced levels of serum albumin, as the free form is what enters the CNS (Court and Greenblatt, 1992). After IM injection, at a dose of 0.5 mg/kg given to dogs, peak plasma concentration averaging 549 ng/ml was measured within 15 min of injection at a measured bioavailability of 90% (Court and Greenblatt, 1992). The therapeutic range of midazolam for dogs and cats is extrapolated from human studies and referenced at <400 ng/ml (Charalambous *et al.*, 2021). In another study, the time to peak concentration after IM injection of 0.2 mg/kg in dogs was approximately 8 min with a bioavailability of approximately 50% (Schwartz *et al.*, 2013). Following intranasal administration, the concentration within the plasma is greater than that attained through rectal administration and is considered to be in the therapeutic range to stop epileptic seizures. Furthermore, the systemic availability is erratic and plasma concentrations are undetectable via the rectal route of administration (Court and Greenblatt, 1992; Schwartz *et al.*, 2013). Peak serum concentrations are attained twice as fast with intranasal dosing compared to oral dosing in dogs. Additionally, serum concentration is 3 times greater, and 2.5 times more midazolam is absorbed through the intranasal route compared to oral dosing (Lui *et al.*, 1991). However, in another study, at a dose of 0.5 mg/kg when given orally to dogs, a peak plasma concentration of 339 ng/ml within 5 min was measured, suggesting the oral route of absorption is primarily through buccal absorption as opposed to GI (Court and Greenblatt, 1992). Following intranasal dosing using a gel formulation of midazolam, mean plasma concentrations after 20 min were statistically equivalent to IV dosing of the same amount (0.2 mg/kg) and the novel gel formulation gave a significantly higher amount of absorption via the intranasal route compared to the parenteral solution used with intranasal administration (Eagleson *et al.*, 2012). Furthermore, the bioavailability of the intranasal gel formulation (70.4%) was significantly greater than the injectable form (52%) when it was given via intranasal or rectal administration (49%). Based on human studies, both the intranasal gel formulation and the parenteral formulation given intranasal to dogs will achieve therapeutic concentrations. A peak plasma concentration of 450 ng/ml was achieved using the intranasal gel formulation of midazolam, which is twice the plasma concentration achieved when the parenteral form was given through the intranasal route to humans (Eagleson *et al.*, 2012). Methylcellulose was used as a bioadhesive gel to prolong the contact time of the midazolam to the nasal mucosa.

Compared to diazepam administered rectally, midazolam takes significantly longer to reach peak plasma concentrations (an average of 39 min for midazolam compared to an average time of 14 min for diazepam when given rectally). When given rectally at a dose of 0.5 mg/kg in a single dog, peak plasma concentration was less than 3 ng/ml (Court and Greenblatt, 1992).

Midazolam is metabolized in dogs primarily through microsomal oxidation to an active metabolite (α-hydroxymidazolam) with a very short half-life and therefore has very limited clinical significance. The half-life of midazolam in the dog is approximately 1 h compared to ~3 h for diazepam (Court and Greenblatt, 1992). Midazolam is primarily eliminated via the urine in humans; however, a significant amount is suspected to be eliminated through the hepatobiliary route in dogs (Court and Greenblatt, 1992).

Toxicity, Side Effects, and Interactions

Midazolam has a very rapid onset of action. Within 3–5 min of a 0.5 mg/kg IM dose, dogs exhibited marked weakness and ataxia (inability to stand or walk) as opposed to a nearly immediate effect with IV administration (Court and Greenblatt, 1992). Within 30 min of administration, all dogs were able to stand and walk. Some dogs exhibited agitation and excitation, which lasted 5–20 min. Most dogs fell asleep but were arousable, following the brief episode of agitation

(Court and Greenblatt, 1992). The use of a lower dose is hypothesized to prevent the agitation stage. In the study by Court, one dog, when given an oral dose of 0.5 mg/kg, demonstrated the effects of the drug within 5 min of dosing supporting the notion buccal and mucosal absorption of the drug is rapid (Scott *et al.*, 1998). Midazolam, like other benzodiazepines, may stimulate eating behavior. This is proposed to be due to enhancement of the inhibitory effects of GABA on the serotonin receptor in the ventromedial "satiety" center of the hypothalamus (Morley, 1980).

Midazolam may increase the effects of other potentially sedating drugs, especially barbiturates, antihistamines, tricyclic antidepressants, phenothiazines, and analgesics. Concurrent use of phenobarbital or rifampin may reduce the effects of midazolam. Antifungals in the azole class, calcium channel blockers, cimetidine, and macrolide antibiotics (e.g., erythromycin) may increase midazolam levels in the blood.

Midazolam should be used with caution in patients who have compromised hepatic, renal, cardiac, or respiratory function. Midazolam has a greater potential for cardiac and respiratory depression compared to other benzodiazepines.

Indications for Use

The primary use of midazolam is as one of the possible first-line benzodiazepine treatments for SE and breakthrough seizures in the hospital (or diazepam or lorazepam). Midazolam may be used IV, IM, and IN and might have potential effects when given orally (through buccal absorption). Midazolam should not be used rectally as its absorption is erratic and incomplete. In a hospital situation where an IV catheter is not established, giving midazolam IN or buccal (transmucosal) is the quickest route to stop the seizure, while the staff is working to place an IV catheter (Talukdar and Chakrabarty, 2009; Charalambous *et al.*, 2017, 2019). The buccal route is less likely to be effective if the patient is foaming saliva from the mouth. It can be given as an IV bolus or as a continuous rate infusion to control cluster seizures or to treat status epilepticus (Bray *et al.*, 2021).

Midazolam may also be used in the home setting to control breakthrough seizures through the intranasal route and may be useful through oral dosing via buccal and sublingual absorption; however, more studies on the pharmacokinetics of mucosal absorption are needed. Midazolam given intranasally has been shown to be more effective than diazepam given rectally (Charalambous *et al.*, 2017). One owner survey reported midazolam as being 97% effective when used IN in a home setting compared to 63% for rectal diazepam (Kähn *et al.*, 2023). The IN absorption of midazolam is improved when the viscosity of the injectable medication is altered by compounding it (midazolam) into a gel formulation (Zhang *et al.*, 2002; Aldawsari *et al.*, 2018). When dispensing midazolam for home use, be cautious of its stability. Once dispensed, the shelf life of the injectable midazolam formulation, when mixed with a vehicle (flavored syrup for pediatric oral use) is reported to be up to 102 days (Steedman *et al.*, 1992; Walker *et al.*, 1997). Midazolam has been shown to be shelf stable for up to 90 days in a diluted form stored in a polypropylene syringe, at room temperature and up to 1 year when kept refrigerated (Gilliot *et al.*, 2020). Midazolam is commonly used as an oral syrup, prepared from the injectable form, for pediatric sedation. Lorazepam, on the other hand, does not stay stable once diluted and stored, for more than 2 days (Colsoul *et al.*, 2020). However, the *undiluted injectable* form of lorazepam, stored in a glass vial (syringe in the study) is stable for up to 150 days at room temperature (Gottwald *et al.*, 1999).

Dose

A dose of 0.07–0.2 mg/kg given IV, IM, IN, or orally may be used in dogs and cats. If epileptic seizures continue, a continuous rate infusion may be useful in dogs and cats (Thomas, 2010; Bray *et al.*, 2021). Thomas reported a dose range of 0.05–0.5 mg/kg/h, while Bray reported a range of 0.1–2.5 mg/kg/h as a CRI. Emphasis should be placed on IV, IM, and intranasal routes of

administration as the first choice with IV being the preferred access in hospital and IN at home. Although as previously stated, the IN route in a hospital setting has been shown to have a quicker onset of action if an IV catheter is not already in place (Charalambous *et al*., 2019). Flumazenil may be used to reverse the effects if significant cardiac or respiratory depression is encountered; however, the effects of midazolam are generally short-lived. If patients have compromised liver function, the dose should be titrated to effect. It is recommended to begin with 25% of the calculated dose. Midazolam is available in an injectable form at concentrations of 1 and 5 mg/ml. It is available as an oral solution (syrup) at a concentration of 2 mg/ml. It is available as a nasal spray for humans at a predefined dose of 5 mg/spray (*Nayzilam*®).

Monitoring

No specific drug concentration monitoring is necessary. The patient's vital signs and disposition following administration of midazolam should be carefully monitored.

PHENOBARBITAL (PB) (FEE-NOE-BAR-BIH-TAL)

Phenobarbital is a barbiturate derivative. This class of chemicals possesses both antiseizure and anesthetic properties. Phenobarbital is one of the most effective and commonly used anticonvulsants for controlling seizures in dogs and cats (Charalambous *et al*., 2014, 2016, 2018; Podell *et al*., 2016). It is considered *broad spectrum* for all seizure types. Most practitioners are very familiar with its use. While generally considered a somatosensory depressant, it does have the ability to create a paradoxical reaction, resulting in many different degrees of behavior alteration, from extreme sedation to a "manic" form of hyperanxiety. It is currently considered the first-choice antiseizure medication for cats and dogs, along with imepitoin. Despite the development of newer, and safer antiseizure medications, its use as a first-choice antiseizure medication persists. Phenobarbital's good control of seizures, wide safety margin, and typically very tolerable side effects make it a good first choice for chronic anticonvulsant therapy. It is still the most prescribed first-choice antiseizure medication for dogs and cats among general practitioners and specialists (Meland *et al*. 2019; Green *et al*., 2022; Gristina *et al*., 2023). At serum therapeutic levels between 15 and 40 µg/ml, 93% of cats (28/30) had their seizures controlled (Finnerty *et al*., 2014).

Phenobarbital 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 drugs. Barbiturates, in general, should be used with caution as they have the potential for not only sensory and motor depression but respiratory depression as well. Due to the potential adverse side effects of phenobarbital on the liver, and the need for strict monitoring, it is reasonable to begin anticonvulsant therapy with newer, safer, and possibly equally efficacious antiseizure medications (e.g., imepitoin, levetiracetam, potassium bromide, etc.). Granted many factors will contribute to this decision (as discussed in Chapter 6). In cases where it is necessary to obtain immediate seizure control with an IV drug, phenobarbital is a very good choice once status epileptic has been controlled through the use of a benzodiazepine (see Chapter 8 and Figure 8.1). The effectiveness and minimal side effects of alternative antiepileptic drugs compared to the potential side effects of phenobarbital when used long term warrant the use of alternatives where applicable. Additionally, the expense and compliance necessary with routine monitoring of phenobarbital, because of its potential adverse side effects, make the slightly higher cost of newer antiseizure medications justifiable when considered against the savings of routine therapeutic drug monitoring, worry of potential hepatotoxicity (although rare) and necessity of a compliant owner to follow through with routine monitoring. Finally, it is a controlled substance, requiring more time, inventory control, and worry of diversion than other first-choice antiseizure medications. Regarding dogs, phenobarbital is 60–80% effective in eliminating seizures, when used as a monotherapy, if within the

therapeutic range of 20–40 µg/ml (Farnbach, 1984a; Schwartz-Porsche *et al.*, 1985). Compared to potassium bromide as the first-choice antiseizure medication, phenobarbital was shown to control seizures in 85% of dogs compared to 53% of dogs becoming seizure-free when treated with bromide (Boothe *et al.*, 2012). Of course, certain *individuals* may be more responsive to one drug over another. As previously discussed, it is very important *not to* consider an antiseizure drug a failure until side effects secondary to the drug are seen in combination with inadequate seizure control. This means intensive monitoring of liver function is necessary in those animals at the high end of the reference range of serum concentrations of phenobarbital. In cases where phenobarbital is used as a monotherapy and seizures are not adequately controlled, a second antiseizure medication with a different mechanism of action may be added.

Mechanism of Action

Phenobarbital's mechanism of action is to bind to the $GABA_A$ receptor and prolong its opening, resulting in an increased influx of Cl^- into the cell (Olsen, 1982; Olsen and Snowman, 1982). The Cl^- ions will hyperpolarize the cell (making it more negative), thereby increasing the seizure threshold necessary for neuronal firing and decreasing the spread of discharge to surrounding neurons by creating an inhibitory postsynaptic potential (IPSP). Phenobarbital (and various other antiseizure medications) will also inhibit glutamine activity (an excitatory neurotransmitter) and decrease the conductance of Ca^{++} across the plasma membrane (Czapiński *et al.*, 2005). It may also interact with Na^+ and K^+ conductance (Parent, 1988; Engel, 2013). Phenobarbital decreases cerebral blood flow and metabolism resulting in an indirect action of motor cortex depression. Its actions are systemic to the brain, affecting normal synaptic transmission and not specific for hypersynchronous neurons, which accounts for its potential sedative effects.

Pharmacokinetics

Phenobarbital is slowly absorbed from the gastrointestinal (GI) tract with a bioavailability of nearly 90% in dogs and 100% in cats (Al-Tahan and Frey, 1985; Cochrane *et al.*, 1990a). GI disease and the presence of food in the stomach will delay its absorption. It is approximately 45% protein bound in dogs and reaches peak serum concentration in 4–8 h after oral dosing. It reaches a steady state in approximately 14–16 days in dogs; however, beagles may reach a steady state in 7 days (Daminet *et al.*, 1999). Like most antiseizure drugs, phenobarbital is lipid soluble and is widely distributed in the CNS, although it is not as rapidly distributed as diazepam, making it less than adequate to control SE. The Vd is ~0.75 l/kg in dogs and ~0.93 l/kg in cats (Cochrane *et al.*, 1990a). The half-life in dogs is 47–74 h in most dogs (25–38 h in beagles) and 34–56 h in cats (Löscher, 1979; Frey, 1986; Cochrane *et al.*, 1990b). Because phenobarbital induces its own metabolism, the half-life will decline with chronic therapy in dogs (along with serum concentration), making dose adjustments necessary to maintain serum therapeutic concentration. A dose change in dogs should be anticipated 3–6 months after starting therapy. The development of tolerance over time may necessitate larger doses to have the same efficacy. If tolerance develops, some dogs may benefit from every 8 h dosing (Boothe, 1998). Cats are not as susceptible to the development of tolerance, and dose schedules comprising once daily dosing have been shown to maintain therapeutic serum concentrations (Cochrane *et al.*, 1990b; Mojarradi *et al.*, 2023). In the Mojarradi paper, seizure remission was reported in 88% of the cats in the study (8/9 cats); however, the serum phenobarbital concentration was reported to be <23 µg/ml in 80% of the samples at the last follow-up visit (4/5 blood samples). This paper noted the samples previously mentioned were "subtherapeutic" (according to Bailey and Dewey, 2008). Although the therapeutic serum concentrations have not been determined in the cat, it is recommended that serum concentrations should fall in the range of 10–30 µg/ml (Shell, 2000). What this shows is no one patient's anticonvulsant needs should be determined by a reported number, but rather, what works for that particular patient (i.e., individualized "therapeutic" range vs. "reference" range).

The liver, through a process of oxidation to para-hydroxyphenobarbital, primarily metabolizes phenobarbital. Glucuronide and sulfate conjugates are also formed through phase II reactions, which, along with the para-hydroxyphenobarbital, are eliminated by the kidneys. About 25% of phenobarbital is eliminated by pH-dependent renal excretion unchanged. Polyuria or alkalization of the urine will increase its elimination (Boothe, 1998; Fukunaga *et al*., 2008). Not only does phenobarbital increase its own metabolism, but it will also increase the metabolism (and elimination) of other exogenous and endogenous substances (e.g., levetiracetam).

Toxicity, Side Effects, and Interactions

Toxicity: Phenobarbital is well known for its toxic effects on the liver in dogs. It causes the proliferation of smooth endoplasmic reticulum in hepatocytes and hepatocellular hypertrophy, resulting in *macronodular* or *micronodular* cirrhosis. It may, however, cause a *nonpathological* increase in serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activity due to hepatic enzyme induction (Bunch *et al*., 1984, 1985, 1987; Gieger *et al*., 2000; Müller *et al*., 2000a). Transient increases in gamma-glutamyl transferase (GGT) and decreases in serum albumin have also been noted (Müller *et al*., 2000b). However, debate exists as to whether the observed increases in liver enzymes are due to *induction* (for which support is ubiquitous in the literature) or early subclinical liver damage. Gaskill reported that increased serum levels of ALP (AP) and ALT are not due to induction (Gaskill *et al*., 2005). If changes in enzyme levels were due to induction, no change in antiseizure therapy is necessary; however, if the increase in liver enzyme activity were due to early liver damage, discontinuing the drug may be warranted. An increase of serum ALP (>5× upper normal value) or ALT (>2× upper normal value) or values showing trends demonstrating increases should raise concern of possible liver damage. Any increase in AST or *persistent* increase in GGT should trigger concern. Cholesterol levels and albumin may also decrease in time with chronic phenobarbital use. If in question, liver function testing (fasting and fed bile acids), abdominal ultrasound, and potentially fine-needle aspirates or liver biopsies should be considered. The elevated serum activity of hepatic enzymes should return to normal in 3–5 weeks after the drug is discontinued (Gieger *et al*., 2000; Ennulat *et al*., 2010). Monitoring of liver function with bile acid levels is an effective method to gauge the potential hepatic toxicity of phenobarbital. If serum liver enzymes are elevated in conjunction with increases in bile acids and decreases in urea nitrogen, cholesterol, or serum albumin, liver pathology should be suspected and an alternative anticonvulsant should be considered. A coagulation panel is recommended if liver failure is a concern prior to any invasive sampling technique such as fine-needle aspirate or biopsy of the liver. Because barbiturates may cause an increase in bromsulfthalein (BSP) retention, bile acid analysis should be used to estimate liver function (Plumb, 2011). Serious liver disease may *resolve* if phenobarbital therapy is discontinued. The incidence of hepatic toxicity increases when serum levels are greater than 35 μg/ml (Dayrell-Hart *et al*., 1991). Most liver complications occur when phenobarbital is combined with other antiepileptics such as primidone and phenytoin (Bunch *et al*., 1982, 1984, 1985). Phenobarbital has been shown to increase ALT or ALP in a minority of cats (33%) when serum levels were >30 μg/ml but no significant statistical changes to serum liver enzyme or other biochemical parameters were found comparing pre to post-treatment in cats (Hermans *et al*., 2022). This study suggests that any increased in serum liver enzyme values in cats being treated with phenobarbital may be due to underlying liver disease and not the medication.

Early investigation shows cannabinoid (CBD) interaction with cytochrome P450, which could influence phenobarbital metabolism if used concurrently. But when phenobarbital was used concurrently with CBD, it only had a minimal effect on increasing CBD levels (Court *et al*., 2024). Studies looking at the concurrent use of cannabidiol—cannabidiolic acid-rich hemp extract do not show any alternations in serum phenobarbital or interactions with phenobarbital concentrations (or bromide or zonisamide for that matter) others have shown phenobarbital serum levels to rise

(McGrath *et al*., 2019; Doran *et al*., 2021; Garcia *et al*., 2022). It is important to remember when treating dogs and cats who only respond to phenobarbital, the risk of hepatic dysfunction/toxicity is less than the risk of being euthanized due to inadequate seizure control. Hepatic complications have not been reported in the cat.

Side effects: Use caution in compromised patients including those with cardiac disease, adrenal insufficiency, renal disease, hepatic disease, respiratory compromise, hypovolemia, or anemia. Phenobarbital may cause polyuria, polydipsia, and polyphagia in dogs and cats. The polyuria is attributed to central inhibition of antidiuretic hormone release with secondary polydipsia (Meyer, 1982). The polyphagia is thought to be due to its suppression of the satiety center in the ventromedial hypothalamus (Jenkins, 1982).

The occasional sedation, ataxia, depression, and lethargy in some dogs and cats exhibited with phenobarbital therapy are usually transient unless a persistently elevated steady state is maintained. These effects stem from the fact phenobarbital is not selective in its interference with normal synaptic activity. The side effects reported following the immediate initiation of therapy usually dissipate within 1–2 weeks. Rarely dogs will become hyperexcitable and restless. This, too, usually resolves within a few days of treatment. These transient side effects are likely due to changes in the postsynaptic membrane receptor regulation (an upregulation in receptor synthesis). Reported side effects in cats include polyphagia, thrombocytopenia, transient facial pruritus, neutropenia with dermatitis, and swelling of the paws (Quesnel *et al*., 1997; Platt, 2001). In one retrospective study, it was found that 47% of cats receiving phenobarbital experienced one or more type A reactions (predictable), of which the likelihood of having a side effect increased 3.2 times when a second anticonvulsant was added (Marsh *et al*., 2021). This information is helpful to warn owners of the potential for side effects even though the safety level of phenobarbital in cats is very high.

Interactions: Phenobarbital may cause reversible depression of certain bone marrow cell lines. This has been attributed to either an idiosyncratic, allergic, or direct toxic effect to the bone marrow (Weiss and Smith, 2002). These changes usually occur within 6 months of starting the medication (Podell, 2013). It may result in anemia, neutropenia, thrombocytopenia, or pancytopenia (Oberholster, 2021). Hematologic values have been reported to return to normal range within 7–21 days after discontinuing the drug in dogs (Jacobs *et al*., 1998; Oberholster, 2021). Phenobarbital has also been shown to cause various forms of cytopenia in *cats* when at or below the therapeutic range (neutropenia, leukopenia, thrombocytopenia, and anemia) (Dohány *et al*., 2023). These may be life-threatening changes. A single case of phenobarbital-induced systemic lupus erythematosus has been reported in a dog (Phillips *et al*., 2023). Clinical signs, including circulating anti-nuclear antibody resolved once the medication was discontinued. A hepatocutaneous syndrome specifically linked to long-term use of phenobarbital has been reported in dogs (March *et al*., 2004; Bevier *et al*., 2010). This condition, termed *superficial necrolytic dermatitis*, may develop years after chronic use of phenobarbital or primidone (Henricks, 1987 and March *et al*., 2004). Hyperkeratosis of the footpads as well as dermatologic disease of the mucocutaneous junctions, pinna, axilla, tarsal region, elbows, and inguinal area may also be present. The disorder is due to a hypermetabolic state characterized by increased amino acid metabolism of the liver (Outerbridge *et al*., 2002). Prior to the onset of the clinical signs, nearly all dogs had elevations in ALP and ALT; however, bile acid measurement and serum albumin concentrations were typically normal. Prognosis, even with the withdrawal of phenobarbital, is poor; however, early recognition; cessation of phenobarbital or any other drugs, which carry potential hepatotoxic effects; and amino acid supplementation may improve the long-term prognosis. Phenobarbital may cause cutaneous reactions and dermatological signs in dogs (dermatitis, pruritus, alopecia, crusty erosive lesions, etc.) (Koch *et al*., 2016). Toxic epidermal necrolysis (related to *Stevens–Johnson Syndrome*) has been reported in a young Great Dane, 6 weeks after initiation of phenobarbital therapy (Cornelis *et al*., 2016). Clinical signs appeared to be improving once phenobarbital was discontinued (the patient was euthanized due to GDV). A phenobarbital-induced fever has been reported in a cat, which resolved within 24 h of

cessation of the medication (Djani and Draper, 2019). Pseudolymphoma following the initiation of phenobarbital has been reported in one dog and several cats which may be accompanied by hematological changes (pancytopenia, auto-immune hemolytic anemia, neutropenia, thrombocytopenia) (Baho *et al*., 2011; Lampe *et al*., 2017; Lieser and Schwedes, 2018; Sohn *et al*., 2019; Lyraki and Wilson, 2020; Walton-Clark *et al*., 2022). In Humans, treatment with certain anticonvulsants may cause skin lesions, hematological abnormalities (anemia, leukopenia, thrombocytopenia), and pseudolymphoma. These type B reactions (unpredictable and idiosyncratic) are known as *anticonvulsant hypersensitivity syndrome*. The mechanism is not completely understood but may result from abnormal toxic metabolites of the drugs and a subsequent T-cell-mediated immune reaction.

The effects of phenobarbital on endocrine function have been studied extensively. Thyroid function, in particular, has been studied for some time. Phenobarbital will *lower* serum T_4 and free T_4 (Daminet *et al*., 1999; Gaskill *et al*., 1999, 2000; Gieger *et al*., 2000; Müller *et al*., 2000b). The changes to thyroid-stimulating hormone (TSH) were variable. It is generally regarded that phenobarbital does not alter TSH (Kantrowitz *et al*., 1999). Ultimately, a dog with hypothyroidism should have biochemical evidence *and* clinical signs of hypothyroidism before it is diagnosed with the disease; however, much debate exists surrounding the potential for hypothyroidism to create *subclinical* disease. Furthermore, some of the clinical signs of hypothyroidism, such as lethargy and weight gain, also occur with chronic phenobarbital use. Additionally, it has been suggested hypothyroidism may *cause* seizures. However, most dogs with true hypothyroidism will have a low T_4, a low free T_4, and a high TSH (although not always a high TSH) (Kantrowitz *et al*., 1999). In the end, if suspected, a trial of levothyroxine may be pursued (start at a low dose and gradually increase over weeks) (Bolton and Panciera, 2023). Phenobarbital increases biliary excretion of T_4 and alters binding of T_4 to plasma proteins. It is hypothesized the increases in metabolism, biliary excretion, and peripheral deiodination of T_4 are responsible for the low total T_4 and free T_4. Furthermore, the increase in peripheral conversion of T_4 to T_3 accounts for the normal T_3 and TSH concentrations commonly observed in dogs that have been on long-term phenobarbital therapy (Kantrowitz *et al*., 1999). Phenobarbital has no effects on the low-dose dexamethasone suppression test or the ACTH stimulation test (Dyer *et al*., 1994; Chauvet *et al*., 1995; Müller *et al*., 2000b). In humans, phenobarbital is reported to increase the metabolism of exogenous and endogenous steroids. A case report of an Addisonian crisis in a dog has been reported after starting phenobarbital therapy (Simerdova *et al*., 2015). Phenobarbital has also been reported to increase triglycerides and pancreatic lipase activity in dogs (Gaskill *et al*., 2000, Kluger *et al*., 2008, Steiner *et al*., 2008).

Because phenobarbital is a barbiturate, the resulting CNS depression may be exacerbated with other CNS depressants such as phenothiazines, antihistamines, narcotics, chloramphenicol, and other anticonvulsants (Plumb, 2011). As the liver primarily metabolizes phenobarbital, its metabolism may be increased by concurrent use of drugs also metabolized primarily by the liver such as chloramphenicol, cimetidine, and rifampin. Drugs, which *inhibit* hepatic microsomal enzymes, such as chloramphenicol, cimetidine, valproic acid, and ketoconazole may lead to phenobarbital toxicity (Houston *et al*., 1989). Additionally, phenobarbital may decrease the effect of certain protein-bound drugs or increase the excretion of certain drugs through the upregulation of hepatic microsomal enzymes such as oral anticoagulants, carprofen, propranolol, corticosteroids, doxycycline, quinidine, theophylline, metronidazole, and griseofulvin (Table 7.1). Phenobarbital is reported to increase the elimination of the benzodiazepines, levetiracetam, and zonisamide if used concurrently (Wagner *et al*., 1998; Orito *et al*., 2008; Moore *et al*., 2011).

Anecdotally, it has been recommended phenobarbital be diluted in saline (1:2) when injected IV and given slowly (no more than 60 mg/min). This is to prevent a possible type I allergic reaction, potentially due to the carrier vehicle or preservative. Phenobarbital is approved for IM use in humans but limited to a total of 5 ml volume and care must be taken to inject the medication into a large muscle as it will cause severe irritation if administered subcutaneously or perivascular (Phenobarbital 2022—manufacturer label information).

Table 7.1 Drug interactions: Phenobarbital.

Drugs which may increase the effects of Phenobarbital	Alpha-2 agonists (dexmedetomidine) + resp dep
	Antihistamines (sedation)
	Benzodiazepines + respiratory depression
	Cannabinoids
	Chloramphenicol
	CNS depressants + resp dep and CNS dep
	Felbamate
	Monoamine oxidase inhibitors (amitraz, poss. selegiline)
	Opiates
	Phenothiazines
	Primidone
	Valproic acid
Phenobarbital may decrease the effects of:	Albendazole
	Amiodarone
	Anticoagulants (warfarin)
	Anti-fungals (azoles)—May increase Pb and decrease antifungal levels
	Benzodiazepines
	Beta-blockers (alprenolol, propranolol, metoprolol)
	Buspirone
	Carprofen
	Chloramphenicol
	Clarithromycin
	Clindamycin
	Corticosteroids
	Cyclosporine
	Digoxin
	Doxorubicin
	Doxycycline
	Estrogens
	Felbamate (decreased felbamate, increased PB)
	Fenbendazole
	Griseofulvin
	Isoniazid
	Levetiracetam (decrease T½ by 50%)
	Levothyroxine
	Medroxyprogesterone
	Methadone
	Metronidazole
	Quinidine

(*Continued*)

Table 7.1 (Continued)

	Paroxetine
	Phenothiazines
	Phenytoin
	Praziquantel
	Progestins
	Rivaroxaban
	Sulfonamides
	Tacrolimus
	Theophylline
	Topiramate
	Tricyclic antidepressants
	Valproic acid (decreased VA, increased PB)
	Verapamil
	Vincristine
	Vitamin D
	Zonisamide
	Acetaminophen: may inc. risk of hepatotoxicity
	Rifampin: may increase metabolism of Pb
Specific interactions	Acetaminophen: may increase risk of hepatotoxicity with PB
	Carprofen: may increase risk of hepatotoxicity with PB
	Cholestyramine: May reduce Pb absorption
	Urinary acidifiers: may increase serum T½ of Pb
	Urinary alkalinizers: may increase serum T½ of Pb

Refer to specific veterinary formulary for latest information.

Indications for Use

Phenobarbital is the current drug of choice for treating epileptic seizures in dogs and cats (Podell *et al*., 2016; Charalambous *et al*., 2018). However, cats tend to be more sensitive to the sedating effects of phenobarbital, and the elimination of the drug is slower in cats compared to dogs. Therefore, the dose is adjusted accordingly. The use of phenobarbital as the first-line antiseizure medication may change as experience is gained with the newer anticonvulsants in their regard to the feline and canine populations, however, it is the most prescribed first-line treatment for canine and feline epilepsy. Phenobarbital is useful for the treatment of all forms of epileptic seizures and is considered broad spectrum. Caution should be used in patients with hepatic compromise. Phenobarbital is generally a preferred drug in patients with known structural brain disease (head trauma, encephalitis, neoplasia) as these patients may have a predisposition to SE, hospitalization, and the potential of a period where oral medication is not feasible (e.g., postoperative, postictal hospitalization, etc.). In these cases, the ability to have a drug, which is available in parenteral form, is beneficial to maintain serum therapeutic concentrations until oral therapy can again be initiated. The use of phenobarbital warrants routine blood work and liver function testing (fasting and fed bile acid analysis). Compared to some of the newer medications that have a greater safety margin and therefore less intense monitoring, phenobarbital loses some of its advantages (especially compared

to imepitoin). The expense of routine monitoring over the lifetime of a pet in many cases will be more than the increased expense of many of the newer antiseizure medications. Although phenobarbital is readily available and very inexpensive, it is a controlled substance, which is another disadvantage when compared to many of the new-generation antiseizure medications.

Phenobarbital is useful for the treatment of fly-biting episodes (or fly-catching), although not necessarily as helpful as fluoxetine (Wrzosek *et al*., 2015).

Phenobarbital is also indicated for the treatment of *idiopathic hypersialosis* (i.e., sialadenosis) in the dog, which may be a form of limbic epilepsy (Mawby *et al*., 1991; Chapman and Malik, 1992; Stonehewer *et al*., 2000; Alcoverro *et al*., 2014).

Dose

Phenobarbital is often used in emergency situations when animals present with SE. *It is not the ideal drug for the immediate control of seizures.* Phenobarbital may take from 3 to 15 min to reach the brain compared to 1 min for IV diazepam (Lane and Bunch, 1990; Boothe, 1998). It can be given as a loading dose of 12–15 mg/kg IV once for dogs and 10–20 mg/kg IV once for cats. The loading doses can also be divided and given every 1–4 h to minimize sedation. The author will dilute the phenobarbital 1:2 with sterile saline and inject slowly (i.e., over 5 min) to avoid any potential hypersensitivity reaction (anecdotally reported), although it is preferable to control the seizure with diazepam first and then immediately load with phenobarbital (or levetiracetam). As with all barbiturates, especially when combined with other anticonvulsants, careful monitoring of heart rate and respiratory rate is necessary.

The starting dose should take into consideration the use of any other antiseizure drugs and be adjusted accordingly. If used as a monotherapy, begin with 3 mg/kg in dogs every 12 h and 1.5–2.5 mg/kg in cats divided into two daily doses (BID) (Boothe, 1998; Platt, 2001). As previously mentioned, cats may be dosed once a day and although have low serum levels, still attain good seizure control. Because the half-life of the drug is longer in cats than in dogs, the dose is subsequently adjusted. In animals with suspected liver disease or portosystemic shunts, and phenobarbital is the only drug at the clinician's disposal, start with 25% of the calculated dose and monitor liver function very closely with fasting and fed bile acids. Some dogs (particularly Beagles) may have an elimination half-life of <20 h. Additionally, the elimination half-life may decrease with chronic use (i.e., fall below <20 h). In a case where the elimination half-life is <20 h, patients may benefit from every 8 h dosing (Stabile *et al*., 2017). The elimination half-life can be calculated by measuring serum phenobarbital trough *and* peak values (see Table 6.4 and Appendix 3 for the complete formula). If you see a dog, which was formerly well controlled, calculation of the elimination half-life is warranted.

If epileptic seizures are not controlled and a dose adjustment is considered, the dose necessary to achieve a new therapeutic concentration can be calculated, although, in practice, a 25% increase is generally considered safe and effective (Table 7.2 and Appendix 3). The following formula can be used to calculate a new dose:

$$\frac{\text{Desired serum concentration}}{\text{Current serum concentration}} \times \text{current dose in mg / day} = \text{new total mg / day}$$

Phenobarbital, like all antiseizure medications, should be titrated *to effect or to side effect*. This is a critical concept for the clinician to remember as failing a medication too early may lead to inadequate seizure control, a patient who has epileptic seizures more frequently, frustrated pet owners, and *pseudoresistance*. Any dose adjustment or the initiation of the drug as a novel antiseizure medication should be given 3 weeks to have an effect (i.e., slightly longer than steady state). If the patient is still having epileptic seizures 3 weeks *after* starting the medication or a recent increase in medication (and not experiencing any side effects from the drug), a dose *increase* of approximately

Table 7.2 Formula for calculation of new drug dose.

This formula may be used to calculate dose increases to achieve a new target serum concentration of any drug where serum concentration can be determined:

$$\frac{\text{Desired serum concentration}}{\text{Current serum concentration}} \times \text{current dose in mg / day} = \text{new total mg / day}$$

Example: A 15 kg dog has a current serum therapeutic concentration of phenobarbital measured at 20 μg/ml. It has been at least 3 weeks since the initiation of phenobarbital or a change in the dose (i.e., the dog has achieved *steady state*). You want to attain a new serum concentration of 25 μg/ml. The dog is currently being dosed at 3 mg/kg every 12 h (45 mg BID) or 6 mg/kg every 24 h or 90 mg/day:

$$\frac{25\ \mu g / ml}{20\ \mu g / ml} \times 90\ mg = 112.5\ mg / day$$

For practical purposes, the dose would be increased from 45 mg every 12 h to 60 mg every 12 h.

25% per dose is recommended. If the patient is already experiencing negative side effects, it would be expected an increase in the dose would only make the side effects worse (assuming the side effects are not the expected, transient side effects often encountered at the initiation of phenobarbital therapy). In these cases, the pet owner and clinician must weigh the benefits against the costs of an increase in the current medication or the addition of a new medication. Prior to the increase in dose, a serum concentration should be evaluated. If the patient is approaching 40 μg/ml in a dog or 45 μg/ml in a cat, the addition of a *second* medication should be considered.

If the medication is not thought to be having any effect at a maximal dose (for that *particular* patient), it may be withdrawn slowly once the new antiseizure medication has achieved serum steady state. In the case of phenobarbital, the drug dose is reduced by 25% every 3 weeks until a point where any further decreases are not practical based on pill size, in order to prevent withdrawal seizures. While the reduction is being made, no changes should be made to the other antiseizure medication to prevent confusion if epileptic seizure activity changes (only change one variable at a time). If during a reduction, epileptic seizures become more frequent, the phenobarbital should be left at the current dose, and *the other* antiseizure medication should be increased by 25% (or as close to a practical dose increase). A "bridge" medication, such as clorazepate, may be used to temporarily fill the gap of epileptic seizure control until the new medication reaches its new steady state (see Chapter 6). Once steady state is achieved, the clorazepate (or other bridge medication) is weaned over a week, and the patient is evaluated for another week to see if seizures continue, and if not, the phenobarbital reduction is then continued.

Phenobarbital is available in 15, 16.2, 30, 32.4, 60, 64.2, 97.2, and 100 mg tablets. It is also available as an oral solution (4 mg/ml) and as an injectable form at concentrations of 65 and 130 mg/ml. A preservative-free, lyophilized form is available at 100 mg. An FDA-approved preparation labeled for dogs is available in 30 and 60 mg (scored), chewable tablets (NOBATOL®) (Jukier *et al.*, 2024a). Transdermal phenobarbital has been experimentally tried in cats (Gasper *et al.*, 2015; Barnes Heller *et al.*, 2019). A dose of 9 mg/kg was able to achieve serum therapeutic concentrations. Overall client satisfaction was good and although the transdermal route required more adjustments to the medication dose, clients preferred it over oral phenobarbital.

Monitoring

Of all the medications we use, phenobarbital has the most rigorous monitoring recommendations. They are:

- Prior to initiating therapy: CBC, Biochemical profile, Urinalysis, Fasting and Fed bile acids.

- At steady state (3 weeks): CBC, Biochemical profile, Fasting and Fed bile acids, serum phenobarbital levels (note: do not use serum separator tubes).
- Two months after starting therapy: CBC, Biochemical profile, Fasting and Fed bile acids, serum phenobarbital levels (note: do not use serum separator tubes).
- Every 6 months if no change: CBC, Biochemical profile, Fasting and Fed bile acids, serum phenobarbital levels (note: do not use serum separator tubes).
- At dose increase: Serum Phenobarbital levels (other blood work if deemed appropriate).
- Three weeks after any dose increase: Serum Phenobarbital levels (other blood work if deemed appropriate).

Anytime a potential interaction with another drug is possible (see Table 7.1)

The published therapeutic range of phenobarbital is between 15 and 45 µg/ml in dogs and cats when used as monotherapy, although some references point to 15–30 µg/ml for cats (Moore, 2014). A general review of the literature looking at the use phenobarbital in cats, found the dose and serum levels to be greater in many studies than the published guidelines (Charalambous *et al*., 2018). When combined with other antiepileptic drugs (particularly potassium bromide in dogs), targeting a therapeutic range of 20–30 µg/ml in dogs is a reasonable goal. In general, dogs who have a serum concentration less than 20 µg/ml are not well controlled, and most cases of hepatotoxicity occur when levels are close to or greater than 35 µg/ml (Dayrell-Hart *et al*., 1991). Failure of the drug should be considered if a negative side effect cannot be overcome (with time or tolerance by the owner) or if the pet reaches a potential *toxic* serum concentration and is still having seizures (as approaching 35 µg/ml). Dogs with refractory epilepsy may not see a reduction in seizure incidence even if the concentration of phenobarbital is raised above 40 µg/ml; however, the addition of a second antiseizure medication, such as bromide, may help reduce seizure incidence (Podell and Fenner, 1993). Failure does not necessarily mean the drug is discontinued (although it should be if resulting in liver compromise); it simply means *more* of the same drug is not a reasonable option. Some side effects are easily dismissed and can be "lived with," while others may be fatal (e.g., hepatotoxicity). A complete blood count (CBC), serum chemistry profile, and urinalysis are recommended prior to starting phenobarbital therapy. Ideally, fasting and fed bile acids would also be performed to have as a "baseline" for future comparison. Serum albumin concentration and cholesterol are also "rough" estimates of liver function. More weight should be placed on fasting and fed bile acid concentration, albumin, and cholesterol than liver enzyme values. It is generally accepted an increase in serum ALP is expected due to phenobarbital induction of hepatic microsomal enzymes. Elevations in serum ALT may be more worrisome as this enzyme is thought to be more reflective of hepatocellular damage (Dayrell-Hart *et al*., 1991; Aitken *et al*., 2003). As mentioned before, the *acceptance* of increased liver enzyme activity as nonpathological due to the induction of liver enzymes by phenobarbital has been questioned (Gaskill *et al*., 2005). A repeat CBC, biochemical profile, serum phenobarbital level, and fasting and fed bile acids are recommended 3 weeks after starting therapy, then 2 months after starting therapy, and every 6 months thereafter while on the medication. It is not necessary to have a *trough* blood sample collected, as in 91% of dogs (treated for at least 3 weeks), there is little change between the timing of the blood draw and serum concentration if dosed every 12 h (Levitski and Trepanier, 2000). However, fasting trough (i.e., immediately before a dose) and peak (4–6 h after a dose) levels should be measured in patients whose seizures are not controlled. This allows the clinician to calculate the half-life of the drug and determine if every 8 h dosing is necessary (see Table 6.4 and Appendix 3). Serum separator tubes *should not* be used for sample transport as the silicone media in the tubes may "bind" phenobarbital resulting in an artificially *low* level (Boothe *et al*., 1996).

POTASSIUM BROMIDE (KBr) (POE-TASS-EE-UM BROE-MIDE)

Potassium bromide (KBr) is regarded as the first medication rationally used for the control of epileptic seizures (Eadie, 2012). Sir Charles Locock, who at the time was president of the Royal Medical and Chirurgical (i.e., *Surgical*) Society of London, is credited with the first *purposeful* and *rational* application of KBr for the treatment of catamenial seizures in women in 1856. His work was unpublished but recognized in 1857, when presiding over a meeting of the Royal Medical and Chirurgical Society of London, he commented on a report of the treatment of epilepsy being made by Sir Edward Sieveking. Locock is reported to have mentioned his use of bromide in practice for the treatment of "hysterical epilepsy" (Locock, 1857). Sir Samuel Wilks was the first physician to publish results on the use of KBr in the treatment of epilepsy in humans (Wilks, 1861). In his report of 13 cases, 12 patients responded positively to bromide therapy. Due to many negative side effects in humans owing to a narrow therapeutic window and a propensity to cause sedation and *psychosis*, its use was replaced by the introduction of phenobarbital in the early 20th century. Albertoni first documented the experimental antiseizure effect of bromide in dogs in 1882 (Albertoni, 1882). The use of bromide to treat epileptic seizures in veterinary patients was first published in 1887 by James Law (Law, 1876). Potassium bromide began to gain favor as a first-line antiseizure medication for dogs in the 1990s, primarily because of its wide safety margin, infrequency of dosing, and reversible side effects. Many of the features of newer anticonvulsants (less side effects, quicker onset of action, ease of dosing) have led to a decline in the use of potassium bromide as a first-line anticonvulsant, however, its effectiveness and safety profile still place it as one of the most useful and safest first choice medications (Charalambous *et al*., 2014; Podell *et al*., 2016). It may be particularly well suited in treating tail chasing of bull terriers (note: author's experience). Tail chasing in bull terriers is suspected to be a form of focal seizure and may also be successively treated with clomipramine (Dodman *et al*., 1996; Moon-Fanelli and Dodman, 1998). Bromide should *not be used* in cats as it can cause fatal respiratory disease (Boothe *et al*., 2002).

Bromide is an inorganic cation which is when combined with either sodium or potassium, becomes a salt. Because it can be absorbed through the skin and humans are very sensitive to its effects, whenever bromide is handled, the handler should wear gloves. In the USA, it is marketed under the trade name *K-BroVet*® (available as a solution and chewable tablets) and is commonly compounded into liquid solutions and capsules.

Mechanism of Action

Bromide's exact mechanism of action is unknown. Bromide is most commonly prepared as a salt in the *potassium* or *sodium* form. Bromide may be one of the most broad-spectrum antiseizure medications (Meierkord *et al*., 2000). While considered safe, it has a fairly narrow therapeutic window of efficacy. Its multiple proposed mechanisms of action include:

- Hyperpolarization of the neuronal membrane, through interaction with the $GABA_A$ receptor much in the same way as the chloride ion but with greater effect (Woodbury and Penry, 1982; Bormann *et al*., 1987; Suzuki *et al*., 1994; Meierkord *et al*., 2000).
- Interference with carbonic anhydrase resulting in extracellular acidosis with subsequent inhibition of epileptiform activity (Woodbury and Penry, 1982; Frey, 1989).
- Influencing the passive movement of other ions across cell membranes, particularly sodium, resulting in membrane hyperpolarization (Woodbury and Penry, 1982; van Leeuwen and Sangster, 1987; Meierkord *et al*., 2000).

Bromide passes through the $GABA_A$ receptor ionophore more readily than chloride (Bormann *et al*., 1987). It has long been suspected bromide hyperpolarizes cell membranes via its preferential

transit through the ionophore, although Balcar *et al*. surmised bromide did not affect the GABAergic inhibitory system when given to rats in their drinking water for up to 1 month (Balcar *et al*., 1987). Other investigators have shown a direct action of bromide on the GABAergic inhibitory system (Suzuki *et al*., 1994; Meierkord *et al*., 2000). The preferential passage of bromide through membrane ion channels is due to its smaller hydrated diameter when compared to chloride ions.

Meierkord *et al*. also proposed bromide's ability to suppress epileptic seizure activity was unlikely due to any inhibition of carbonic anhydrase, in contrast to Woodbury's description that bromide inhibits the activity of carbonic anhydrase, which subsequently results in intracellular acidosis (Woodbury and Penry, 1982). Meierkord also demonstrated bromide has direct cellular membrane action through its suppression of all epileptiform activity resulting from experimental low-calcium-induced epileptiform activity and low-magnesium activation of *N*-methyl-D-aspartate (NMDA)-type glutamine receptors (Meierkord *et al*., 2000). Through the collection of these experiments, bromide has been shown to be one of the most broad-spectrum antiseizure medications. However, as with much benchtop research, translation into clinical practice has been less than ideal owing to its narrow therapeutic window in some patients.

Pharmacokinetics

Bromide has an oral bioavailability of 46% and reaches peak serum concentration within 30–45 min after oral dosing in dogs (Trepanier and Babish, 1995a). The significantly lower bioavailability of bromide in dogs compared to humans (approximately 96% in humans) may be the reason why dogs are more tolerant to its effects. The daily dose estimated to reach serum therapeutic concentrations of 1–2 mg/ml is 21–30 mg/kg/day (Schwartz-Porsche and Jürgens, 1991; Trepanier and Babish, 1995a). A dose of 30 mg/kg *every 12* h will attain a serum concentration that averages 2.4 mg/ml (March, 2002). Bromide reaches all body tissues at equilibrium similar to chloride although concentrations in the CNS and muscles are lower than in other tissues. Bromide is transported out of the CNS through the choroid plexus. The Vd of bromide is reported to be 0.3 l/kg (Podell and Fenner, 1993) to 0.45 l/kg (Trepanier and Babish, 1995a). Bromide is primarily eliminated through the kidneys, although it may also be excreted in other fluids (e.g., saliva, nasal and conjunctival secretions, sweat, and feces). The liver does not metabolize bromide. It is reabsorbed in the renal tubules where it competes with chloride. The half-life of bromide is reported to be between 15 and 45 days, and consequently, time to steady state may be several weeks to several months (Trepanier and Babish, 1995a; March *et al*., 2002).

Toxicity, Side Effects, and Interactions

Bromism, or bromide toxicosis, results from the ingestion of toxic doses of bromide or bromide-containing compounds. A thorough review of the literature regarding the safety of bromide in dogs is available (Baird-Heinz *et al*., 2012). The most common side effects observed with bromide therapy are typically seen when the serum concentration approaches or is greater than 3.0 mg/ml; however, toxic reactions may also occur at much lower levels. Side effects typically result from the antiseizure effects of the compound and include sedation and ataxia. These side effects are usually dose dependent and reversible through titration of the medication. Additionally, more frequent monitoring of serum levels is associated with a lower risk of the development of toxicity (Rossmeisl and Inzana, 2009). A slight reduction in bromide may result in an attenuation of side effects (25% reduction typically), although it is important to remember and advise the caretaker the side effects may take several weeks to resolve owing to bromide's long half-life. Additionally, if being used with another antiseizure medication, a reduction in the adjuvant medication may also result in a reduction of side effects (e.g., phenobarbital reduction).

Hyperexcitability in dogs is occasionally reported by owners and may be the manifestation of "psychosis," which was a commonly reported problem in humans who used the medication.

The psychotic effects of bromide are thought to be potentially due to a reversible reduction in cerebral blood flow (Rossmeisl and Inzana, 2009).

Polyuria, polydipsia, and polyphagia are also common side effects (Podell and Fenner, 1993; Boothe, 1998). If a patient exhibits polyphagia, ask the caretaker about the eating habits, and if the feeding behavior seems a little "psychotic" as in eating drywall, cat litter, socks, etc., you may consider reducing the dose to avoid the possibility of foreign body retrieval surgery. Dogs have been known to die from inappropriate ingestion while taking bromide.

Tetraparesis, paraparesis, cranial nerve deficits, cerebellar ataxia, anisocoria, and generalized lower motor neuron signs have been reported in dogs receiving bromide therapy (Rossmeisl and Inzana, 2009; Steinmetz *et al*., 2012). It is suspected that the action potentials of peripheral nerves are reduced because of bromide in hyperpolarizing the neuronal membranes. This may lead to a dose-dependent reduction in the conduction of the peripheral nervous system. Changes in electrodiagnostic evaluation including reduced conduction velocity, alteration of brainstem auditory evoked potentials, EMG changes, and histopathological changes in muscles and nerves have been demonstrated (Rossmeisl and Inzana, 2009; Steinmetz *et al*., 2012). Clinical signs would be expected to resolve with a reduction of the medication. Most patients who present with possible bromide intoxication have a normal neurological exam, although they demonstrate a mild to moderate truncal ataxia.

Pancreatitis has been reported with combination therapy of bromide and phenobarbital (Schwartz-Porsche and Jürgens, 1991; Gaskill *et al*., 2000). Pancreatitis may be due to inappropriate garbage ingestion (Podell and Fenner, 1993). Pancreatitis has also been proposed to be more likely to develop with increased triglycerides induced by bromide (Kluger *et al*., 2008). Vomiting may be secondary to gastric mucosal irritation of the hyperosmolar compound or as an initial clinical indication of impending pancreatitis. Gastric irritation may be overcome through the use of a bromide *solution*. Dosing twice a day *and with* food may also reduce the chance of gastric irritation. The osmolality of the solution may be reduced through a less concentrated preparation. Solutions of 250 mg/ml of potassium bromide are generally well tolerated. Sodium bromide is reported to have potentially less GI side effects (Boothe, 1998). The possibility for the development of pancreatitis with any novel medication should always be a concern; however, a comprehensive review of the literature regarding bromide therapy could not find substantial evidence to support a link between the development of pancreatitis and the bromide therapy (Baird-Heinz *et al*., 2012).

Pruritic skin lesions may occur in dogs treated with bromide and are more commonly associated with dogs that have a history of pruritus (Boothe, 1998; Chandler, 2011). Panniculitis, secondary to potassium bromide therapy has also been reported in dogs (Boynosky and Stokking 2014). The "bromide rash" commonly observed in people is less common in veterinary patients. Skin lesions are reported as a pustular dermatitis or white macules with scales. If suspected, short courses of anti-inflammatory doses of corticosteroids may alleviate signs while the dose of bromide is adjusted. Of course, ruling out other possible causes of skin disease is necessary. An ulcerative, neutrophilic dermatitis, like human *bromoderma* has been reported in a dog who was treated with potassium bromide for idiopathic epilepsy (Dedola *et al*., 2022). The clinical sign resolved within 6 weeks of stopping therapy.

Cats treated with bromide have an increased risk of developing lower airway disease (Platt, 2001; Wagner, 2001; Boothe *et al*., 2002; Bertolani *et al*., 2012). A nonproductive cough and/or dyspnea may develop months after starting therapy; however, clinical signs may develop anytime following the initiation of therapy and are not dose dependent (Boothe *et al*., 2002). It is suspected the disorder is due to an allergic reaction or hypersensitivity to the medication. Bronchoalveolar lavage showed high eosinophil counts (Wagner, 2001). The most common form of respiratory disease in cats is feline bronchial asthma. Eosinophilic inflammation is a common feature of this condition. A possible link between the use of bromide by eosinophils to form oxidants and subsequent cytotoxicity to pulmonary tissue has been made, potentially explaining the propensity

for cats to develop this complication of bromide therapy (Baird-Heinz *et al*., 2012). Histologic changes include emphysema, thickened bronchiolar walls, granulomatous inflammatory infiltrates, alveolar exudate, and necrosis (Bertolani *et al*., 2012). The clinical signs associated with the lower airway disease resolve in the majority of cases once bromide therapy is discontinued; however, fatalities have been reported and some cats continued to have a nonproductive cough despite having their bromide discontinued. Chronic steroid administration may also be necessary to control the cough. Because of this potential complication, the effectiveness of phenobarbital in treating cats with epilepsy with few side effects, and the newer antiseizure medications that seem to be well tolerated in cats, *bromide is not recommended for use in cats*.

Bromide and chloride compete for renal tubular reabsorption through an active transport mechanism (Rauws and Van Logten, 1975). High levels of dietary chloride (ammonium chloride or sodium chloride) will *enhance* the elimination of bromide potentially leading to loss of epileptic seizure control (Trepanier and Babish, 1995a). Diets containing increased levels of chloride, primarily for the management of crystalluria, may potentially lead to increased bromide excretion and loss of seizure control (Shaw *et al*., 1996; Kriechbaumer *et al*., 2022). However, even routine, maintenance veterinary diets may contain variable amounts of chloride (Trepanier and Babish, 1995b). Rapid changes in routine diets should be avoided in patients receiving bromide therapy. Less common but possible, ingestion of salt water (i.e., seawater, spa, or pool water) may also lead to increased excretion of bromide. Pool or spa water treated with bromide-containing solutions may lead to signs of bromism (even in animals not taking bromide). Conversely, low levels of dietary chloride may lead to increased absorption of bromide and subsequent toxicosis (Fantinati *et al*., 2021). Dogs being fed a homemade diet with inappropriate salt content may experience either increased retention of bromide (low salt diet) and toxic signs or increased excretion of bromide (high salt diet) and loss of seizure control. Renal disease may result in bromide toxicosis due to reduced glomerular filtration of bromide (Nichols *et al*., 1996). Bromide elimination may be artificially increased, in cases of toxicosis, either through administration of chloride-containing fluids (e.g., 0.9% NaCl lactated Ringer's) or diets high in chloride content (Fukunaga *et al*., 2018). Typically, saline diuresis alone will result in the reversal of clinical signs associated with bromide toxicity within 48 h of the institution of fluid therapy. With intractable cases of toxicosis, elimination of bromide may also be enhanced using loop diuretics (e.g., furosemide). The clinician should use diuresis carefully, as serum concentration of bromide may drop dramatically leading to increased seizure activity *and* small decreases in serum bromide concentration often result in resolution of clinical signs associated with toxicosis, without affecting seizure control. Additionally, in a situation where fluids are necessary (i.e., surgery) but the clinician does not want to enhance bromide clearance, the Fukunaga paper demonstrates that this could be achieved through a careful selection of various fluids.

Regarding endocrine function, bromide does not affect serum total thyroxine, free thyroxine, TSH, or tri-iodothyronine (Kantrowitz *et al*., 1999; Paull *et al*., 2003). It has been recommended that dogs with *hypo*adrenocorticism be treated with sodium bromide rather than potassium bromide to help maintain normal potassium homeostasis (Podell, 1998). Bromide will artificially increase serum chloride measurement. This is an *artifact* as most analytical equipment cannot distinguish the two halides.

Indications for Use

Potassium bromide is conditionally approved by the USA FDA for the control of seizures associated with idiopathic epilepsy in dogs. The availability of potassium bromide (KBr), coupled with an efficacy that approaches that of phenobarbital (~60–70%) for the monotherapeutic control of seizures and the minimal side effects associated with long-term treatment with the drug, make it a good candidate for initial therapy in animals which do not require acute cessation of seizures (such

as those in status as discussed previously). Bromide would also be a good add-on antiseizure medication for those patients who might have compromised liver function (Royaux *et al*., 2017). Bromide would be a good choice for owners of pets who might have difficulty with compliance of dosing more than once a day. Because of its long half-life, missing a dose or two will not significantly alter serum concentrations. Bromide can be used rectally, if in solution, for patients who may not be able to take oral medication but where it is desired to maintain therapeutic serum concentrations. Because of potential complications associated with rapid infusion of large amounts of potassium, *intravenous use of potassium bromide is not recommended*. A sodium bromide infusion is acceptable; however, care must be taken to ensure a sterile preparation is given. The need for IV use should be questioned, as either the rectal administration (to maintain serum concentration during long periods of time whereby oral administration is not possible) or skipping doses for short periods of time may be acceptable alternatives to the need for an injectable form.

Dose

The content of bromide relative to each salt (sodium or potassium) is not the same. The sodium form contains approximately 10% more bromide than the potassium form (77.7% for sodium and 67.2% for potassium) (Frey, 1989). To create equal solutions of bromide, a concentration of 211 mg/ml of NaBr would be used compared to 250 mg/ml of KBr (Boothe, 1998). Bromide should be titrated to effect; however, a recommended starting dose as a monotherapy is 20–30 mg/kg every 12 h. If using in addition to another antiseizure medication, start with a dose of 15–20 mg/kg every 12 h. The disposition of bromide will be slightly different for each dog; however, a target serum concentration of 1.5–2.0 mg/ml would be expected when dosed at 20–30 mg/kg once a day. A dose of 20–30 mg/kg given every 12 h will more likely result in a serum concentration above 2.0 mg/ml. The actual dose the patient receives is not as important as the plasma concentration. It may take many months to reach steady state. It is recommended to give the medication twice a day and to give it with food to prevent GI side effects (vomiting/anorexia). Additionally, liquid forms of bromide may also help prevent GI upset. If tolerated, the total daily dose can be given once a day (40–60 mg/kg/day).

To achieve a more rapid serum therapeutic concentration, an oral loading dose of bromide can be given. A dose of 45–60 mg/kg every 12 h for 5 days should result in a plasma concentration of 1–1.5 mg/ml. This must also be given *with* the calculated daily maintenance dose (20–30 mg/kg every 12 h) (Boothe, 1998). Therefore, the total daily dose for the first 5 days would be 65–90 mg/kg every 12 h. This dose is approximately 600 mg/kg given over 48 h which has been shown to result in serum levels in the low end of the therapeutic range (Gindiciosi *et al*., 2014). Patients may be temporarily groggy and ataxic at this dose. The author typically gives 15 of the calculated maintenance doses over 1–2 days and then begins the every 12 h maintenance dose. This usually prevents ataxia and GI side effects; however, if they do occur, they usually resolve within a few days of reducing to the maintenance dose. While a target therapeutic range of 1–3 mg/ml is the goal, the level can be increased beyond 3 mg/ml to achieve better epileptic seizure control (dose to effect or to side effect). Some patients may experience toxic side effects even at low plasma concentrations. For an example of a potassium bromide dose calculation, see Table 7.3 or Appendix 3.

Bromide is available in 250 and 500 mg chewable tablets (liver-flavored K-BroVet® with B12 vitamin) and as a 250 mg/ml oral solution (butterscotch-favored K-BroVet® with B12 and B6 vitamins).

Monitoring

It is recommended to measure serum medication levels 1 month after starting therapy. Theoretically, the concentration should be halfway to its steady-state point, although this may vary significantly from patient to patient. At this time, adjustments may be made depending on where the patient is and what the target therapeutic concentration is, as well as, if the patient is beginning to show any signs of toxicity (negative but *reversible* side effects). Dogs monitored on a routine basis

Table 7.3 Potassium bromide dosing example.

The *loading* dose for potassium bromide in the dog is ~15 rapidly given maintenance doses. If used as a monotherapy, begin with 30 mg/kg every 12 h by mouth. If used in combination with phenobarbital, initially give 20 mg/kg once a day. The dose range is anywhere from 15 mg/kg once a day to 80 mg/kg once a day. The drug is only given in divided doses to alleviate some of the gastric irritation that may be present. If tolerable, the entire daily dose can be given at once (with food). Remember, it is not the actual dose the animal gets but the serum concentrations that the animal attains which is important.
A loading dose of 400–600 mg/kg can be given. Typically, the maintenance dose will be figured followed by an appropriate loading dose of the same capsule size that can be given over several days. For example:
A 20 kg dog would need (30 mg × 20 kg = 600 mg every 12 h) as a maintenance dose. A loading dose would be in the range of 8,000–12,000 mg (400–600 mg × 20 kg).
If 600 mg capsules are obtained, then the loading dose would be 14–20 capsules (8,000/600 = 13.3 capsules, 12,000/600 = 20 capsules).
The loading dose can be given as quickly as possible as long as there are no adverse side effects, usually 1–2 capsules every 4–6 h until the loading dose is achieved, followed by the maintenance dose 12 h after the last portion of the loading dose.
In the above example, the maintenance dose would be 600 mg every 12 h. The same dose or capsules can be used for the loading dose. Regardless of the capsule size calculated for the maintenance dose, if you give 15 "maintenance" doses over a short period of time (1–2 days), you will have *loaded* the patient (easy-peasy).

are much less likely to develop bromism compared to those with an increased monitoring interval (Rossmeisl and Inzana, 2009). Once a target steady state has been achieved and the patient is on a maintenance dose, serum levels should again be checked at 120 days (4 months after starting therapy) and routinely no less than every 6 months (Podell and Fenner, 1993). Serum levels should be checked anytime there is a loss of seizure control or the development of suspected toxicity secondary to bromide use. If a loading dose has been given, serum levels should be checked following the loading dose and then at 1 month after the loading dose. The 1-month sample should be close to the immediate post-loading dose sample. If it is not, the dose can be adjusted up or down to achieve the desired therapeutic drug concentration (see formula in Table 7.2). If a patient has compromised renal function, routinely takes a loop diuretic (e.g., furosemide), or is on a diet with altered chloride concentration (i.e., to dissolve urinary bladder stones or prevent crystalluria), serum monitoring of bromide concentration should be more routine. Once a steady state is achieved, a CBC, biochemical profile, urinalysis, and serum bromide concentration should be monitored every 6 months. These tests may help to predict future necessary changes in bromide dose and screen for impending comorbidities, which could affect the disposition of bromide in the patient. This is particularly important considering some of the "accepted" side effects of bromide (e.g., polyuria, polydipsia) may also mimic significant diseases (e.g., renal disease, endocrine disease). Pet owners should also watch closely for skin issues such as pruritis and pustules. As with all antiseizure medications, the effectiveness of the therapy should be based on clinical examination and history of seizure control as opposed to serum medication concentration. It cannot be overemphasized the individual response to a medication can vary considerably within the population. The clinician should use the published reference range of the medication as a guide only. Laboratory measurement of bromide should be with spectrophotometry and not an ion-selective probe (Boothe, 1998).

TOPIRAMATE (TPM) (TOE-PIE-RAH-MATE)

Topiramate was introduced and approved as an antiseizure drug in the USA in 1996. Additionally, it may have potential to act as a prophylactic in preventing migraine headaches and tremors in humans. Topiramate is marketed under the brand name *Topamax*®, Qudexy *XR*®, and

Trokendi XR®. It is also available in generic forms. Topiramate is available in both normal-release and extended-release forms, an oral solution and in an injectable form. Originally developed as a fructose-related analogue with hypoglycemic activity to help with obesity, it was discovered to have antiepileptic activity (Engel, 2013). Very little is known about its disposition in dogs and cats; however, anecdotal reports and individual experience have shown it to be well tolerated, safe, and efficacious in treating pharmacoresistant epilepsy and for use in patients who may not tolerate other more commonly used antiseizure medications.

Mechanism of Action

Topiramate has five principal mechanisms of action, which may act to inhibit epileptic seizures. The actions of topiramate include:

- Inhibition of voltage-activated sodium channels in a dose-dependent manner
- Increasing the opening of GABA-mediated chloride channels
- Increase of GABA content in the brain
- Decrease of glutamate-mediated excitatory neurotransmission through interaction with the kainate and AMPA receptors
- Modulation of calcium current through a direct effect on L-type voltage-sensitive calcium currents

Topiramate may also facilitate potassium channel function, thereby enhancing inhibitory effects. Finally, topiramate has weak carbonic anhydrase activity, although this action is thought to be more important in the creation of kidney stones in humans rather than in preventing epileptic seizures.

Topiramate inhibits cortical spreading depression in cats. Cortical spreading depression is a reduction of spontaneous electrical activity of the cerebral cortex, which is apparent in experimental forms of epilepsy and is thought to be the cause of neurological signs associated with the aura experienced prior to migraine headaches in humans (Leao, 1944; Akerman and Goadsby, 2005). The action of topiramate on AMPA receptors (antagonism) may also help reduce epileptic seizure spread and therefore reduce the possibility of seizure-induced excitatory neurotransmitter brain damage (Dingledine *et al*., 1999).

Pharmacokinetics

The reference range for effective seizure control in humans is 5–20 µg/ml. The bioavailability of topiramate in the dog is dependent on the form ingested, with the oral *solution* being 2× more bioavailable than capsules. The time to peak plasma concentration following oral dosing in the dog is 0.6–3.8 h with a bioavailability being 27–59% depending on the form from which it was given (Streeter *et al*., 1995). Although in another study, the bioavailability ranged from 61 to 102% (Vuu *et al*., 2016). The study by Vuu investigated the possible use of the injectable form of topiramate to treat SE. The group found that an IV bolus of topiramate given over 5 min at 20 mg/kg would achieve serum concentration at the high end of the reference range (20–30 µg/ml) by 30 min post-injection (using a simulation model). They also found if a dog was being treated with an enzyme-inducing co-medication (e.g., phenobarbital, primidone, phenytoin, or valproic acid), a dose increase to 25–30 mg/kg over 5 min was necessary to achieve the same reference values. Topiramate has low plasma protein binding and Vd similar to total body water. It does not appear to result in autoinduction or inhibition of liver enzymes. In humans, it is highly metabolized with metabolic by-products being found in the urine, bile, feces, and plasma. In humans, about 70% is excreted unchanged in the urine.

The half-life of topiramate in dogs is approximately 3 h (Streeter *et al*., 1995). In regards to cats, at a dose of 10 mg/kg once a day for 30 days, using the extended-release form (opened capsules

and sprinkled on cat food), a study group of cats was able to maintain desired serum concentrations (Graham *et al*., 2023). The half-life in this small group of cats ranged from 8 to 24 h. In cats, as in dogs and humans, topiramate demonstrated linear kinetics. No obvious, clinically noticeable side effects were observed, however, 4 of the 10 cats developed subclinical anemia.

Toxicity, Side Effects, and Interactions

Very little data is available on the toxicity, side effects, and interactions of topiramate in dogs and cats. In humans, 1–2% of patients will develop kidney stones, thought to be due to the weak inhibition of renal tubular carbonic anhydrase activity by topiramate which causes urine alkalinization and possibility of the formation of uroliths. Other common human side effects include weight loss, fatigue, double vision, dizziness, and tremor. Most side effects are dose related.

In dogs, GI distress, anorexia, and anxiety/irritability are reported, as well as, facial rubbing, and chewing on the digits, although in another study no negative side effects were noted (Plessas *et al*., 2015; Vuu *et al*., 2016). In cats, the most common side effects are anorexia and sedation. It should be used with caution in patients who have urinary bladder stones and crystalluria, particularly if the crystals are calcium phosphate. In a small number of cats given extended-release topiramate for 30 days, 4 out of 8 cats developed subclinical anemia (not a side effect reported in humans or dogs) (Graham *et al*., 2023). Additionally, the cats in the Graham study showed a significant *reduction* in intraocular pressure, postulated to be due to inhibition of the carbonic anhydrase II isoenzyme (present in the ciliary body, from which inhibition may lead to reduced production of aqueous humor). Based on this finding, they recommend periodic monitoring of IOP in cats.

Serum topiramate levels may increase when used with amitriptyline and propranolol and it should be used with caution with other carbonic anhydrase inhibitors (e.g., acetazolamide) and other CNS depressants. Using enzyme-inducing drugs such as phenobarbital, primidone, phenytoin, or valproic acid concurrently with topiramate may lead to reduced topiramate levels (Plumb, 2011; Engel, 2013). When given to dogs also being treated with phenobarbital, the clearance rate of topiramate was increased ~5.6× and the T½ was reduced significantly (from 3.7–5 to 0.5–1 h) (Vuu *et al*., 2016). This study suggests an IV dose of 20 mg/kg for dogs not receiving concurrent phenobarbital and 25 mg/kg for those who are treated with phenobarbital in order to achieve a serum concentration between 20 and 30 µg/ml (for the possible control of SE). With oral dosing the amount of topiramate may need to be increased if given concurrently with phenobarbital. Phenobarbital is an inducer of cytochrome P3A4, which is the main enzyme necessary for the metabolism of topiramate. Topiramate increases clearance of digoxin in humans and may have similar effects in veterinary patients.

Indications for Use

Topiramate is a broad-spectrum antiseizure medication in humans. Topiramate may be used as a primary prophylactic antiseizure medication in dogs and cats when more traditional drugs have failed or are not tolerated. It is generally considered a third-tier option for dogs and cats. It may also be used as an add-on medication for refractory and pharmacoresistant epileptics. In humans, topiramate is also used to treat neuropathic pain. Early investigation suggests topiramate may be useful as an IV bolus to stop SE, given its multiple mechanisms of action and ability to reach serum reference values after IV injection in dogs (Vuu *et al*., 2016).

Dose

For dogs, start with a dose of 2.5 mg/kg every 12 h and titrate to effect up to 10 mg/kg every 12 h. If tolerated, further incremental increases can be made but generally consider the medication ineffective at 15–20 mg/kg every 12 h. The medication may need to be dosed every 8 h to maintain serum therapeutic concentrations.

For cats, begin with a dose of 12.5–25 mg (total dose) every 8–12 h. Watch closely for anorexia, which commonly develops at higher ends of the dose (Podell, 2008). Topiramate is available in 25, 50, 100, and 200 mg tablets. It is also available as a 15 and 25 mg capsule and in an extended-release form in 25, 50, 100, 150, and 200 mg capsules. Topiramate is available as an oral solution at a concentration of 25 mg/ml. Because the experience of its use is limited, warn clients to pay particular attention to negative side effects.

The extended-release capsules (Qudexy *XR*®) may be opened and sprinkled on a cat's food. It is suggested a dose of 10 mg/kg every 24 h may achieve therapeutic serum concentrations (Graham *et al*., 2023). An injectable form of topiramate is not commercially available at this time.

Monitoring

Serum therapeutic levels for humans are 5–20 µg/ml. This is a suggested target range for dogs and cats. Monitor for efficacy and safety. It is recommended to routinely monitor blood work and urine, especially for crystalluria in dogs and cats and anemia and decreases IOP in cats.

ZONISAMIDE (ZON) (ZOE-NIS-AHH-MIDE)

Zonisamide is a newer antiseizure medication approved for use in the USA in 2000 and is marketed under the proprietary name of *Zonegran*®. It is also available as a generic. It is a sulfonamide-based drug. It is used to treat epileptic seizures in dogs and cats as either a first-line therapy or an add-on therapy due to its apparent effectiveness and minimal side effects. An additional consideration is the ability to dose every 12 h in dogs, thereby improving compliance (every 24 h in cats). Although, from a literature analysis regarding evidence of effectiveness and safety, it is considered a fourth or fifth-level choice as first-line therapy after imepitoin, phenobarbital, potassium bromide, and levetiracetam in dogs (Charalambous *et al*., 2014; Podell *et al*., 2016). As in dogs, analysis of the literature shows it to be considered a fourth or fifth-level choice for cats (Charalambous *et al*., 2018). Zonisamide was initially approved in Japan as a human anticonvulsant in 1989, over a decade prior to its approval in the USA and Europe. This may explain why it is the most commonly prescribed anticonvulsant for dogs and second most prescribed (after phenobarbital) for cats in Japan (Mizuno *et al*., 2022). Zonisamide was the first anticonvulsant approved for use in dogs in Japan (in 2014). While the literature base of zonisamide may not lend it to be recommended as a first-line treatment, this is changing with more recent studies showing its effectiveness for dogs and cats as either a monotherapy or add-on medication. Its safety profile makes routine plasma concentration monitoring unnecessary. However, as will be discussed under the toxicity, side effects, and interactions section, patients' bloodwork and demeanor should be closely monitored. Many clinicians in the USA and Europe are using zonisamide as a first-line antiseizure medication over the more commonly used phenobarbital and potassium bromide both because of its efficacy and safety profile. Multiple pill sizes, also make it convenient to dose smaller-sized patients. Zonisamide is not a controlled substance.

Mechanism of Action

While the exact mechanism of zonisamide is unknown, its broad-spectrum antiseizure activity is thought to be due to its antagonism of voltage-gated sodium channels and T-type calcium channels in the thalamus and inhibition of potassium-mediated glutamate release. These actions result in a reduction of transient inward currents leading to the stabilization of neuronal cellular membranes. Zonisamide may prevent neuronal hypersynchronization. Additionally, it accelerates the hippocampal release of GABA and may possess *neuroprotective* actions (Biton, 2007). Furthermore, it has weak carbonic anhydrase activity, which may result in extracellular acidosis with subsequent inhibition of epileptiform activity, although this action is not thought to be an important consideration. Zonisamide, through inhibition of potassium-mediated glutamate release, also

increases extracellular levels of dopamine and serotonin. Increased serotonin levels may account for the side effects of anorexia, which are anecdotally reported and apparently dose dependent.

Pharmacokinetics

Zonisamide has an oral bioavailability in dogs of about 70% and is thought to be similarly well absorbed in cats. Zonisamide is approximately 40% bound to plasma proteins and has a half-life of approximately 17 h in dogs (Boothe and Perkins, 2008). Steady state is achieved within 3–4 days of dose initiation in dogs (Fukunaga *et al*., 2010). As the dose is increased (i.e., from 5 to 10 mg/kg), the time to a new steady state across all dose increases, up to 30 mg/kg, was approximately 4–5 days in dogs (Fukunaga *et al*., 2010). The half-life in cats is approximately 33 h, resulting in a time-to-steady state of approximately 7–10 days (Hasegawa *et al*., 2008). Following absorption, zonisamide reaches peak serum concentrations in dogs at about 2.5 h and at approximately 4 h in cats (Boothe and Perkins, 2008; Hasegawa *et al*., 2008).

Zonisamide is partially metabolized by the liver (approximately 20% in dogs) through conjugation with glucuronide in dogs and cats but has no cytochrome P450 enzyme induction. Zonisamide is excreted in the urine (up to 83%) and feces with approximately 70% of the drug being excreted in the urine as metabolites of zonisamide (Boothe and Perkins, 2008). The half-life is longer in cats, likely due to their natural deficiency in glucuronyl transferase when compared to dogs (Wilcke, 1984). This allows for once-a-day dosing in cats (Hasegawa *et al*., 2008).

Serum therapeutic values are not reached when zonisamide is administered rectally (Brewer *et al*., 2015; Michaels *et al*., 2016).

Toxicity, Side Effects, and Interactions

Side effects that are commonly reported include vomiting, ataxia, sedation, and reduced appetite. These side effects are mild and reversible (Type A). More idiosyncratic and often fatal reactions have also been reported (Type B) (Table 7.4). A concern often arises regarding the safety of

Table 7.4 Reported zonisamide abnormalities.

Hepatic disease
Blood dyscrasia
Skin eruptions
Erythema multiforme
Keratoconjunctivitis sicca
Arthropathies
Renal tubular acidosis
Immune-mediated polyarthritis
Anterior uveitis
Abnormal behavior
Lymphadenopathy
Hyperglobulinemia
Leukopenia
Neutropenia
Lymphopenia
Anemia
Behavior changes

zonisamide, in particular, in regards to the liver. A retrospective, multicenter study found the incidence of hepatotoxicosis to be less than 1% in treated dogs (with one euthanasia reported due to liver failure) (Smith *et al*., 2022). A case of acute, idiosyncratic, fatal hepatic necrosis has been reported in a dog receiving zonisamide at a dose of 7.7 mg/kg PO for 10 days (Miller *et al*., 2011). The presentation and progression were like hypersensitivity reactions of humans and dogs to sulfonamide antibiotics (Trepanier *et al*., 2003). These clinical signs characteristically are fever, skin eruptions, hepatotoxicity, blood dyscrasias, keratoconjunctivitis, and arthropathies in dogs, usually developing within 10 days (but up to 45 days) after initiation of therapy. In a similar case, clinical and biochemical signs of hepatotoxicity developed 21 days after initiation of zonisamide for the control of epileptic seizures in a dog. Zonisamide was discontinued, liver values were normalized, and the affected dog recovered completely (Schwartz *et al*., 2011). A fatal case of hepatocellular necrosis has also been reported in a dog receiving zonisamide for 1 year (Takami *et al*., 2020). Clinicians and pet owners should also watch for common sulfonamide-related drug reactions such as erythema multiforme and keratoconjunctivitis sicca, which have also been reported in dogs treated with zonisamide (Dewey *et al*., 2004; Ackermann *et al*., 2015; Tanaka *et al*., 2021). Renal tubular acidosis has been reported in humans and dogs, secondary to zonisamide therapy (Cook *et al*., 2011; Itoi *et al*., 2022). The mechanism for the acidosis is suspected to be due to the acetazolamide—like activity of a sulfonamide side chain of zonisamide. Dysfunction of metabolic pathways involving proton secretion in the renal tubules is suspected to be due to this acetazolamide activity of zonisamide (Itoi *et al*., 2022). Zonisamide should be used with caution if concurrently used with carbonic anhydrase inhibitors. Immune-mediated polyarthritis and anterior uveitis have also been reported in a dog, who was treated with zonisamide. Clinical signs resolved after stopping the medication (Baya *et al*., 2024).

Abnormal behavior episodes related to zonisamide therapy (which resolved after discontinuation) consisting of sudden rage/aggression, insomnia, restlessness, and/or incessant attention-seeking behavior have also been reported in dogs (Kanazono *et al*., 2021). "Psychotic" episodes have been reported in humans (Miyamoto *et al.,* 2000).

A cat was reported to suffer from zonisamide-related hypersensitivity syndrome (generalized lymphadenopathy, hyperglobulinemia, neutropenia, lymphopenia, anemia (Collinet and Sammut, 2017). Zonisamide should be used with caution in animals with a known sensitivity to sulfonamide drugs, however, Plumb's online formulary states, "zonisamide is unlikely to cause keratoconjunctivitis sicca or other sulfonamide-related adverse effects in dogs or cats." The *possibility*, however, is always one of the author's concerns.

In humans and dogs, zonisamide may lower circulating thyroid hormones (T4 and T3) (Boothe and Perkins, 2008). This may be due to a similar mechanism whereby *sulfonamide-based* drugs affect serum thyroid hormone levels through inhibition of thyroid peroxidase (Hall *et al*., 1993; Bolton and Panciera, 2023).

Adverse side effects reported include sedation, ataxia, and anorexia. Most side effects resolve with a dose reduction or are transient, resolving within a few days of either initiating therapy or decreasing the dose. Most side effects are reported at doses up to 10 times the initial starting dose, although idiosyncratic reactions are certainly possible.

When used in conjunction with phenobarbital, the clearance of zonisamide increased, resulting in lower serum peak concentrations, shortened half-life, and reduced bioavailability of zonisamide (Orito *et al*., 2008). This effect persisted for up to 10 weeks following the withdrawal of phenobarbital. No change in liver values was observed in a long-term study evaluating the use of zonisamide as add-on to phenobarbital in 11 dogs, although liver function tests were not measured (von Klopmann *et al*., 2007).

In 9/10 dogs being treated with phenobarbital, serum phenobarbital concentrations increased following the addition of zonisamide despite no increase in phenobarbital dose (Mahon *et al*., 2024). In 5 of the 9 dogs, who showed an increased in phenobarbital serum concentrations, trough levels

were >35 µg/ml. This effect is hypothesized to be due to zonisamide's effect of decreasing cytochrome P450 activity leading to a decreased metabolism of phenobarbital, however, in the Mahon study only 1/2 of the evaluated dogs (5/10) had an increase in phenobarbital half-life. It is recommended phenobarbital dose should be *decreased* by 25% if used concurrently with zonisamide (Podell, 2013). Additionally, if used with phenobarbital, the starting dose of zonisamide should be increased to 7–10 mg/kg every 12 h (Bhatti *et al.*, 2015). Functional tolerance to zonisamide may develop; however, this effect is not well documented.

Because little information is known regarding the possible long-term treatment side effects in dogs and cats, a vigilant owner and veterinarian must accompany treatment with this and all new antiseizure medications.

Indications for Use

In humans, zonisamide is thought to be helpful for the control of generalized absence seizures, as well as focal onset seizures, due to its interaction with T-type calcium channels in the thalamus (Engel, 2013). Zonisamide is indicated to treat all forms of canine and feline epilepsy either as a primary antiseizure medication or an add-on medication. Much of the initial experimental work looking at the effectiveness of controlling epileptic seizures was performed on an experimentally kindled model in cats.

Zonisamide as an add-on (10 mg/kg PO every 12 h) to phenobarbital therapy was effective in 9 out of 11 dogs, in reducing seizure frequency and, to some degree, intensity, by up to 70% (von Klopmann *et al.*, 2007). These results are similar to another study, which looked at zonisamide as an add-on therapy for dogs with genetic (primary or idiopathic) epilepsy (Dewey *et al.*, 2004). When used as a monotherapy, there was a 60% favorable response in dogs dosed up to 10 mg/kg PO every 12 h (Chung *et al.*, 2012). In the report by Chung, the average serum concentration for the responders was approximately 15 µg/ml. A greater response may have been achieved with an increase in dose. Saito *et al.* showed zonisamide treatment as a monotherapy resulted in 76% of the study participants having a ≥50% reduction in seizure frequency and 55% of the participants achieving seizure freedom with minimal side effects (Saito *et al.*, 2024).

Studies on its efficacy related to cats show it is effective in suppressing paroxysmal discharges in Familial Spontaneous Epileptic cats (Ukai *et al.*, 2018). Retrospective studies of the use of zonisamide either as a monotherapy or add-on in cats, showed a 56% to 77% response rate (similar to dogs) and was well tolerated with minimal side effects mostly related to gastrointestinal issues, which were reversible (Yoshida *et al.*, 2023; Djani *et al.*, 2024).

Zonisamide is recognized to be helpful in treating tremors in humans. Tremors due to stroke, degenerative disease (e.g., Parkinson's disease), and essential (benign or senile) tremors may be attenuated with zonisamide treatment (Sadeghi and Ondo, 2010; Suda *et al.*, 2012). The effects of tremor suppression are thought to be mediated through the block of T-type calcium channels (Miwa and Kondo, 2011). The author uses a standard dose of 10 mg/kg every 12 h and has observed positive results in ameliorating (though not eliminating) benign tremors in dogs, in particular, senile tremors. Zonisamide may help reduce the clinical signs associated with paroxysmal dyskinesia.

Dose

For monotherapy, a starting dose of 3–7 mg/kg PO every 12 h is recommended for dogs, and if used concurrently with phenobarbital, it is recommended to increase the starting zonisamide dose to 7–10 mg/kg every 12 h (Bhatti *et al.*, 2015). The dose may be gradually increased to effect or side effect, however, once 20 mg/kg every 12 h is reached, further increases in dose are not likely to be helpful for the control of epileptic seizures, and the potential for negative side effects becomes even greater. Because of its high degree of safety, dose increases are warranted in non-responders. At a

dose of 10 mg/kg PO every 12 h in dogs, all patients had serum concentrations of zonisamide within the reference range (von Klopmann *et al*., 2007). Similar results were reported at a dose range between 5 and 11 mg/kg PO every 12 h in dogs (Dewey *et al*., 2004). At increasing doses, the plasma concentration of zonisamide is reported as 5 mg/kg q 12 h (~12 µg/ml), 10 mg/kg q 12 h (~30 µg/ml), 15 mg/kg q 12 h (~50 µg/ml), and 30 mg/kg q 12 h (~100 µg/ml) (Fukunaga *et al*., 2010).

Cats are initially dosed at 3–5 mg/kg PO *once* a day. The dose may be gradually increased to effect or side effect; however, once 15 mg/kg every 24 h is reached, further increases in dose are not likely to be helpful for the control of epileptic seizures, and the potential for negative side effects becomes even greater. Cats may benefit from every 12 h dosing, if with every 24 h dosing they do not appear to have a beneficial effect.

Zonisamide is available in 25, 50, and 100 mg capsules in generic and proprietary (Zonegran®) forms. Its small pill sizes make it particularly useful as an add-on where the larger pill sizes of levetiracetam would make dosing every 8 h a necessity. Zonisamide would allow the pet owner to dose every 12 h in small patients.

Monitoring

An average peak serum concentration of 55 µg/ml was achieved when dogs were dosed at 10 mg/kg PO every 12 h for 8 weeks (Boothe and Perkins, 2008). Another study showed that zonisamide as monotherapy in dogs with genetic or unknown (idiopathic) epilepsy, at an average dose of 7.5 mg/kg PO every 12 h, yielded an average serum concentration of ~15 µg/ml in the respondents (Chung *et al*., 2012).

When zonisamide was used in dogs at a dose of 10 mg/kg PO every 12 h, *combined with phenobarbital* for 8–28 weeks, the average serum concentration of zonisamide was reported to be 19.2 µg/ml (von Klopmann *et al*., 2007). Similar results were found at a dose range of 5–11 mg/kg PO every 12 h (Dewey *et al*., 2004). The reference range for therapeutic concentration in dogs is 10–40 µg/ml (Dewey *et al*., 2004). If you are chasing the "goldilocks" zone in a dog or cat, where seizures are controlled with no side effects, it would be wise to check levels routinely as there can be significant individual variability. However, another option would be to simply increase the dose to *effect* or *side effect*, along with careful monitoring with routine blood work (but not necessarily therapeutic levels). Be careful about zonisamide side effects. Unlike levetiracetam, the side effects associated with zonisamide have the potential to be significantly more harmful. Therefore, dose increases should be approached cautiously and with careful monitoring. We tend to use the same reference levels for cats.

Baseline CBC, biochemical profile, venous blood gas, and urinalysis are recommended when treatment is initiated and then repeated 1 month later. Routine monitoring of CBC, biochemical profile, and urinalysis is recommended every 6 months if there are no concerns.

NEWER OR LESS COMMON DRUGS

FELBAMATE (FBM) (FEL-BAH-MATE)

Felbamate was originally synthesized in 1954; however, its antiseizure effects were not discovered until the 1980s. It was initially approved for the treatment of various forms of epilepsy in humans; however, due to a high incidence of the development of aplastic anemia, its use in human medicine is limited. It is related (chemically) to the antianxiety drug *meprobamate*. It is available in generic and proprietary forms under the trade name Felbatol®.

Felbamate has been investigated in dogs to treat epileptic seizure disorders; however, the experience in cats is very limited. In general, it is historically expensive, often requires every 8 h dosing (start with q 12 h), and, while considered safe at therapeutic doses, it does have the potential to cause hepatotoxicity in dogs and cats (Dewey *et al*., 2022). Therefore, its use is limited as a

sixth-tier antiseizure medication. Because of its broad-spectrum ability to control seizures, some veterinary neurologists still use it as an add-on medication for the treatment of focal seizures or cases of drug-resistant epilepsy. An additional benefit may be its lack of additive CNS depression (i.e., sedation) when combined with other antiseizure medication.

Mechanism of Action

The exact mechanism whereby felbamate helps to prevent epileptic seizures is unknown. It is thought to antagonize intracellular calcium currents through interaction with the glutamate subtype of the NMDA receptor (GluN2B subunit) and to potentiate $GABA_A$-mediated inhibition similar to the action of barbiturates (Ticku *et al*., 1991; White *et al*., 1992, Hakami, 2021). This results in a reduction of excitatory neurotransmission and an increase in inhibitory neurotransmission.

Pharmacokinetics

Felbamate is well absorbed after oral administration in adult dogs but significantly reduced (by about 30%) in pediatric dogs (Adusumalli *et al*., 1992). About 70% of felbamate is eliminated unchanged by the kidneys, and approximately 10–20% is conjugated and eliminated in the urine (Yang *et al*., 1991). The liver metabolizes the remainder and it is a potent inducer of hepatic microenzymes. The half-life of felbamate in the adult dog is about 6 h and that of the pediatric dog is significantly less at about 2.5 h. However, the half-life may vary from 5 to 14 h (Boothe, 1998; Plumb, 2011). The half-life decreases with time and multiple dosing.

Toxicity, Side Effects, and Interactions

At doses as high as 300 mg/kg/day (10 times the usual starting amount) in dogs, the drug is reported to be safe (Boothe, 1998). Felbamate has the potential to cause liver damage, and this effect may be exacerbated through the concurrent use with phenobarbital (Dayrell-Hart *et al*., 1996; Dewey *et al*., 2022). While generally considered safe in dogs, side effects of sedation, ataxia, GI distress, liver disease, and keratoconjunctivitis sicca have been reported (Ruehlmann *et al*., 2001).

Felbamate levels will usually drop when phenobarbital is added to it. Likewise, when felbamate is added to phenobarbital, serum levels of phenobarbital may increase.

Felbamate may result in aplastic anemia in humans. This complication has *not* been reported in dogs, although blood dyscrasias (thrombocytopenia, lymphopenia, and leukopenia) have been reported (Ruehlmann *et al*., 2001). The safety and use of felbamate in cats have not been established.

Indications for Use

Felbamate has been demonstrated to be efficacious in the treatment of focal seizures in dogs when added to phenobarbital or potassium bromide with few side effects (Dayrell-Hart *et al*., 1996; Ruehlmann *et al*., 2001). Dewey reported felbamate was effective in reducing or eliminating seizures in drug-resistant, presumed idiopathic epileptic dogs (Dewey *et al*., 2022). Five of the six dogs in the retrospective case series showed a 50% or greater reduction of seizures and 3/6 became seizure-free. Some dogs responded to every 12 h dosing and others had their dosage increased to every 8 h. Still, because of limited experience with the drug, expense, limited availability, and the need for 8 h dosing, it is typically reserved for those patients who have failed more commonly used medications (i.e., phenobarbital, imepitoin, potassium bromide, levetiracetam, zonisamide, topiramate, etc.).

Dose

The recommended dose in dogs is 15–20 mg/kg every 8–12 h. The dose is increased by 15 mg/kg increments every 2 weeks until seizures are controlled or a negative side effect is experienced. Doses as high as 70 mg/kg every 8 h may be required to affect epileptic seizures in some dogs and seem to be well tolerated (Thomas, 2010).

Monitoring

Although no established reference range is available for dogs, serum concentrations between 25 and 100 µg/ml are thought to be effective. Steady-state trough serum concentrations between 13 and 55 µg/ml were measured in four dogs considered to benefit from felbamate at doses ranging from 62 to 220 mg/kg/day (Ruehlmann *et al*., 2001).

Monitoring liver values, in particular bile acids (fasting and fed samples), is recommended routinely if dogs are being treated with felbamate. Enhanced vigilance is recommended if being concurrently treated with phenobarbital or any other medications, which induce hepatic microenzymes.

Patients should be monitored for efficacy and side effects, and clients should be warned about the *potential* for serious side effects related to the blood and liver.

KETAMINE (KET) (KEE-TUH-MEEN)

Ketamine is commonly associated with the *induction* of seizures and should be approached very cautiously if its use is considered. Numerous references and veterinary drug formularies express caution when considering the use of this drug in known epileptic patients or those who might be at increased risk of developing seizures (i.e., following myelography). Ketamine is a dissociative general anesthetic commonly used for short surgical procedures, restraint, and analgesia, typically in combination with other agents. Its use often requires intubation. Ketamine is marketed under the trade names *Ketaject*®, *Ketaset*®, *Keta-sthetic*®, *Ketalar*®, *Vetalar*®, and *VetaKet*®. It is also available in a generic preparation. While commonly used as a short-acting anesthetic and induction agent, ketamine may be used for the treatment of *refractory* status epilepticus (SE) (see Chapter 8 and Figure 8.1).

Mechanism of Action

Ketamine is an NMDA receptor *antagonist*. NMDA receptor activation is the primary mediator of CNS excitotoxicity. Experimental models of rodent epilepsy show NMDA receptor activation is associated with increased duration of SE and loss of GABAergic neuronal inhibition (Kapur and Lothman, 1990). The self-sustaining phase of SE is stopped with the use of ketamine in rodent models (Borris *et al*., 2000). Benzodiazepines become *less* effective after a prolonged seizure and NMDA receptor antagonists (i.e., glutamine antagonism), such as ketamine, may be beneficial for a protracted seizure (i.e., SE lasting longer than 20 min) (Kapur and Lothman, 1990; Borris *et al*., 2000; Serrano *et al*., 2006). This is due to the internalization of $GABA_A$ receptors and the external synaptic membrane expression of NMDA receptors in the later stages of SE (Wasterlain and Chen, 2008). Ketamine has also been shown to have neuroprotective effects. In rats treated with ketamine 15 min following the induction of SE, there was a significant reduction in neuronal damage when compared to rats treated with saline (Fujikawa, 1995). The mechanism of action of neuroprotection is through the inhibition of intracellular calcium influx and through the antagonism of NMDA-mediated glutaminergic excitotoxicity. However, excessive NMDA receptor antagonism has also been suggested to result in neurotoxicity, calling into question the use of ketamine to treat refractory SE in humans (Ubogu *et al*., 2003). Ketamine has been successfully used to treat refractory SE in dogs (Serrano *et al*., 2006; Roynard *et al*., 2021), although others report it to be an inciting cause of seizures (Adami *et al*., 2013). Ketamine may also result in extreme muscle tone and spontaneous movement, which may be harmful in a patient who is already hyperthermic. This is unlikely to occur in a setting where ketamine is used as a fourth line of defense in stopping SE, as it will have been used following benzodiazepines and at this point, any of the *potential* risks of ketamine use are outweighed by the benefits.

Pharmacokinetics

Ketamine is rapidly distributed to all body tissues after IV or IM injection. It has also been shown to have an effect when delivered sublingually in the cat, although at very high doses (20–80 mg/kg) (Issabeagloo, 2008). It concentrates in the brain, liver, lungs, and fat. Ketamine is approximately 53% protein bound in the dog and cat. Ketamine is primarily metabolized in the liver of dogs through demethylation and hydroxylation and excreted unchanged in the urine of cats.

Toxicity, Side Effects, and Interactions

Ketamine may result in apneustic breathing patterns, which could be mistaken for brainstem compression (i.e., inhibition of the respiratory centers) secondary to increased intracranial pressure. Although it may cause an increased respiratory rate, it is not considered a respiratory depressant unless given at high doses (note: as it is to treat SE). Respiratory support (e.g., intubation and ventilation) may be necessary. Ketamine will increase cerebral blood flow and intracranial pressure (Boothe, 2001). Caution should be used if a patient has reduced hepatic or renal function. It should also be used cautiously when increased intracranial pressure is suspected or there is known structural brain disease or head trauma. Ketamine may induce hypertension. Ketamine is reported to cause seizures, and many clinicians have experienced this effect when it is used as an anesthesia agent. This will result in a natural trepidation for its use to treat SE. *This is not unwarranted*. Ketamine should only be used at the appropriate time in the refractory status epilepticus cycle. It should be titrated to effect as a *last resort* prior to the induction of a barbiturate coma (see Chapter 8).

Indications for Use

Ketamine may be considered for use to treat refractory SE when other more conventional methods have failed, such as multiple doses of various benzodiazepines, phenobarbital, levetiracetam, and propofol. It is considered a fourth-level antiseizure medication, preceding only the use of a barbiturate such as **pento**barbital to induce coma. Because of the temporal expression of NMDA receptors late in the stages of prolonged SE (i.e., over 30 min) and experimental evidence showing its beneficial effects, it is justified to try ketamine to stop refractory SE.

Dose

Ketamine should be titrated to effect. The dose required to stop an episode of SE is reported at 5 mg/kg as an IV bolus followed by a continuous rate infusion of 5 mg/kg/h when seizures once again resumed (Serrano *et al*., 2006). It has also been used successfully with multiple, 5 mg/kg IV boluses (Roynard *et al*., 2021). Ketamine has been reported to successfully treat *super refractory status epilepticus* in three dogs, along with dexmedetomidine and hypothermia (body temp maintained between 36.7 and 37.7 °C) using 1 mg/kg IV bolus of ketamine over 5 min followed by an IV bolus of dexmedetomidine at 3 μg/kg over 5 min, followed then by a CRI of ketamine and dexmedetomidine over 12 h (ketamine at 1 mg/kg/h and dexmedetomidine at 3–7 μg/kg/h) (Gioeni *et al*., 2020). Ketamine is available as an injectable form at 10, 20, 50, and 100 mg/ml. The clinician should be certain of the concentration they have at their disposal prior to injection.

Monitoring

Careful monitoring is necessary when ketamine is used to stop and prevent epileptic seizures. Respiratory depression and apnea may result in the need for intubation and mechanical ventilation, especially when used at high doses. Be careful of the cardiovascular depressant effects. If stereotypic movement is observed, do not necessarily give more ketamine assuming it is a continuation of epileptic seizure activity as it may be due to the excitatory effects of ketamine on the CNS.

Monitor blood pressure closely as ketamine is known to cause hypertension. Monitor the patient closely for signs of increased intracranial pressure. EEG monitoring for continued epileptiform activity is recommended.

LACOSAMIDE (LCM) (LAH-COE-SUH-MIDE)

Lacosamide was approved in the USA in 2008 for treating focal seizures with or without secondary generalization and is marketed under the trade name *Vimpat*®. Its use in veterinary medicine is limited to experimental data derived in preclinical trials looking at mechanisms of action of the medication and toxicology studies. Lacosamide was specifically synthesized from a class of functionalized amino acids having antiseizure properties. Additionally, it is efficacious in the treatment of neuropathic pain and chronic inflammatory pain in humans (Beyreuther *et al*., 2007). Lacosamide differs from many other antiseizure medications as it inhibits neural activation but at the same time does not impair normal brain metabolic activity (Duncan and Kohn, 2005).

Mechanism of Action

Lacosamide was originally thought to inhibit repetitive action potential firing by selectively enhancing sodium channel *slow inactivation* with no effect on fast inactivation. However, it is now thought its mechanism is mediated through *very slow* binding to the *fast inactivated* state of the sodium channel (Jo and Bean, 2017). It binds to the same site as lidocaine. By reducing the number of sodium channels available for activation, neuronal excitability is attenuated. This significantly differentiates lacosamide from other sodium channel inactivators such as carbamazepine, phenytoin, and lamotrigine, which all affect slow and fast inactivation of sodium channels (Beyreuther *et al*., 2007). Lacosamide also binds to collapsin-response mediator protein 2 (CRMP-2). This protein has been implicated in the transduction of various neurotropic signals, which have a range of effects on myelination, gene expression, axonal outgrowth, neural sprouting, and neuroprotection. The effects of deranged neural outgrowth have been previously implicated in the generation of epilepsy and neuropathic pain. In multiple rat models of epilepsy including MES and kindling models, lacosamide has been shown to be very effective in preventing these experimentally induced seizures. Additionally, lacosamide may have neuroprotective effects in experimental models of SE determined through histopathological study of hippocampal brain slices.

Pharmacokinetics

In a pilot study evaluating the potential for HPLC analysis of lacosamide, the half-life in dogs, dosed at 3 mg/kg PO, was determined to be ~3.5 h with a Vd of 0.4 l/kg (Martinez *et al*., 2012). In humans, lacosamide is completely absorbed after oral administration, and less than 15% of it is bound to plasma proteins. It is partially metabolized by the liver and excreted 40% unchanged by the kidneys (Engel, 2013).

Toxicity, Side Effects, and Interactions

Lacosamide is considered generally very safe in animal models of toxicity. Long-term dosing safety data is available for dogs. Dose-dependent ataxia, reduced GI motility, tremor, and seizures were observed at high doses when given to dogs (Beyreuther *et al*., 2007). All side effects were reversible. It has the potential to reduce blood pressure in dogs at doses nearing the high end of the proposed therapeutic concentration for humans. This has been determined to be a direct cardiac depressant effect (reduced contractility) as opposed to a vasopressive effect.

Lacosamide has minimal interaction with cytochrome P450 (Beyreuther *et al*., 2007). However, caution should be used if patients have hepatic impairment. Lacosamide is considered to have very few drug interactions.

Indications for Use

Lacosamide may be considered as an add-on antiseizure medication when other more commonly used antiseizure medications have failed. In this regard, it is considered currently to be a *fifth-tier* antiseizure medication like rufinamide, although anecdotal experience shows promise with the medication, regarding efficacy and safety. It is expensive.

Dose

A dose of 50–100 mg every 12 h is recommended as an *anecdotal* starting point for *dogs*. In humans, the recommended starting dose begins with 50 mg every 12 h for 1 week, then increases by 50 mg each dose in weekly intervals (Engel, 2013). Use caution, as there is very limited experience with the use of this drug in dogs and cats. Lacosamide is available in 50, 100, 150, and 200 mg tablets. It is also available in a 10 mg/ml syrup (does *not* contain xylitol) and a 10 mg/ml solution. An injectable form is available at a concentration of 10 mg/ml. In humans, it is recommended to give the injection over 15–30 min.

Monitoring

Because little is known regarding this medication, monitor for efficacy and safety. Routine blood work is recommended at least every 6 months. Caution owners that clinical experience is limited (currently) to anecdotal accounts of its use. Other more *traditional* antiseizure medications may be more suited. The therapeutic range for humans is considered to be 10–20 μg/ml.

PREGABALIN (PGN) (PRE-GAB-AH-LIN)

Pregabalin is a second-generation "gabapentin." It was approved for use in the USA in 2005. It is currently available as a veterinary-labeled oral solution (50 mg/ml) called *Bonqat*® approved for use to help alleviate feline anxiety. Human-labeled oral capsules in multiple sizes and an oral solution (20 mg/ml) under the proprietary name of Lyrica®. It is also available in generic forms. It possesses antiepileptic, analgesic, and anxiolytic activity. It has demonstrated increased binding and affinity for the α2γ subunit of the voltage-gated calcium channel, thereby reducing the releases of excitatory neurotransmitters at the presynaptic nerve terminal. Its half-life is longer and has an increased bioavailability when compared to gabapentin. Because of this, its efficacy in preventing epileptic seizures is thought to be greater than that of gabapentin and its side effects are fewer. Very little data on the long-term effects and efficacy of pregabalin in dogs or cats is available. In a study looking at the efficacy of pregabalin as an add-on therapy (3–4 mg/kg *TID*) to potassium bromide, phenobarbital, or both, in dogs with drug-resistant epilepsy, a reduction in seizure frequency occurred in 9 of 11 dogs (23–83% seizure frequency reduction) (Dewey *et al*., 2009). Of the 11 dogs in the study, 7 (63.6%) were considered "responders" (a minimum reduction of seizure frequency of 50%) within 3 months of study initiation. In a more recent study, no effect was found when pregabalin was used as an add-on medication in dogs at 4 mg/kg *BID* (Kriechbaumer *et al*., 2022). As noted in the Kriechbaumer study, evaluating responders via a minimum reduction of seizure frequency of 50% (the Dewey paper) is recognized as being potentially prone to the placebo effect as opposed to measuring a 3× increase in the interseizure interval (as in the Kriechbaumer paper) (Schneider *et al*., 2020; Kriechbaumer *et al*., 2022). The differences in outcomes between the two studies may also be in dosing parameters. In the Dewey study, TID dosing was employed with an almost double mean serum pregabalin concentration (6.8 mg/l) compared to the Kriechbaumer study (3.8 mg/l) which used BID dosing. Despite the BID dosing, dogs in the Kriechbaumer study did achieve pregabalin levels that were in the recognized human reference range.

Mechanism of Action

The mechanism of action of pregabalin is not completely understood; however, it is suspected to exert its effects through its binding to the α2γ subunit of the voltage-gated calcium channel (P, Q, and N). The voltage-gated calcium channel is thought to play a primary role in the control of neuronal excitability by inhibiting the release of excitatory neurotransmitters (e.g., substance P, norepinephrine, and glutamate) at the presynaptic nerve terminal (Gee *et al*., 1996). It is 3–10 times more potent than gabapentin in this effect (Plumb, 2011).

Pharmacokinetics

When pregabalin was given as a single oral dose to dogs (~4 mg/kg), peak serum concentration was reached in 90 min and remained at therapeutic concentrations (2.8–8.2 μg/ml in humans) for up to 8 h in five of six dogs and greater than 2.8 μg/ml for up to 11 h (Salazar *et al*., 2009). The half-life was calculated at approximately 6–8 h. In cats, the time to peak serum concentration after a single oral dose (4 mg/kg) of pregabalin was 3 h, with a maximum serum concentration of 8.3 μg/ml and a calculated half-life of 10.4 h (Cautela *et al*., 2010). In another disposition study, four of six cats given a single 4 mg/kg oral dose experienced sedation (Esteban *et al*., 2018). In this study, a dose of 1–2 mg/kg every 12 h is suggested for cats. Cats given an oral formulation of pregabalin (*Bonqat*®), a feline-specific formulation to alleviate fear and anxiety, at a recommended dose of 5 mg/kg had a mean plasma concentration of 10.1 μg/ml, after a single 5 mg/kg dose at 0.5–1 h after dosing, with a bioavailability of 94% and a T½ of 14.4 h (Lamminen *et al*., 2022). Metabolism and elimination of pregabalin are suspected to be like gabapentin. Based on this presumption, the liver may metabolize a portion of pregabalin, and the majority is presumed to be excreted through the kidneys.

Toxicity, Side Effects, and Interactions

Side effects consisting primarily of sedation, ataxia, or apparent "dizziness" were reported in 10 of 11 dogs enrolled in a long-term study of the effects of pregabalin when combined with phenobarbital, potassium bromide, or both medications (Dewey *et al*., 2009). None of the side effects were severe enough to warrant discontinuation of the medication. Some of the side effects were reduced by a reduction in the pregabalin dose (from 4 mg/kg every 8 h PO to 2 mg/kg every 8 h PO). Nine of the 11 dogs had serum concentrations within the therapeutic range). Moderate sedation occurred in four of six cats treated when their serum concentrations were within the therapeutic range considered efficacious for humans (2.8–8.2 μg/ml). Pregabalin may increase the sedative side effects of other CNS depressants. In humans, concurrent use of pregabalin along with ACE inhibitors (e.g., benazepril, enalapril) may lead to edema and hives (Plumb, 2011). A single case of cutaneous lesions has been reported in a cat after receiving pregabalin (Clark *et al*., 2017).

Indications for Use

Pregabalin may be considered as an add-on therapy for the control of generalized and focal seizures in dogs and cats. It has been shown to be effective in the management of clinical signs associated with *syringomyelia* (Sanchis-Mora *et al*., 2019; Thoefner *et al*., 2020). Pregabalin has also been shown to be effective in alleviating fear and anxiety associated with transportation in cats (Lamminen *et al*., 2021). It is regarded as a fourth or fifth-tier anticonvulsant, so you need to burn through a lot of other options prior to reaching for the pregabalin. In a study looking at the ability of add-on pregabalin to increase intra-seizure interval, no benefit was found in the study group (Kriechbaumer *et al*., 2022). However, it may be pertinent to note that dogs in this study were recruited based on having either phenobarbital or potassium bromide serum levels at the low end of what is considered the therapeutic range. Furthermore, the doses of both imepitoin and levetiracetam were at levels, many clinicians would consider starting doses or middle doses, but not maximum doses for those medications (Imepitoin max dose ~40 mg/kg BID and Levetiracetam

max dose at 40 mg/kg TID or 60 mg/kg BID of the extended release). The definition of a drug-resistant epileptic was based on a previous consensus statement from the IVETF, whereby a drug-resistant epileptic was defined as a patient who did not achieve seizure freedom with two therapeutic trials (Potschka *et al*., 2015). This reminds us that an add-on should not be considered until the primary medication has failed—either through a dose that results in toxicity, intolerable side effects, or that reaches the maximum dose considered for that medication, whereby more of what is not working has little chance of having an effect. Just dosing a patient without regard to the individual *effective seizure control window* (see Figure 4.7) and calling it a failure when it does not respond will increase your failure rate dramatically and is a common reason many epileptic patients are referred. We should *completely* fail a medication before we consider an add-on, which will only complicate treatment. Let's review failure again from the author's perspective:

Start with a first-tier anticonvulsant and titrate the dose gradually to *effect or side effect*. Or in the case of phenobarbital, when you reach the high end of serum therapeutic concentrations and are concerned about impending liver toxicity. Just because the serum level falls within the reference range does not mean you have maxed the drug. It must be at the top of the reference range, without the desired effect, to fail.

If you start with a well-tolerated medication with a high safety profile, such as levetiracetam or imepitoin, increase the dose to effect, side effect, or *double* the starting dose. If you get to double the starting dose, and still do not have the desired effect, chances are more medication beyond this point, will have little effect.

If either of these situations occurs, that is the time to reach for the add-on.

This idea is covered in more detail in Chapter 6 under the heading "Dosing" (Page 205).

Dose

A dose of 4 mg/kg PO every 8 h is recommended to achieve and maintain serum plasma concentrations in dogs (Dewey *et al*., 2009; Salazar *et al*., 2009). A dose of 1–2 mg/kg PO every 12 h is recommended to achieve and maintain serum plasma concentrations in cats (Cautela *et al*., 2010). Pregabalin is available as oral capsules in 25, 50, 75, 100, 150, 200, 225, and 300 mg sizes. It is also available as a 20 mg/ml oral solution (Human label) and a 50 mg/ml oral solution (veterinary label). Unlike the oral solution of gabapentin, which contains xylitol, pregabalin as Lyrica® contains sucralose.

Monitoring

Pregabalin appears to have a safety profile in dogs and cats like gabapentin such that therapeutic monitoring is not necessary. Rather, the medication is titrated to effect or side effect. Monitoring is primarily based on clinical and home observation of the patient for clinical efficacy and adverse side effects.

PROPOFOL (PRO) (PROE-POH-FOLE)

Propofol is a short-acting hypnotic used for general anesthesia and marketed under the trade names *Rapinovet®*, *PropoFlo®*, and *PropoClear®*. While commonly used as a short-acting anesthetic and induction agent, propofol may be used for the treatment of SE in certain situations (see Chapter 8 and Figure 8.1).

Mechanism of Action

The mechanism of action of propofol is poorly understood. It appears to have a direct effect on inward hyperpolarizing chloride currents, resulting in prolongation of inhibitory postsynaptic currents (Vanlersberghe and Camu, 2008). It is a $GABA_A$ agonist but in a way that differs from

benzodiazepines and barbiturates. Propofol has other effects including the modulation of inflammatory cytokines, impairment of monocyte and neutrophil functions, and alteration of the expression of nitric oxide, and it is a potent free radical scavenger (as potent as vitamin E). Propofol has been shown to have neuroprotective effects; it reduces cerebral blood flow, cerebral metabolic rate of oxygen, and intracranial pressure. It also possesses excellent free-radical scavenging effects (Kikuta *et al*., 2007; Vanlersberghe and Camu, 2008).

Pharmacokinetics

Propofol rapidly reaches the CNS after IV injection. Its onset of action is typically within 1 min of administration. It is 90–95% bound to plasma proteins and has an effect generally lasting only minutes after a single IV bolus. Prolonged anesthesia requires a CRI to be maintained. It has a very rapid hepatic metabolism via glucuronidation and is nearly completely metabolized to inactive compounds, which are then excreted through the kidneys.

Toxicity, Side Effects, and Interactions

If given too rapidly, apnea and associated cyanosis occur. This potentially dangerous side effect can be avoided by a slow infusion and readily available endotracheal tube with associated mechanical ventilation. Pretreatment (5 min) with flow-by oxygen is often recommended. Because of their reduced ability to conjugate with glucuronide, cats are susceptible to Heinz body anemia secondary to oxidative injury of red blood cells. Successive or chronic dosing in cats should be avoided. Propofol is a myocardial depressant and may cause arterial hypotension. Anaphylactic reactions are rarely reported and result in acute histamine release.

A commonly reported side effect of propofol is "proconvulsant" properties. Episodes of dystonia, paddling, opisthotonus, and *seizure-like movements* are observed. This paradoxical reaction *in some cases* is the true induction of generalized seizures, which warrants caution if propofol is used in a patient with known epilepsy (Smedile *et al*., 1996). Conversely, propofol is advocated for the treatment of epileptic seizures, in particular SE and seizures following portosystemic shunt surgery in dogs (Heldmann *et al*., 1999; Steffen and Grasmueck, 2000; Dewey, 2006; Gommeren *et al*., 2010; Thomas, 2010).

Propofol is thought to have glycine antagonism properties at the level of the spinal cord. Glycine is an inhibitory neurotransmitter that potentiates chloride conductance resulting in an inhibitory postsynaptic potential. Propofol antagonizes glycine. The mechanism of action, like strychnine, may result in the development of tonic–clonic movement of the limbs (Bevan, 1993). Glycine is also a co-agonist with glutamine at the NMDA receptors, resulting in excitatory effects. This effect may explain some of the paradoxical behavior of propofol in various patients. Often this effect is mistaken as seizures (the tonic–clonic movements of the limbs while the patient is under anesthesia).

Propofol has numerous potential drug interactions. When used in conjunction with inhalation anesthetics, propofol concentrations will increase, potentially necessitating a dose reduction. The use of opioid premedications may exacerbate propofol-induced bradycardia, and the serum concentrations of both propofol and the opiate may increase if used together. Drugs known to inhibit cytochrome P450 may reduce the clearance of propofol (chloramphenicol, azole antifungals, cimetidine, etc.). Use care when dosing propofol after medetomidine, as patients may be more prone to hypoxia. Propofol may have synergistic effects with midazolam, increasing serum midazolam concentrations by up to 20% (Plumb, 2011).

Indications for Use

Propofol should be used as a third or fourth-line agent to stop SE and treat cluster seizures, when the benzodiazepines are either ineffective (tolerance) or contraindicated (hepatic disease) and phenobarbital or levetiracetam has failed to stop a seizure. Once the seizure is stopped, the patient may

be maintained on a propofol CRI; however, intubation is recommended, whereas with a diazepam CRI, intubation is not *typically* necessary (use your clinical judgment).

Patients whose seizures are observed to cease when given propofol may still have continuous epileptiform activity in the brain (Raith *et al*., 2010). EEG monitoring is recommended and further treatment (diazepam, phenobarbital, or levetiracetam) would be appropriate to halt epileptiform activity. There are still some significant advantages to stopping the abnormal muscle contractions associated with SE as much of the danger of the prolonged seizure is due to the potential for hyperthermia and associated multiorgan dysfunction.

Dose

An initial bolus of 1–6 mg/kg is administered slowly and to effect (Steffen and Grasmueck, 2000). Following cessation of a SE event, propofol can be administered as a CRI at a dose of 0.1–0.6 mg/kg/min, titrated to effect. The time on a CRI of propofol will vary from patient to patient and should consider many factors. A generally conservative time frame would be to continue the CRI after the episode of SE has stopped for a minimum of 4–6 h if no further seizure activity is observed. After 4 h, reduce the CRI by 25% every 2 h. Other factors such as administration of loading doses of phenobarbital or levetiracetam, as well as, any other comorbidities (structural brain disease, hepatic compromise, etc.) should also be considered for the propofol CRI time course. Repeated doses and continuous rate infusion should be avoided in cats. Propofol is available as an injectable form at 10 mg/ml in both single- and multiple-dose vials.

Monitoring

Careful monitoring is necessary when propofol is used to stop and prevent epileptic seizures. Respiratory depression and apnea may result in the need for intubation and mechanical ventilation. Be careful of the cardiovascular depressant effects. If dystonic movement is observed, do not necessarily give more propofol assuming it is a continuation of epileptic seizure activity as it may be due to glycine receptor antagonism at the level of the spinal cord. EEG monitoring for continued epileptiform activity is recommended.

RUFINAMIDE (RUF) (RUE-FINN-AH-MIDE)

Rufinamide was approved for use in treating epileptic seizures in humans in the USA in 2008. It is marketed under the trade name *Banzel*® and *Inovelon*®. It is available in a generic form. There is no data on the efficacy or long-term safety of this drug in either dogs or cats. Anecdotal information (including the author's own experience) suggests it is safe and effective in treating pharmacoresistant epileptic dogs but is considered a sixth-tier anticonvulsant.

Mechanism of Action

Rufinamide is thought to modulate voltage-gated sodium channels through the *prolongation* of the inactive state, although the exact mechanism of action is unknown (White *et al*., 2008). Rufinamide has been shown to reduce the incidence of induced seizures in all experimental models of epilepsy in animals suggesting it has broad-spectrum activity (Wheless and Vazquez, 2010). It has no effect on GABA or benzodiazepine receptors. It does not appear to directly influence any neurotransmitter function in the CNS.

Pharmacokinetics

There is no information on the pharmacokinetics of rufinamide in cats. In dogs, at a dose of 10 mg/kg PO, given with food, a peak plasma concentration of 10.6 μg/ml at 18 h after oral administration was achieved (Wright *et al*., 2012). The average therapeutic concentration in humans is

recommended at 15 µg/ml (Perucca *et al.*, 2008). The Vd in dogs was 1.25 l/kg and the half-life is calculated at 8.78 h (Wright *et al.*, 2012). When dosed at 20 mg/kg, a peak plasma concentration of 19.6 µg/ml was attained and the time to peak plasma concentration was reduced to ~9.3 h. The half-life was similar at 9.86 h (Wright *et al.*, 2012). Rufinamide is metabolized in the liver primarily by hydrolysis and in humans is not cytochrome P450 dependent (Engel, 2013).

Toxicity, Side Effects, and Interactions

Limited data suggests no significant side effects are associated with single dosing of rufinamide in dogs. In humans, rufinamide is considered safe and used primarily in children with Lennox–Gastaut syndrome (atonic seizures). The author has observed it to be effective in treating a single dog with atonic seizures (see Video 5). It is reported to increase QTc interval. In humans, rufinamide will increase phenobarbital levels.

Indications for Use

Rufinamide may be considered as an add-on antiseizure medication when other more commonly used antiseizure medications have failed. In this regard, it is considered a sixth-tier antiseizure medication, although anecdotal experience shows promise with the medication, regarding efficacy and safety. There are many, many other medications to try before rufinamide.

Dose

A dose of 20 mg/kg every 12 h should be adequate to achieve what are considered therapeutic plasma levels in humans (10–45 µg/ml). An appropriate starting dose may be 5–10 mg/kg every 12 h and then titrate to effect or side effect. Some variability exists with the elimination in dogs; therefore, every 8 h dosing may be necessary. Rufinamide should be given with food. Rufinamide is available as a generic form. It is marketed as *Banzel*® and *Inovelon*®. It is available in 200 and 400 mg tablets. It is also available as a 40 mg/ml oral suspension that does *not* contain xylitol.

Monitoring

Because little is known regarding this medication, monitor for efficacy and safety. Routine blood work is recommended at least every 6 months. Caution owners that clinical experience with this drug is limited to anecdotal accounts of its use. Other more *traditional* antiseizure medications may be more suited.

RARELY USED DRUGS

CARBAMAZEPINE (KAR-BAM-AYE-ZUH-PEEN)

Carbamazepine is an older antiseizure medication commonly used in humans to treat both focal seizures and generalized tonic–clonic seizures but has the potential to *exacerbate* absence, myoclonic, and atonic seizures (Engel, 2013). Carbamazepine was approved for use in the USA in 1974 and is marketed under the trade name *Tegretol*®. It is also available in generic forms.

In addition to treating epileptic seizures, carbamazepine may be useful in the treatment of behavioral disorders and neurogenic pain in dogs and cats. It was determined early on that due to its pharmacokinetics in dogs, it would *not be* a useful anticonvulsant (Frey and Löscher, 1980; Frey *et al.*, 1984). Its current use is in treating aggression in dogs (Haug, 2008). A newer generation and structural analogue to carbamazepine, *oxcarbazepine*, has similar pharmacokinetics in the dog, rendering it useless for the treatment of epileptic seizures as well (Schicht *et al.*, 1996). It is anecdotally reported to be effective, and the author has used it to successfully treat a single dog with

paroxysmal extreme pain disorder (formally familial rectal pain syndrome), similar to the reported condition in humans (Fertleman *et al.*, 2007) (see Video 44). Therefore, we will include it in our discussion.

Mechanism of Action

Carbamazepine, like many antiseizure medications, has significant anticonvulsant activity in experimental models of epileptic seizures utilizing cats. Its primary effects are like those of phenytoin in reducing sustained repetitive firing of action potentials, thereby stabilizing neuronal membranes through an effect on voltage-dependent sodium channels (McLean and Macdonald, 1986). Multiple other mechanisms of action have been postulated, such as carbamazepine acting as an adenosine receptor antagonist. Adenosine is thought to be involved in the suppression of the spread of epileptic activity through the brain and plays a role in the termination of seizures (Skerritt *et al.*, 1983a, 1983b). Other effects on neurotransmitters, including GABA modulation, either by carbamazepine or its metabolites are possible, and ongoing investigations will likely discover more of the mechanisms. In experimental animal models of epilepsy, the primary metabolite of carbamazepine, carbamazepine-10,11-epoxide, has similar antiseizure activity (Frey and Löscher, 1985).

Pharmacokinetics

Carbamazepine is well absorbed after oral administration in dogs, although the bioavailability of the oral solution is greater than the tablets. The peak concentration in the plasma of carbamazepine is reached within 1 h, and its epoxide metabolite is detected at peak concentrations within ~4 h after oral dosing. The epoxide form is present in the plasma at elevated concentrations even after the parent form has dropped below 1 μg/ml. Carbamazepine is less protein bound in dogs than in humans. It has a protein binding of ~71% and the epoxide form binds at about ~40%, which is also lower in dogs than in humans. The initial half-life of carbamazepine was calculated at approximately 1.2–1.6 h; however, with repeated dosing, a marked induction occurs, resulting in a marked decrease of the half-life to 0.63–0.73 h, making this form of the medication not terribly useful for the control of epileptic seizures in dogs (Frey and Löscher, 1985).

When dosed with a sustained-release preparation of the drug, no significant benefit in delayed absorption or metabolism was found in dogs; however, an experimental preparation did show a significant delay in absorption and an increased bioavailability when compared to the commercially available sustained-release preparation (Barakat *et al.*, 2008). This suggests further investigation into drug formulation may provide a more lasting drug level in the dog.

A potential explanation for the lack of effect of carbamazepine may be the reduced ability to concentrate in the CNS. One proposed mechanism for this and in general the pharmacoresistance of many epileptic animals and humans is the p-glycoprotein carrier-mediated efflux of substances out of the CNS, although carbamazepine has been shown to not be a substrate of this mechanism (Baltes *et al.*, 2007; West and Mealey, 2007).

Toxicity, Side Effects, and Interactions

Due to the consensus of a lack of therapeutic benefit, little data is available regarding the potential toxicity and side effects of carbamazepine in dogs and cats. The primary side effect reported in experimental studies of the drug is transient sedation. In humans, reported side effects include dizziness, sedation, nausea, and vomiting. Other possible side effects in humans include abnormalities of the heart, liver, skin, and hematopoietic system (Plumb, 2011).

Carbamazepine may have significant drug interactions and a veterinary formulary should be consulted (e.g., Plumb's) if its use is considered. Most commonly, this drug would be used for behavior applications.

Indications for Use

While an important first-line drug for the treatment of focal seizures, which do not secondarily generalize in humans, carbamazepine is not used in dogs and cats for the treatment of epileptic seizures due to the inability of the drug to maintain comparable serum therapeutic concentrations (Frey and Löscher, 1985). It is used in a behavior application for dogs with psychotropic aggression (Haug, 2008). Carbamazepine has demonstrated antiseizure effects in experimental models of penicillin-focal epilepsy in cats. In these studies, cats are dosed with 40 mg/kg given as an intraperitoneal injection. Peak serum and brain concentrations were detected within 30 min of the injection. Electroencephalographic recordings of spike wave activity showed a significant decrease in frequency after carbamazepine injection (Monaco *et al*., 1982). No long-term studies regarding dosing, disposition, or efficacy have been performed in cats.

Dose

A dose of 30 mg/kg every 8 h in dogs failed to maintain serum concentration due to significant hepatic enzyme induction. The liquid preparation was far better absorbed in dogs compared to tablets (Frey and Löscher, 1985). A reported dose of 4–8 mg/kg every 6 h or 29 mg/kg every 12 h is used for behavioral applications (Haug, 2008). Carbamazepine is also used for the treatment of paroxysmal extreme pain disorder in humans. This condition, mediated through a sodium channelopathy, results in brief episodes of extreme rectal pain triggered through the act of defecation, usually beginning at infancy. The author has treated one patient with similar clinical signs to those described in humans with some benefit using carbamazepine at a dose of 30 mg/kg every 8 h. No apparent adverse side effects were noted in the patient (see Video 44). The drug is very effective when used in humans for this disorder (Fertleman *et al*., 2007).

Monitoring

If used, the patient should be monitored for safety and clinical efficacy. Because of the potential for extensive hepatic metabolism, routine CBC and biochemical profile, including liver function tests (fasting and fed bile acids) are recommended.

ETHOSUXIMIDE (ETHO-SUCKS-IH-MIDE)

Ethosuximide was introduced in the USA in 1960 primarily for the treatment of absence seizures in humans. The incidence of absence epileptic seizure is rarely documented in dogs and cats. They have been documented in one dog and are often induced in experimental models of seizures with cats (Poma *et al*., 2010). The treatment of these seizures is called into question. Unless the absence seizure was causing physical harm, the patient was suffering from the disorder, or there was a recognized pattern of increasing frequency or intensity, the need for treatment may be questioned.

Mechanism of Action

The primary mechanism of action of ethosuximide is through blockage of T-type calcium channels (Coulter *et al*., 1989b; Gomora *et al*., 2001). The main effect is medicated through blockage of the calcium channels in the thalamus, which are responsible for the spread of the characteristic 3 Hz spike and wave discharges associated with absence epilepsy (Coulter *et al*., 1989a).

Pharmacokinetics

Very little information is available regarding the disposition of ethosuximide in the dog. No information is available for the cat other than the general efficacy in experimental models (generalized feline penicillin model). Using an IV dose of 20–60 mg/kg in dogs, ethosuximide had a half-life of 17–18 h. With oral dosing, there was rapid absorption with a Vd similar to water.

Ethosuximide distributes equally in all tissues except fat and does not accumulate in any tissues. Peak plasma concentrations were reached 1–4 h after oral dosing. Penetration into the CSF is rapid and equivalent to plasma levels within 20–30 min. There is very little (1.5–9.5%) protein binding in the dog (el Sayed *et al*., 1978).

Toxicity, Side Effects, and Interactions

There are no reported negative side effects or toxicity studies in dogs or cats. In humans, ethosuximide is considered relatively safe with minimal side effects primarily associated with psychosis and other behavioral problems.

Indications for Use

Ethosuximide may be beneficial in treating absence seizures in dogs (Frey and Löscher, 1985). No disposition data is available for cats, although presumably it would be effective. Whether or not an animal patient should be medicated for absence seizures is debatable. If it were decided to medicate a dog or cat for absence seizures, it is recommended to use either a more familiar (i.e., phenobarbital or bromide) or newer generation medication with known disposition (i.e., imepitoin, zonisamide or levetiracetam). However, if those fail, ethosuximide may be considered a *sixth- or seventh-tier* anti-absence medication. Caution should be exercised if it is used.

Dose

Following an initial oral loading dose of 40 mg/kg, a dose of 15–25 mg/kg every 8 h should result in plasma concentration of ethosuximide in the range of 50–70 μg/ml in dogs (Frey and Löscher, 1985).

Monitoring

The necessity to control absence seizures in dogs and cats should be questioned; however, if the seizures are increasing in frequency or intensity, if the patient is suffering from the seizure or the seizures are dangerous to the patient, and if other more traditional antiseizure medications have failed to control the episodes or cause toxicity, ethosuximide could be considered. If used, the patient should be monitored for safety and clinical efficacy. Because disposition data on the dog is limited (and not available for the cat), routine CBC and biochemical profile, including liver function tests (i.e., fasting and fed bile acids), are recommended although induction of hepatic enzymes is reported *not* to occur (el Sayed *et al*., 1978).

PHENYTOIN (FEN-IH-TOE-IN)

Phenytoin is not commonly used in veterinary medicine to treat epileptic seizures. With the development and introduction of more effective and safer antiseizure medications, phenytoin should not be used in dogs and cats to treat epileptic seizures. There are multiple factors which make its use difficult, expensive, and unsafe (Frey and Löscher, 1985; Boothe, 1998). These include a short half-life in dogs, combined with induction of hepatic enzymes, which leads to an inability to maintain serum therapeutic concentrations, as well as an increased risk of hepatotoxicity in dogs and cats. It is commonly used in humans to treat epileptic seizures. Its mechanism of action is through prolonging the recovery of voltage-gated sodium channels from inactivation.

Phenytoin was successfully used to treat a cat with myotonia congenita resulting from a mutation of the voltage-gated chloride channel 1 gene (CLCN1) (Woelfel *et al*., 2022).

Mephenytoin is similar to phenytoin although absorbed much better and is able to maintain therapeutic concentrations in dogs. The half-life of mephenytoin is 25 h in dogs. However, it is hepatotoxic, especially when combined with phenobarbital (Boothe, 1998).

PRIMIDONE (PRIM-IH-DONE)

Primidone is a *precursor* to phenobarbital. It is metabolized by the liver to phenylethylmalonic acid (PEMA) and phenobarbital. While it does possess antiseizure activity, this effect is significantly less than phenobarbital. Due to an increased risk of hepatotoxicity, particularly in cats, its use is not recommended, as it does not confer any advantage to the treatment of epileptic seizures when compared to phenobarbital, which is less toxic (Farnbach, 1984b, 1984c; Schwartz-Porsche *et al*., 1985).

VALPROIC ACID (VAL-PROE-ICK)

Valproic acid or *sodium valproic acid* is an old antiseizure medication. Valproic acid was first synthesized in 1882 but not used as an antiseizure medication until the 1960s when it was accidently found to have antiseizure properties while being used as a carrier vehicle to test *new* antiseizure drugs. It was approved for use in the USA as an antiseizure medication in 1978. It is marketed in the USA under the trade name *Depakene*®. It is also available in a generic form. It is commonly used in human medicine because of its broad spectrum of activity in controlling many types of epileptic seizures, including absence seizures and myoclonic seizures.

Valproic acid has limited use in veterinary medicine due to its rapid half-life and subsequent difficulty in maintaining serum therapeutic concentrations, *although it does concentrate in the CNS and therapeutic concentrations may be reached when they are considered low in the serum*. Another limitation is its apparent hepatotoxicity due to its extensive hepatic metabolism.

So why are we taking the time to discuss this obscure antiseizure medication? Valproic acid may have been overlooked for its antiseizure capabilities, especially in cats. By no means is this section meant to encourage clinicians to use this untried medication; however, when all else fails, it may be a consideration. Very little to no safety and long-term clinical efficacy trials in dogs and cats have been performed. However, future research may be warranted.

Mechanism of Action

Valproic acid likely has multiple mechanisms of action, which contribute to its broad-spectrum antiseizure properties.

It significantly increases the concentrations of GABA and enhances its release in the presynaptic axon terminals of CNS by:

- Inhibition of GABA degradation
- Increase of synthesis of GABA
- Increase of presynaptic release and potential interaction at postsynaptic $GABA_A$ and $GABA_B$ receptors

Valproic acid has a general effect on increasing GABA concentrations in the brain and potentiates the action of GABA on its receptor, leading to a greater postsynaptic inhibition (Johnston and Slater, 1982; Löscher and Frey, 1982). Taken together, these broad-spectrum effects on GABA by valproic acid at multiple different areas of the brain, are thought to contribute to its ability to act as an antiseizure, anticonflict, antianxiety, and neuropathic pain medication in humans (Löscher, 1999).

Valproic acid has demonstrated effects on amino acids other than GABA. Gamma-hydroxybutyric acid (GHB) is a by-product of the degradation of GABA, and increased concentrations of GHB result in absence-like epileptic seizures (Snead, 1988). Valproic acid causes a dose- and time-dependent reduction in the synaptic release of GHB in the brain, which may be why it is effective in the treatment of absence seizures in humans (Vayer *et al*., 1988).

Various other descriptions of valproic acid interacting with glutamate and aspartate have also been described; however, no clear evidence of these interactions resulting in antiseizure activity is available. It is hypothesized some of the effects on stimulating the release of glutamate contribute to valproic acid's antianxiety effects similar to the effects of lithium (Dixon and Hokin, 1997).

A postsynaptic effect of valproate through interaction with amino acidergic neurotransmitters is also considered to be a primary mechanism whereby it exerts its effects. This action involves enhanced neuronal responses to GABA through blockage of NMDA receptor neuronal excitation by valproic acid and has been demonstrated in numerous studies (Löscher, 1999).

Valproic acid is suspected to have a direct effect on neuronal membranes, leading to neuronal inhibition. While expected to be due to the reduction of inward sodium currents, this hypothesis has not been substantiated. Enhanced activation of potassium channels, resulting in membrane hyperpolarization, has also been proposed as a possible mechanism for valproic acid's antiseizure effects. However, these effects have only been demonstrated at very high concentrations. Various effects on antagonism of T-type calcium currents have been demonstrated in some areas of the brain. Certain areas of the brain are more affected than others in regard to T-type calcium channel antagonism. Preventing the influx of calcium into neurons is thought to be a major effect of valproic acid (Coulter *et al*., 1989a; Kelly *et al*., 1990).

The antipsychotic and antianxiety effects of valproic acid may be due to antagonism of dopamine and potentiation of serotonin in the brain, which has been demonstrated (Löscher, 1999). Valproic acid is also thought to exert indirect effects on cyclic guanosine monophosphate (cGMP) (i.e., reduced levels). cGMP levels are increased at the onset of experimentally induced seizures. This *second messenger* may be involved in numerous cellular signaling pathways involved in the maintenance of seizure activity by Purkinje cells in the cerebellum (McCandless *et al*., 1979). Similar to lithium, valproic acid has been shown to downregulate the protein kinase C substrate *myristoylated alanine-rich C kinase substrate* (MARCKS), which is suspected to be involved in the delayed-onset antimania effects of both drugs (Watson *et al*., 1998).

A possible explanation for valproic acid's antiseizure effects, despite not reaching therapeutic concentrations comparable to humans, may be the active metabolites of the drug. The primary metabolite of valproic acid, *trans*-2-en-valproate, has more potent antiseizure activity than the parent compound and is less hepatotoxic. This may explain the persistent antiseizure effects even after valproic acid has been discontinued. However, concentrations in the CNS of dogs are low, making the activity of *trans*-2-en-valproate less likely (Löscher and Nau, 1983). As Löscher and others have previously mentioned, further investigation into the potential of *trans*-2-en-valproate and other valproate analogues may be warranted considering its increased ability to suppress epileptic seizure activity and reduced hepatotoxicity (Löscher, 1999). Unfortunately, for dogs and cats, the drug *is* effective and well tolerated in humans, making the expense associated with further drug development, regarding dogs and cats, unlikely to be undertaken by pharmaceutical companies. Adding to the low chances of further investigation in the veterinary world are the many medications we already have at our disposal that have known effects and safety profiles.

Pharmacokinetics

Valproic acid is well absorbed in the dog after oral administration. An oral solution has a greater bioavailability (~89%) compared to tablets (~78%) in dogs (Frey and Löscher, 1985). Peak plasma concentrations are reached within 1 h. Valproic acid is less protein bound in dogs than in humans, which may explain why it has a greater elimination rate in dogs when compared to humans. The half-life in humans is 8–16 h, whereas in dogs it is ~3 h (Löscher, 1981). Little information on the half-life of valproic acid in cats is available. However, when used in an experimental setting, the half-life in cats has been calculated at 5–7.5 h (Pellegrini *et al*., 1978).

Another estimate of serum half-life in the cat (although considered to be a *cautious* estimate) was calculated at 36.1 days (Zoran *et al*., 2001). The report by Zoran is interesting as it measured valproic acid levels in the serum of a cat, which had been inadvertently ingesting the medication (mixed in baby food) off the bib of a baby and from the food the baby dropped on the ground. The investigators noted while attempts were made to prevent the ingestion of medicated food by the cat's owners, it could not be guaranteed. While potentially not accurate, this clinical report raises some questions concerning the potential for an extended half-life of valproic acid in cats, when other reports measure it as being only a little longer than that of dogs (a result that must also be questioned as to its validity).

Relative to plasma concentration, valproic acid (free form) is concentrated in the CNS of dogs (Frey and Löscher, 1985). Its low protein binding might explain why it concentrates in the CNS. Other possible mechanisms for CNS penetration include its lipid solubility and carrier-mediated transportation. Valproic acid is nearly completely ionized at physiological pH, which suggests another mechanism, other than lipid solubility, would explain its rapid and profound entrance into the CNS. It has been shown to inhibit the transport of GABA out of the CNS, suggesting it uses the same carrier as GABA to gain entrance to the brain (Löscher and Frey, 1982). However, another mechanism of active transport, a medium-chain fatty acid transporter, has also been proposed (Adkison and Shen, 1996). Additionally, alterations in active efflux transport have also been suspected as a potential additional explanation for the inability of valproic acid to maintain high concentration in the CNS (Gibbs *et al*., 2004). Pretreatment with probenecid also enhances the rate of entry into CNS (Löscher and Frey, 1982).

Through glucuronidation and β-oxidation, the liver metabolizes valproic acid in the dog. It is excreted in the urine. It does not induce its own metabolism (Lockard and Levy, 1976). Of the three major metabolites of valproic acid, all are thought to have potential antiepileptic activity, although only one reaches significant concentration in the CNS (Boothe, 1998). Valproic acid can significantly alter liver enzymes in dogs, much more significantly than in humans, which is why it may possess a higher chance of liver toxicity in dogs compared to humans.

At doses of up to 60 mg/kg every 8 h in dogs, plasma concentrations in the reference range referable to humans (40–100 μg/ml) were not attained. Enteric-coated (slow-release) capsules also failed to reach *therapeutic levels* in dogs (Löscher, 1981). Löscher calculated a dose of 220 mg/kg would need to be given every 8 h to maintain a plasma concentration of 40 μg/ml in the dog. This would undoubtedly lead to hepatotoxicity in dogs.

Toxicity, Side Effects, and Interactions

Typically, valproic acid is used as an add-on therapy combined with phenobarbital. Its high rate of glucuronidation by the liver combined with that of phenobarbital makes its safety and potential to cause liver damage of paramount importance when considering its use. Hepatotoxicity is the most serious side effect in humans and likely to be significant in dogs. Ironically, it is used in conjunction with phenobarbital, which accelerates valproic acid elimination through the autoinduction of hepatic microenzymes.

Potential side effects include CNS depression, sedation, ataxia, GI upset, alopecia, rash, hematologic abnormalities (thrombocytopenia, leukopenia, and anemia), pancreatitis, and edema (Plumb, 2011).

In a single case of chronic (inadvertent) valproic acid ingestion in a cat, hyperexcitability, excessive grooming, and bilaterally symmetrical alopecia were reported (Zoran *et al*., 2001). The alopecia was deduced to be a direct effect of the medication and not due to excessive grooming. Hair thinning is also a commonly reported side effect of the medication in humans. The cat's serum valproic acid concentration was measured at 3.5 μg/ml, which is far less than the reference range of therapeutic serum concentration for humans, again *suggesting* cats may be significantly more sensitive to valproic acid when compared to dogs and humans.

Valproic acid may interact with many other drugs; consequently, caution should be used if it is considered for therapy. Valproic acid affects platelet aggregation; therefore, those patients with coagulopathies or on medications to prevent coagulation should be monitored closely. Free valproic acid concentration may be increased by the concurrent use of aspirin, which has the potential to displace it from plasma proteins. As previously mentioned, probenecid and phenylbutazone can increase valproate concentrations in the brain, although these drugs are rarely if ever used in dogs and cats. Valproic acid may interact with other CNS depressants to increase their sedative effects, and when used in conjunction with clorazepate, the antiseizure effects of both drugs may be lowered (Plumb, 2011).

Indications for Use

Several arguments have been proposed supporting the use of valproic acid for the treatment of epileptic seizures in dogs; these include:

- The reduced protein binding in the dog while speeding up its elimination also may result in greater CNS concentrations in dogs compared to humans. CNS concentration in dogs is approximately 22% of that in the blood, whereas in humans, the concentration in the CNS is 10% of that in the blood (Frey and Löscher, 1978). Valproic acid has a rapid entrance into the CNS and is considered one of the few antiseizure medications utilizing carrier-mediated transport (Löscher and Nau, 1983).
- Metabolites of valproic acid have antiepileptic activity. Their elimination rate may be significantly reduced to a point whereby they could have immeasurable antiepileptic effects. Although only one metabolite reaches significant concentrations in the CNS, antiepileptic effects of the drug may persist even after serum concentrations have been reduced to a *subtherapeutic* level. Experimental models of epilepsy support this notion, whereby the antiepileptic effects of valproic acid persist for hours even after serum concentrations are immeasurable (Lockard and Levy, 1976; Pellegrini *et al*., 1978). A reversibly acting antiepileptic drug has the characteristic of an effect that is directly related to its presence at the site of action and correlates with the concentration of the drug in the plasma.
- Valproic acid may be metabolized more complexly, whereby its effects are dependent on multiple biochemical processes, each with its own pharmacokinetics. This may explain why it is anecdotally reported to help control epileptic seizures in dogs and may have a greater potential than previously exploited in dogs and cats (assuming safety).

The addition of probenecid, a renal tubular secretion inhibitor used to treat *gout* in humans and reptiles, increases the concentration of and the rate of entry of valproic acid in the CNS in dogs by 40% (Frey and Löscher, 1978). Phenylbutazone (a nonsteroidal anti-inflammatory drug [NSAID], primarily used in horses) displaces valproic acid from its carrier proteins, thereby increasing the available amount of the free form to enter the CNS (Frey and Löscher, 1978). Phenobarbital may also have a similar effect, which is why some clinicians find valproic acid to be efficacious as an add-on therapy to phenobarbital in dogs being treated for epileptic seizures.

Very little is known about the disposition of probenecid in dogs and cats. The clinical use of phenylbutazone is also quite limited as "safer" NSAIDs are available for dogs and cats.

Valproic acid has been shown to be very effective in preventing epileptic seizures in experimental models of epilepsy using cats (Leviel and Naquet, 1977; Pellegrini *et al*., 1978). Because cats have a deficiency in hepatic glucuronidase, compared to dogs, the serum half-life would be expected to be greater. Therefore, cats may have the ability to maintain serum therapeutic concentrations in the range comparable to or greater than humans. Although little information regarding toxicity of cats given valproic acid is reported (note: research in general is not that

interested in the long-term safety of the experimental model), its safety and efficacy in an experimental or clinical setting have not been evaluated for cats. However, the characteristics of feline metabolism and efficacy in treating experimental models of epileptic seizures in cats, combined with the relative paucity of available antiepileptic medication for use in the cat, make valproic acid a potential interesting candidate for this species. Certainly, more research looking at the clinical efficacy and safety is necessary.

The combination of little clinical data suggesting efficacy, a need for tremendous experimentation in attempting to "force" CNS concentrations (by using adjunctive therapy), and an increased potential for hepatotoxicity makes valproic acid a complicated drug to be used in treating epileptic seizures in dogs and cats. Certainly, the availability of many other safe, efficacious, and relatively inexpensive medications will continue to limit the use of valproic acids in veterinary patients.

Dose

When used as add-on therapy in conjunction with potassium bromide or phenobarbital, the starting dose is 60 mg/kg every 8 h in dogs. However, there is very little *clinical* use of valproic acid published. Additionally, as previously mentioned, phenobarbital will increase the elimination rate of valproic acid, and the extensive hepatic metabolism of valproic acid, combined with phenobarbital, creates a greater potential for serious liver disease. Therefore, the use of valproic acid should be performed with caution. Valproic acid is available in multiple forms including 250 mg oral capsules, a 50 mg/ml oral syrup, and extended-release tablets and capsules in 125, 250, and 500 mg sizes. It is also available as a 125 mg oral sprinkle capsule and in a parenteral form for injection at a concentration of 100 mg/ml.

Monitoring

Monitor for efficacy and safety. It is recommended to routinely monitor CBC and biochemical profile including liver function tests (fasting and fed bile acids) if used chronically. In humans, valproic acid will alter thyroid function tests; however, it is not known if this effect is also present in dogs or cats.

ANTISEIZURE MEDICATIONS NOT USED IN DOGS AND CATS

When looking at the available medications used to treat humans with epileptic seizures, the clinician or veterinary caregiver will quickly realize there exist many more treatment options for humans compared to veterinary patients. This is partially due to a greater focus on the research community and pharmaceutical companies toward the study and development of medications, primarily for use in humans. In the development of drugs, a particular focus is the use of animal models, which have a disposition of the drug similar to humans.

Clobazam, a benzodiazepine, is a good example of why studies of the use of a drug have not been applied to the dog. The dog's species-specific metabolism of this drug creates a metabolite not found in other animals, including humans (Volz *et al.*, 1979). Because of the presence of this metabolite, the dog is not used as a model for the efficacy of clobazam in treating seizures. While the majority of efficacy and safety data is performed either with animal models of epilepsy or in animals for safety data, translation into common use for veterinary patients is limited due to a general lack of long-term safety and efficacy data. In the case of clobazam, a potentially useful drug for the treatment of canine epilepsy is lost to obscurity in the literature regarding the dog. Possible benefits of the use of clobazam in the dog include:

- Less serum protein binding (83% contrasted to 98% for diazepam)
- An extended half-life (3.2 h compared to 1 h for lorazepam)

- CNS concentrations equal to plasma concentration
- Maintenance of a long-term steady state

In addition to a metabolite not created in man, the above characteristics of clobazam may warrant further investigation for use in veterinary patients (Volz *et al.*, 1979). Like other benzodiazepines, clobazam has a high margin of safety in dogs (Schütz, 1979).

Other potential reasons for certain antiseizure medications used in humans but not used in veterinary patients include:

- Pharmacokinetic parameters (usually rapid elimination, occasionally too slow)
- Adverse effects (hepatotoxicity, cardiotoxicity, etc.)
- Lack of effect
- Lack of perceived benefit
- Lack of empirical data relating to drug disposition, safety, and efficacy

INAPPROPRIATE PHARMACOKINETICS

Commonly used drugs in human medicine may not achieve therapeutic concentrations in veterinary patients. The metabolic disposition of drugs is also very different between dogs and cats. Cats have a deficiency in glucuronide transaminase, a major metabolic pathway, for drugs, occurring in the liver. This makes some medications, rapidly metabolized by the dog liver, and *slowly* metabolized by the feline liver. The primary examples are the benzodiazepines, which have a significantly greater long-term effect in cats when compared to dogs and consequently also may have a greater risk of hepatotoxicity (although at the same time have increased efficacy when used long term). Due to profound hepatic metabolism, drugs such as carbamazepine, oxcarbazepine (and presumably eslicarbazepine), and valproic acid *do not* achieve serum therapeutic concentrations in dogs and are therefore not used to treat epileptic seizures in this species. They may be empirically used for other conditions such as behavior modification and neuropathic pain (e.g., carbamazepine and gabapentin).

ADVERSE EFFECTS AND TOXICITY

Numerous drugs that are well tolerated and commonly used for the treatment of epileptic seizure in humans are either toxic to dogs and cats or create negative side effects, which outweigh the positive effect of reducing seizures.

Primidone and *phenytoin* place an added stress to the liver in dogs and cats, making their use a challenge and a greater risk when compared to better-tolerated, safer, and more efficacious antiseizure medications.

Bromide is contraindicated in cats due to a substantially increased risk of developing typically reversible lower airway disease (Bertolani *et al.*, 2012).

Verapamil, a calcium channel blocker, fails to exert a therapeutic effect at doses lower than those that create negative side effects in dogs treated with the medication (Jambroszyk *et al.*, 2011). At higher doses, the calcium channel effects of verapamil begin to have a negative effect on the canine (and human) heart.

Lamotrigine, a blocker of voltage-activated sodium channels, has been discredited as a potential antiseizure medication in dogs due to the metabolism of the medication, which creates a 2-*N*-methyl metabolite unique to the canine species. The metabolite has been shown to prolong the

PR interval in a dose-dependent fashion when given to dogs (Wong and Lhatoo, 2000). The effect of prolonging the PR interval is also reported in humans but considered inconsequential and resolves with discontinuation of the drug (Buckley *et al*., 1993; Shorvon and Stefan, 1997). There is no published direct evidence that states lamotrigine is *definitely* cardiotoxic in dogs; however, because of the potential and availability of so many other well-tolerated antiseizure drugs, it is not used.

LACK OF EFFECT

Certain drugs, which are apparently well tolerated and exert a positive effect in humans, do not have an effect on reducing epileptic seizure frequency or intensity in dogs and cats (to a lesser degree in cats due to lack of investigation).

Vigabatrin is an analogue of GABA, which binds irreversibly to GABA *transaminase*, resulting in the permanent inactivation of the GABA-metabolizing system of the CNS. Side effects of using vigabatrin in dogs, including hemolytic anemia, combined with low efficacy have prevented its use in veterinary patients (Speciale *et al*., 1991). An irreversible retinal toxicity is reported in humans (Engel, 2013). At high doses (300 mg/kg/day), reversible intramyelinic edema will occur in dogs (Peyster *et al*., 1995).

LACK OF PERCEIVED BENEFIT

Of particular interest is the drug ethosuximide related to a lack of perceived benefit for the treatment of absence seizures in dogs. This drug has a narrow focus of treatment in humans and is only used to treat absence seizures. Absence seizures in humans may have a greater need to be treated when considering the psychosocial ramifications of the events and how these types of seizures may affect a person's day-to-day routine (driving, social interactions, work, etc.). Absence seizures have been documented in dogs (Poma *et al*., 2010), and they likely exist in cats; however, a significant amount of weight is considered when evaluating the benefit-to-cost/risk ratio of giving a pet a medication for a problem that may not significantly alter their quality of life. Could ethosuximide could have an effect on other types of seizures, especially for drug-resistant epileptics?

LACK OF DATA RELATING TO DRUG DISPOSITION, SAFETY, AND EFFICACY

Numerous drugs simply have not been evaluated in dogs and cats, as far as efficacy and safety are concerned. Clobazam, nitrazepam, and tiagabine are medications currently used in human medicine but for which little data exists in veterinary medicine.

ANTISEIZURE DRUGS UNDER DEVELOPMENT

The Antiepileptic Drug Development Program (ADD) screens potential new drugs for the treatment of epilepsy. New promising compounds are identified every year, and drug development in general is at a fast pace. There is no doubt by the time this publication is read, new potential anticonvulsants will be on the horizon and compounds mentioned in this section may be in clinical use (at least in humans). While most drugs used for the treatment of epileptic seizures in dogs and cats are primarily analyzed for their use and benefit in humans, we are fortunate there is a significant crossover in beneficial effects allowing dogs and cats to profit from drugs targeted for human development. Laws in the USA and Europe prevent the introduction of potentially harmful or ineffective drugs into the marketplace. The off-label use of the majority of antiseizure medications prescribed for dogs and cats allows veterinarians a great breadth of "experimentation." Keep in mind the development of most drugs approved for use in humans underwent extensive testing in

animal models of epilepsy, often with dogs and cats as the main test subjects. There are certainly many examples of drugs well tolerated in humans, which should not be used in veterinary patients. Many of the drugs listed in the following section are either in the final stages of clinical evaluation for use in humans or at the investigatory stage of development.

BRIVARACETAM

The discovery of levetiracetam led to a more directed search for other drugs that interacted with the Sv2a ligand (Kaminski *et al*., 2012). The Sv2a is responsible for assisting with exocytosis of synaptic vesicles, especially those involved with the release of excitatory amino acids. Brivaracetam was discovered to not only interact with Sv2a but do so with 15–30× times greater binding affinity than levetiracetam in rodent models (Gillard *et al*., 2011). Furthermore, brivaracetam also inhibits voltage-dependent sodium channels (Bialer *et al*., 2013). One potential important difference between brivaracetam and levetiracetam is brivaracetam's ability to reduce the occurrence of spontaneous busts. Spontaneous bursts are an indicator of drug resistance, making this medication a potential add-on to drug-resistant epilepsy (Bialer *et al*., 2007). Brivaracetam appears to be very safe in dogs, showing only transient CNS effects in an acute oral toxicity model (100 mg/kg and above). Brivaracetam appears to have similar efficacy and tolerability with minimal side effects as levetiracetam. Research on the use of brivaracetam in dogs or cats at the time of publication is not existent, however, initial pharmacokinetics in cats are showing promise. A single IV or oral dose (10 mg/kg) given to cats was well tolerated with some cats showing light sedation and one cat developing ptyalism (Jukier *et al*., 2024b). Oral bioavailability was 100% with a half-life of 6.6 h and following a single oral dose, median maximal concentration was within the reference range for humans (900 ng/ml for the cats with a reference range of 200–2000 ng/ml for humans). Brivaracetam also had a shorter T_{max} compared to levetiracetam in cats with the authors suggesting this as a potential advantage to using brivaracetam as a rescue medication. The authors also speculate, brivaracetam at a dosing interval of every 8 h, would reach a steady state in ~30 h with less fluctuations in serum levels (compared to levetiracetam) which may lead to better long-term seizure control for cats. Brivaracetam (Briviact®) was approved by the USA FDA in 2016 and is used to treat focal (partial-onset) seizures in humans 1 month of age and older. It is available in an injectable form (50 mg/ml), 10, 25, 50, 75, and 100 mg tablets, and a 10 mg/ml, oral solution.

CARBENOXOLONE

Carbenoxolone is a gap junction inhibitor that has been shown to suppress epileptiform activity in the brain through the regulation of neuronal synchronization via gap junction inhibition (Volnova *et al*., 2022). Carbenoxolone was shown to increase the latency time of seizure onset, as well as, the decreasing the seizure severity score after systemic administration to genetically epilepsy-prone rats (Gareri *et al*., 2004). Carbenoxolone has been investigated for use in treating pituitary-dependent hyperadrenocorticism in dogs and found to be well tolerated (Teshima *et al*., 2016). The dose used was 60–80 mg/kg/day. No published studies are looking at the use of carbenoxolone for the treatment of epileptic seizures in dogs or cats at the time of publication and it is not available commercially. Because pharmaco-resistance is a significant problem, the development of anticonvulsant medications, working through novel mechanisms is important to increase the multi-modal treatment of epilepsy.

FLUOROFELBAMATE

Fluorofelbamate has a mechanism of action like felbamate; however, substituting a fluorine atom for a hydrogen atom at the two-position of the propanediol moiety prevents the formation of atropaldehyde through the metabolism of felbamate, making it potentially less toxic (Łuszczki, 2009).

Atropaldehyde is a toxic metabolite of felbamate. It is suspected to interact with proteins (through conjugation) to produce free radical toxicity and has been implicated in the development of aplastic anemia associated with felbamate use in humans (Pellock, 1999).

GANAXOLONE

Ganaxolone, a synthetic neurosteroid, is a $GABA_A$ antagonist with activity like benzodiazepines without the development of tolerance (in humans) following continuous use. It has been shown to be effective for the treatment of epileptic seizures in humans (Laxer *et al.*, 2000; Pieribone *et al.*, 2007). Compared to benzodiazepines, neurosteroids have an equivalent potency but demonstrate a significantly greater effect (Akk *et al.*, 2007). Whether or not tolerance in dogs and cats develops is unknown. As a positive allosteric modulator of the $GABA_A$ receptor, chloride channel permeability will increase when ganaxolone binds to the $GABA_A$ receptor complex. Ganaxolone is a synthetic form of allopregnanolone, a neurosteroid, which has similar activity. The benefit of ganaxolone over the naturally occurring neurosteroid is lack of metabolism into hormonal active steroid by-products. Neurosteroids are known to be endogenous modulators of epileptic seizure susceptibility and exhibit broad-spectrum anticonvulsant activity (Reddy and Rogawski, 2012). Ganaxolone has been shown to be beneficial in treating humans with refractory status epilepticus (as an IV infusion) with a median time to cessation of seizure of 5 min (Vaitkevicius *et al.*, 2022). Additionally, it is has been shown to be beneficial when treating humans with nonconvulsive status epilepticus.

LOSIGAMONE

The exact mechanism of action of losigamone is unknown. It reduces the frequency of spontaneous epileptiform discharges through its effects on presynaptic sodium channels, as well as through the enhancement of chloride uptake in the absence of GABA. Furthermore, losigamone enhances the activity of GABA (Dimpfel *et al.*, 1995). Its broad spectrum of activity associated with *in vitro* settings extends to reduction of potassium-induced release of the excitatory neurotransmitters, glutamate and aspartate. It has also been demonstrated to suppress NMDA-induced depolarization (Xiao *et al.*, 2012). In one study of its use in humans, as an add-on therapy for focal epileptic seizures, those patients taking the medication were more likely to achieve a 50% (29.3% of participants) or greater reduction in seizure frequency in a dose-dependent manner (Baulac *et al.*, 2003). However, those treated with losigamone were also more likely to withdraw from the study compared to placebo.

PERAMPANEL

Perampanel is a novel antiseizure medication with a history of also being used to treat multiple sclerosis, Parkinson's disease, and neuropathic pain (Bialer *et al.*, 2013). Because of its widespread use, its tolerance and toxicity are well known. The novelty of perampanel stems from its mechanism of action, which is highly selective antagonism of the glutamate AMPA receptor. Excessive glutamate has long been suspected to have a role in the spread of epileptic seizures. Perampanel exerts its effects post-synaptically to reduce neural excitability (Rogawski and Löscher, 2004). AMPA receptors have been suspected to be involved in the spread of epileptic seizures; therefore, the antagonism of AMPA receptors may aid in the prevention of brain damage associated with seizures (Dingledine *et al.*, 1999). During episodes of status epilepticus, GABA receptors become internalized making benzodiazepines and second-line antiseizure medications (levetiracetam and phenobarbital) less effective. Prolonged, refractory status epilepticus may be induced partially

through the actions of glutamate and its binding to AMPA receptors. Perampanel has been shown to be effective for the treatment of refractory status epilepticus (Renna *et al*., 2024). Perampanel is approved for use in the USA and Europe as an add-on therapy for focal seizures with or without generalization, as well as generalized tonic–clonic seizures in people diagnosed with idiopathic epilepsy (older than 12 years).

TONABERSAT

Tonabersat is being developed as an antimigraine and antiseizure medication. It is thought to exert its effect through uncoupling of neuronal gap junctions, likely working at the level of blockage of connexin43 hemichannel pores (Lyon *et al*., 2020). It has shown promise in laboratory settings against maximal electroshock seizures (MES) and the tonic forms of PTZ-induced epileptic seizures (Bialer *et al*., 2013). Tonabersat displays significant ability to prevent the spread of seizures in several models of generalized epilepsy (Blower *et al*., 2013).

RETIGABINE (EZOGABINE)

The KCNQ potassium channels are a group of five voltage-gated potassium channels encoded by the KCNQ (Kv7) gene family. Mutations of these genes result in reduction of potassium current available to depolarize the cell. This creates a *hyperexcitable* cell. Retigabine has a direct effect on opening KCNQ2–5 potassium channels, enhancing voltage-gated M-current (neuron-specific *outward* potassium current) and subsequent depolarization. The M-current opposes other further depolarizing events, which subsequently reduces the likelihood of neuronal firing by lowering the membrane potential below the action potential threshold (Gunthorpe *et al*., 2012). KCNQ2–5 channels are predominantly expressed in neurons. Retigabine is a unique and novel anticonvulsant different from all other currently approved antiseizure medications, however, due to negative side effects (peripheral skin discoloration, bladder dysfunction, and abnormalities of the retina), it has been withdrawn from the market (in 2017). The toxicity stemmed from phenazinium (responsible for blue discoloration of skin and retina) metabolites derived from the oxidation of the triaminoaryl scaffold (Wang *et al*., 2024). Retigabine was the first specific Kv7.2/7.3 channel opener. It was originally approved for the treatment of focal seizures in 2011. At higher doses, retigabine also enhances GABAergic inhibition (Maljevic *et al*., 2008). A new compound (1025c) with a more photo-stable structure has been developed and shows improved antiseizure abilities compared to retigabine (Wang *et al*., 2024).

2-DEOXY-D-GLUCOSE

While investigating the efficacy of the ketogenic diet, the glucose analogue 2-deoxy-D-glucose was discovered to have antiseizure effects (Bialer *et al*., 2010). 2-deoxy-D-glucose is a structural analogue of glucose, differing only by the removal of an oxygen atom at the 2 position. Areas of the brain undergoing active seizures (i.e., uncontrolled neural activity) have an increased demand for energy, and glucose is delivered to these regions within seconds of increased demand. 2-Deoxy-D-glucose is *preferentially* delivered to these areas, and as a glycolytic inhibitor, it is thought to exert its primary mechanism of seizure control. 2-Deoxy-D-glucose is taken into active cells through the glucose transporter. Once in the cell, it is phosphorylated at the six-position by hexokinase to 2-deoxy-D-glucose-6-phosphate. However, unlike glucose-6-phosphate, further metabolism is prevented, thereby preventing the successive steps of glycolysis (Bialer *et al*., 2010). 2-Deoxy-D-glucose has a wide safety profile and is currently being investigated as an adjunctive therapy for neoplasia, migraine headaches, and epilepsy.

SUMMARY

Dogs and cats with refractory epilepsy are likely to benefit in the future with the development of new, more specific, more efficacious, and better-tolerated antiseizure medications. There are no true "antiepileptic" drugs as no drug can prevent the disease from occurring; however, drugs under development for use following head injury or other acquired insults to the brain may lessen the chance or prevent the development of epilepsy in these patients. The identification of genetic mutations leading to the development of channelopathies may provide future-specific gene therapy to prevent these forms of epilepsy. While animal models are primarily used to test the pharmacokinetics, mechanism of action and safety of antiseizure medications, the primary goal of research and pharmacological development lies in the *treatment* of human epilepsy, not its prevention. Fortunately, companion animals may also benefit from this development. An interesting side note is the case of imepitoin. While the drug has been largely abandoned for use in the treatment of human epilepsy, it shows promise for the treatment of canine and feline epileptic seizures and is the first drug specifically marketed for the treatment of canine epileptic seizures (at the time of this writing).

The newer generation of antiseizure drugs has very diverse molecular mechanisms of action, potentially providing novel and more specific treatment for refractory epileptics. Clinical trials with veterinary patients are essential to determine the efficacy and safety of these new medications. Furthermore, basic research elucidating the underlying cause of the various epilepsies affecting dogs and cats will also be beneficial as an enhanced understanding of the basic pathophysiological models of epileptogenesis and neuronal hyperexcitability will aid in the development of new antiseizure drugs. Many other drugs are currently under development, which were not included in this writing. New drugs are discovered and evaluated continuously and most likely, by the time of this publication, more experience with the drugs listed previously will have led to their use in veterinary patients.

Choosing an antiseizure drug should be based on the need for therapy, clinician's familiarity with the drug (or high safety profile), demonstrated efficacy of the drug, side effects of the drug, (as well as, safety) comorbidities of the patient, cost of the drug, dosing schedule (compliance), and effects on the lifestyle of the pet and its caretakers. It is important to consider all of these factors in order to achieve the best compliance. Try to avoid getting into a "rut." Remember to *fail a drug completely* (lack of effect at maximal dose or negative side effect), before adding on another.

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Emergency Management of Seizures

CHAPTER 8

KEY TAKEAWAYS

Give intranasal midazolam (0.2 mg/kg) upon presentation of a patient in status epilepticus unless IV access is present, then give IV.

Emergency management of status epilepticus should be approached similar to CPR.

Different time stages of status epilepticus will be responsive to different therapies.

Treat increased intracranial pressure early.

A team approach to management of status epilepticus is essential.

Hypothermia: Target: 36.7–37.7 °C (98–99.9 °F)

Hyperventilation: Target: $PaCO_2$ 28–32 mmHg (briefly)

QUICK JUMP

Emergency Treatment: Figure 8.1 and A2.17

Emergency Drugs Used to Treat Status Epilepticus: Table 8.1

Understanding Intracranial Pressure: Figure 8.2

How to wean off long-term (ER) medications 370

Status Epilepticus 351

Emergency Hospital/Clinic Management 356

Intracranial Pressure (ICP) 360

Traumatic Brain Injury (TBI) 372

Continued Monitoring and Care 373

Emergency Home Treatment 374

Myelominutia: Understanding the Cushing Reflex

STATUS EPILEPTICUS

INTRODUCTION AND DEFINITION

Status epilepticus (SE) is one of the most frightening events a pet owner can experience. It is also a significantly worrisome condition for the veterinarian to treat, creating an anxiety level similar to what many feel during the treatment of cardiac and respiratory arrest. Refractory SE

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can be particularly frustrating to treat. The veterinarian often feels as though they have run out of "tools" if a few doses of diazepam do not stop the event. Fortunately, the incidence of SE is uncommon, accounting for only 0.44–2.6% of veterinary hospital admissions (Bateman and Parent, 1999; Zimmermann *et al*., 2009). Treatment recommendations continuously change and are updated as the basic understanding of the pathophysiology of SE advances. It is important for the clinician to choose a treatment protocol they are comfortable with and stick with it rather than continuously changing methods as a result of the most recent literature. However, the clinician should be aware of the most current, accepted treatment modalities and their uses and limitations. Like cardiopulmonary resuscitation, there is no *half-hearted* treatment of status epilepticus. I approach every seizure in the hospital as though it has the potential to turn into SE. Status epilepticus is a pathophysiological state where the brain's inherent seizure-limiting mechanisms fail. It is essentially a seizure so severe it can create a lasting epileptic condition through permanent neuronal damage. The actual definition of SE has been debated for decades. Most definitions place a time constraint on the duration of a seizure for it to qualify as SE. A long-held definition was a seizure lasting greater than 30 min, as that time frame was associated with pathological brain damage in animal models of SE and a greater chance of inducing an epileptogenic site in deranged areas of the brain (Nevander *et al*., 1985; Cavalheiro *et al*., 1991). A 5 min time point has also been considered as seizures lasting longer than 5 min are less likely to spontaneously cease on their own and the majority of human generalized tonic–clonic seizures last less than 5 min (Lowenstein *et al*., 1999). Whether it is 5 or 30 min, SE is a *medical emergency*. The longer a patient is having a seizure, the greater the chance of medical complications. Outside of a research setting, an *operational definition* is best applied and can be defined as:

> *Repeated seizure activity without an intermission consisting of either continuous seizure activity lasting at least 5 minutes or 2 or more seizures with incomplete recovery between seizures.*
>
> (*Saito et al., 2001*)

Since most generalized tonic–clonic seizures last less than 1 min, any seizure lasting greater than 2–3 min should be considered as potentially *impending SE*. This does not include repeated seizures over a given period, where the patient regains consciousness. However, these *serial seizures* should be treated like SE (Engel, 2013). We should not watch a seizure and wait for the time period of 5 min to decide whether to treat or not. If in the time it takes you to draw up medications the seizure has stopped; give them anyway. It may prevent the next one.

Cluster seizures are defined as two or more, self-limiting seizures occurring within 24 h (Berendt *et al*., 2015).

EPIDEMIOLOGY/ETIOLOGY

It is estimated up to 60% of dogs with genetic epilepsy (primary or idiopathic) will have an episode of SE in their life (Saito *et al*., 2001). Like humans, SE is more likely to occur in dogs and cats with structural brain disease or reactive (i.e., toxic or metabolic) causes of seizures (Platt and Haag, 2002; Schriefl *et al*., 2008). In cats, SE is more commonly associated with a nonconvulsive state characterized by focal facial seizures, often with normal mentation (Platt, 2001). Sudden unexplained death syndrome, with death usually occurring during or shortly after a generalized tonic–clonic seizure, has been previously reported in dogs but considered rare (~0.02%) (Arrol *et al*., 2012). However, *probable* sudden unexplained death in dogs with epilepsy (pSUDED) (where

dogs died due to recurrent or unprovoked seizures, where no pathological confirmation was performed) has been estimated as high as 10% (range 4.5–10%) (Huenerfauth *et al*., 2021). In humans, sudden unexplained death in epilepsy patients (SUDEP), where no pathological cause of death can be found is estimated to be as high as 17% of all epilepsy-related deaths (Li and Buchanan, 2019).

Severe epileptic syndromes reported in specific breeds (e.g., Border Collies and Australian Shepherds) tend to result in more episodes of SE, cluster seizures, and pharmaco-resistance (Hülsmeyer *et al*., 2010; Weissl *et al*., 2012). The longer a seizure is present, the more refractory to treatment it becomes (Serrano *et al*., 2006). The prognosis associated with SE is variable and must consider several factors. Considerations such as the length of time of the seizure, the cause of the seizure, the presence of comorbidities, the patient's body temperature, and the state of consciousness following the seizure, to name a few, are important indicators of prognosis. The faster the seizures are brought under control, the better the prognosis. Patients who have SE lasting longer than 6 h, those who have another episode of SE within 6 h of the first, and those with structural brain disease (particularly meningitis of unknown etiology—i.e., granulomatous meningoencephalomyelitis), brain tumor, or traumatic brain injury (TBI) have a more guarded prognosis (Bateman and Parent, 1999). Complications associated with SE include (but are not limited to) cardiac arrhythmia, electrolyte and glucose imbalances, rhabdomyolysis, and pulmonary edema. SE with generalized tonic–clonic seizures almost always results in hyperthermia and a more profoundly altered brain metabolic state. Hyperthermia may lead to complications associated with multiorgan failure, respiratory distress, and disseminated intravascular coagulation. Sustained muscle contractions and subsequent rhabdomyolysis can result in myoglobinuria, which may damage the kidneys. Other types of seizures may also progress to SE. These include absence seizures and focal seizures, although the lack of severe muscle contractions makes those seizures naturally less dangerous to the patient. These focal (i.e., "psychomotor") seizures may go unnoticed for hours in cats (Kline, 1998; Pakozdy *et al*., 2014a). Even without obvious motor manifestations or subtle behavior changes, persistent epileptiform activity on EEG monitoring may indicate SE. Electrographic seizures (non-convulsive seizures NCS) and non-convulsive status epilepticus (NCSE) can only be determined by EEG examination. In a retrospective examination looking at the incidence of NCS and NCSE in dogs and cats with cluster seizures, 29% had NCS diagnosed with EEG (9/38 patients—9 dogs and 2 cats) and 16% (4 dogs and 2 cats) had NCSE (Tästensen *et al*., 2024). Patients who do not recover from SE or have repeated episodes of SE in the hospital or cluster seizures should ideally be evaluated with EEG. Prolonged states of unconsciousness (either due to pathology or chemically induced) increase the risk of aspiration pneumonia and metabolic disturbances.

Economic euthanasia is a significant concern in veterinary medicine. Pet owners may be unable to bear the cost associated with extended hospitalization stays and diagnostics, even though, if given enough time and supportive care, most animals experiencing an episode of SE will recover. A major difference in the prognostic outcome is the underlying etiology of the seizures. Most episodes of SE, in dogs or cats, are due to *acute symptomatic* causes such as brain tumor, stroke, hemorrhage, or encephalitis (Schriefl *et al*., 2008; Rossetti and Lowenstein, 2011). Due to the severity of most of the underlying causes, mortality in these cases tends to be very high. It's also important to be aware of the clinician's power to influence an owner's decisions. For example, while statistically, it may be more likely for a patient who has or is experiencing SE, to have structural brain disease, using statistics to paint a *doom and gloom* prognosis for owners without offering time or diagnostics, may unintentionally "coach" them to euthanize their pet. The mortality rates in humans are about 50% if associated with

structural brain disease and would certainly be higher in veterinary patients due to the financial limitations of owners and practical treatment differences (i.e., uncommon to use routine intracranial pressure (ICP) monitoring, continuous EEG, induced coma, etc.) (Barry and Hauser, 1993). The mortality rate of dogs admitted to a veterinary teaching hospital suffering from SE was determined to be 25%. Only 2% of the dogs naturally died because of their disease. The other 23% were euthanized (Bateman and Parent, 1999). Death rates of dogs with cluster seizures and SE associated with genetic or unknown causes (i.e., idiopathic epilepsy) due to euthanasia are reported from 66 to 100% (Hülsmeyer *et al.*, 2010; Monteiro *et al.*, 2012). Euthanasia due to suffering or economic factors is one aspect of the decision-making process. There is, however, another element that is often unrecognized by clinicians. This element is *euthanasia due to ignorance*. In these cases, the decision to euthanize a patient by the owners of the pet is prompted by a general unawareness or lack of knowledge regarding the disease and its potential ramifications. It is further supported by a clinician who does not understand the condition and who may be frustrated due to lack of response to treatment (because of lack of knowledge or lack of specific therapeutic modalities and patient care). This is not ignorance in the pejorative but rather simple *unawareness*. As previously mentioned, the pet owner may be frightened, worried, and emotionally tapped after several days in the hospital and facing the unknown. They often ask if their pet is feeling "pain" when they are having a seizure. They seek validation (from the veterinarian) for decisions to euthanize based on the "suffering" of the pet. While the clinician cannot predict the future, their experience and advocacy for the patient can provide valuable insight to a caregiver and "peace of mind." Knowledge of the potential outcome may help to prevent premature euthanasia (see Chapter 4). Empathy toward the client naturally generates compassion. A generally good tenet to follow is "always expect the best, until proven otherwise." As stated previously, for example, just because a geriatric Golden Retriever presents with new-onset seizures, do not assume brain tumor, stroke, or hemorrhage until proven otherwise (i.e., imaging of the brain, cerebrospinal fluid (CSF) analysis, or progressive interictal deficits unrelated to seizure activity). All that aside, dogs and cats with stroke or hemorrhage often make a full recovery and brain surgery to remove a tumor can be "curative" for both the neoplasia and epilepsy (see Figure 5.3 and Chapter 10).

SE is more common in large-breed dogs (Knowles, 1998; Saito *et al.*, 2001). Intact males tend to be overrepresented, and Labrador Retrievers are the most common breed presenting with SE (Podell *et al.*, 1995; Jaggy and Bernardini, 1998; Monteiro *et al.*, 2012). The condition is also common in cats although they more frequently present with focal seizures. Episodes of SE are estimated to be as high as 33% of cats with a seizure disorder (Quesnel *et al.*, 1997; Fatzer *et al.*, 2000). It can often be a complete surprise as prior to their first episode of SE, 44% of dogs had not experienced any previous epileptic seizure activity (Platt and Haag, 2002).

PATHOPHYSIOLOGY

Why do most seizures stop? While the exact mechanisms are unknown, a polymechanistic modality is suspected, resulting in the cessation of seizures. Mechanisms include active inhibition of neuronal firing (i.e., GABAergic inhibition), loss of synchrony, depolarization blocking mechanisms, and increases in extracellular potassium. Experimentally, endogenously secreted neuromodulators, such as adenosine, are released during SE. Adenosine controls neural networks through a variety of mechanisms including presynaptic inhibition of glutamine release, stabilization of postsynaptic membranes, and other G-protein-mediated effects to result in neuronal homeostasis (Boison, 2013). Numerous changes occur within the brain during a seizure, which have the potential to create a self-sustaining event becoming progressively

pharmacoresistant (Wasterlain and Chen, 2008). These mechanisms are not completely understood but include:

- Abnormal persistence of excessive excitation and ineffective recruitment of inhibition.
- Internalization of $GABA_A$ receptors. Hippocampal expression of $GABA_A$ receptors declines after 1 h of SE. Additionally, $GABA_A$ receptor subunits are increased within the cells, and synaptic expression declines. The internalized GABA receptors are either destroyed by lysosomes or recycled back to the cell surface by the Golgi apparatus.
- Increased expression of NMDA receptors. Contrary to $GABA_A$ movement internally, there is an increased expression of NMDA receptors (glutaminergic–excitatory) in the synaptic membrane leading to enhanced neural excitability.
- Increased glutamate release due to altered synaptic activity.
- Reduction of the chloride gradient across the neuronal cell membrane.
- Depletion of inhibitory neuropeptides, such as dynorphin, galanin, somatostatin, and neuropeptide Y.
- Overexpression of proconvulsant neuropeptides, such as tachykinins, substance P, and neurokinin B.
- Changes to calcium/calmodulin-dependent kinase II.

These multiple mechanisms may explain why a seizure event can become self-sustaining. Excessive and sustained glutaminergic neurotransmission is thought to play a major role along with the inherent anatomy of the hippocampus and parahippocampal structures, leading to the formation of *reverberating* circuits (Nair *et al.*, 2011). Additionally, the time-dependent nature of the changes may explain why benzodiazepines become *less* effective after a prolonged seizure and NMDA receptor antagonists (i.e., glutamine antagonism), such as ketamine, may be beneficial for a protracted seizure (i.e., SE lasting longer than 20 min) (Kapur and Lothman, 1990; Borris *et al.*, 2000; Serrano *et al.*, 2006). These mechanisms may explain why pets treated prior to admission with at-home pulse therapy (e.g., rectal valium or intranasal (IN) lorazepam or midazolam) may have a better long-term outcome. Using benzodiazepines in the home environment, prior to $GABA_A$ receptor internalization, may prevent the development of or attenuate an episode of SE. The idea of a polymechanistic cause for the development of SE also raises the question of using concurrent multimechanistic approaches to stopping the seizure (i.e., a benzodiazepine *and* levetiracetam at the same time) (Chen and Wasterlain, 2006). Waiting for one drug to fail prior to giving a second or third drug may allow time for further proconvulsant properties to be expressed. This knowledge may also open the door for the use of other antiseizure drugs, known to be effective in stopping experimentally induced seizures but lost in obscurity as treatment for veterinary patients, due to failure to maintain long-term therapeutic concentrations in dogs and cats. Valproic acid (VA) may be one of the "older" drugs up for new consideration for the treatment of SE in veterinary patients. It is considered relatively safe, and significant research has been performed in animal models, including dogs and cats, showing it to be effective and having broad-spectrum effects at seizure suppression (Pellegrini *et al.*, 1978; Löscher, 1981, 2002). VA is used for treating refractory SE in humans (Rossetti and Lowenstein, 2011). The old notion of giving more benzodiazepine if the first or second dose did not stop the seizure should be questioned (although, it is still recommended). Seizures lasting longer than 30 min in experimental models are rarely controlled by benzodiazepines and other GABAergic mechanisms (i.e., phenobarbital), although NMDA receptor antagonists and other blockers of glutaminergic neurotransmission are highly effective (Chen and Wasterlain, 2006). It may be more appropriate to switch to a different

mechanistic approach in cases of prolonged SE (i.e. greater than 10 min). However, there is still a significant concern that most clinicians "underdose" even the first administration of benzodiazepines.

EMERGENCY HOSPITAL/CLINIC MANAGEMENT

INITIAL ASSESSMENT AND TREATMENT

Dogs and cats may *arrive* at the hospital in a state of actively having (or recovering from) an epileptic seizure, or they may already be at the hospital when they have an epileptic seizure. We should be as concerned with *serial seizures* and *nonconvulsive* SE as with *convulsive* SE. When a pet arrives at the hospital, an owner who is scared, worried, and emotionally charged will accompany them. It is important at first to take care of the pet but also to take care of the client. The pet should be triaged and immediately taken to a treatment area by hospital staff. Reception staff or other hospital staff should comfort the client and ensure them the pet is being taken care of. A private exam room is usually very helpful. The client should be updated as soon as possible and kept apprised as to the status of their pet.

Emergency management of seizures should follow some general guidelines (Figure 8.1). It is important to consider all necessary steps to proceed at the same time as much as possible. A team approach like that employed in CPR will be beneficial to the patient. It is helpful to have specifically designated duties for triage nurses, assistants, and doctors. If the required people are not available at the time, establishing an airway, normalizing blood pressure, and stopping the seizure should be the priority. All the following should be occurring at approximately the same time (note: there is significant variability in dosing recommendations, especially for the benzodiazepines. Please refer to a veterinary formulary for ranges):

- *Stop the seizure* (Table 8.1). Give IN **Midazolam** while another team is establishing IV access. Use the IN gel formulation if possible or the injectable form with a nasal atomizer. Administer appropriate drug in the correct route. Intravenous (IV) access is always preferred; however, *IN* (**midazolam or** lorazepam), *intramuscular* (lorazepam or **midazolam**), or *rectal* (diazepam) routes can be used if IV access is not available. Oral (i.e., buccal) administration of the injectable form of lorazepam or midazolam is also acceptable; however, ptyalism and trismus may limit its absorption. If a patient has been historically treated with phenobarbital, increase diazepam dose by 25–50%. Note: lorazepam binds to the GABA receptor with an affinity that is 2–4 times greater than midazolam and almost 10 times greater than diazepam (see Figures 7.1 and 7.2).
- *Level one*
  - First-choice drug for seizure less than 30 min **with IV access** (choose 1)
    - **Midazolam:** 0.1–0.2 mg/kg IV
    - **Lorazepam:** 0.1–0.2 mg/kg IV
    - **Diazepam:** 0.5–1 mg/kg IV (increase by 25–50% if with history of chronic phenobarbital)
  - Second choice (if no IV access)
    - **Midazolam:** 0.1–0.2 mg/kg IN, IM, or buccally
    - **Lorazepam:** 0.1–0.2 mg/kg IN, IM, or buccally
    - **Diazepam:** 1–2 mg/kg rectally or IN

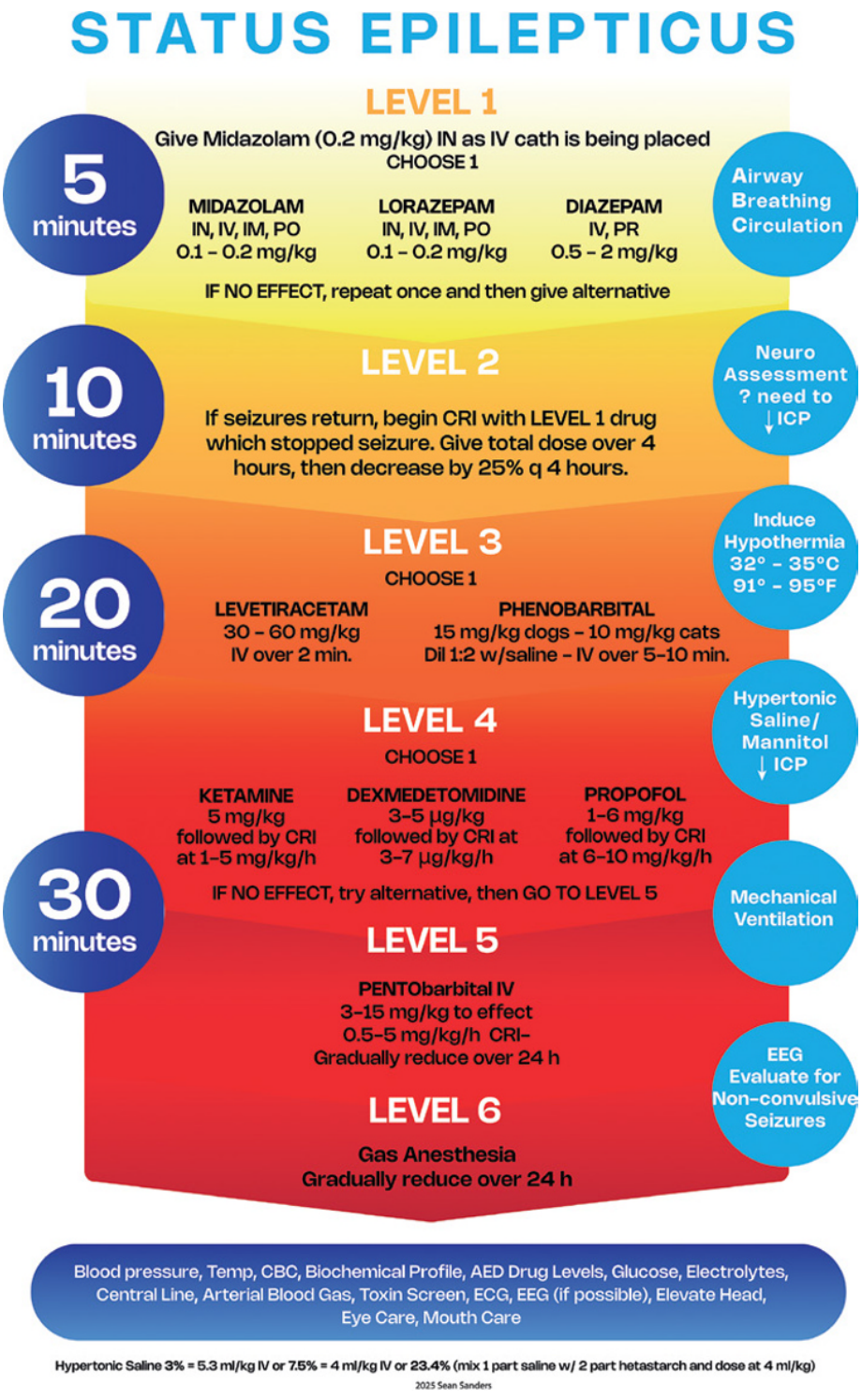


FIGURE 8.1 Flowchart for the management of acute seizure or status epilepticus. If the patient started having seizure 20–30 min prior to presentation, start at LEVEL 1. If no effect, skip to LEVEL 4. If patient is currently managed with phenobarbital, increase benzodiazepine dose by 25–50% and phenobarbital dose by 25%. Note: upon entrance to the hospital, give IN midazolam while an IV catheter is being placed. *Source:* Sean Sanders—www.theneurovets.com.

Table 8.1 Emergency drugs used to treat status epilepticus.

Drug	Starting dose	Time to effect	CRI	Level
Midazolam	0.1–0.2 mg/kg **IV**, IM, **IN**, or buccally	30 s to 5 min	0.1–0.2 mg/kg/h	1, 2
Lorazepam	0.1–0.2 mg/kg **IV**, IM, **IN**, or buccally	30 s to 5 min	0.1–0.2 mg/kg/h	1, 2
Diazepam	0.5–2.0 mg/kg **IV**, IN Double dose for rectal admin. Incr. by 25–50% if taking Pb chronic	30 s to 10 min	0.25–0.5 mg/kg/h	1, 2
Phenobarbital	10–15 mg/kg IV—dog 10 mg/kg IV—cat (dilute 1:2 with saline) over 5–10 min	5–30 min	No	3
Levetiracetam	30–60 mg/kg IV over 2 min	5–60 min	No	3
Propofol	1–6 mg/kg IV or to effect	Immediate	6–10 mg/kg/h, not recommended for cats	4
Dexmedetomidine	3 μg/kg IV over 5 min	Immediate	3–7 μg/kg/h	4
Ketamine	1–5 mg/kg IV over 5 min	Immediate	1–5 mg/kg/h	4
Pentobarbital	5–15 mg/kg IV or to effect	Immediate	0.5–5 mg/kg/h	5
7.5% hypertonic saline	4 ml/kg IV PRN[a] over 2–5 min	5 min	No	1–5
3% hypertonic saline	5.3 ml/kg IV PRN[a] over 2–5 min	5 min	No	1–5
23.4% hypertonic saline with hetastarch	Mix 1 part 23.4% saline with 2 parts hetastarch dose at 4 ml/kg IV PRN[a]	5 min	No	1–5
Mannitol (20%)	7.5 ml/kg IV q 6–8 h[b] (1.5 g/kg) over 15–20 min	20–30 min	No	1–5
Dopamine	1–10 μg/kg/min IV; adjust as needed	Immediate	1–10 μg/kg/min; adjust as needed	1–5
Dobutamine	5–15 μg/kg/min IV; adjust as needed	Immediate	5–15 μg/kg/min; adjust as needed	1–5

[a] Do not use if hyper- or hyponatremic. Monitor sodium levels consistently.
[b] Do not use if hypovolemic. Be careful if serum osmolality is >310 mOsm/l or sodium >155 mg/l.

If seizure continues, **repeat** or use alternative benzodiazepine above. If seizure stops and then starts again, start:

- *Level two*
  - Continuous rate infusion (CRI) after giving another bolus of the benzodiazepine which stopped the seizure the first time.
    - **Begin CRI** of the benzodiazepine, which stopped the seizure. Give total dose used to stop the seizure as a CRI over 1 h.

If seizure does not stop after two doses of benzodiazepines or starts again while on a benzodiazepine CRI, administer loading dose of prophylactic antiepileptic drug (AED) (choose 1 below):

- *Level three (choose 1)*
  - **Phenobarbital** (recommended if no concurrent liver disease): loading dose at 15 mg/kg (10 mg/kg cats) IV slowly over 5–10 min. Best to dilute phenobarbital injection with sterile saline at a ratio of 1:2. May need to intubate. May take 5–20 min to have effect. If patient has historically been treated with phenobarbital, increase dose by 25%.
  - **Levetiracetam:** loading dose at 30–60 mg/kg IV over 2 min.

If seizure does not stop by the end of the prophylactic AED infusion, administer injectable general anesthetic (choose 1 below):

- *Level four (choose 1)*
  - **Propofol:** 1–6 mg/kg followed by a CRI at 6–10 mg/kg/h (0.1–0.6 mg/kg/min) if seizure resumes
  - **Ketamine**: 5 mg/kg IV followed by a CRI at 5 mg/kg/h if seizure resumes (Serrano *et al*., 2006)
  - **Dexmedetomidine**: 3–5 µg/kg IV followed by a CRI at 3–7 µg/kg/h if seizure resumes

If seizure starts again after giving one of the above, administer the other.
If seizure continues, institute barbiturate coma (level 5). Mechanical ventilation may be necessary as well as maintenance of blood pressure (e.g., dopamine or dobutamine). Avoid phenylephrine due to potential for CNS excitation:

- *Level five*
  - **PENTObarbital**: 3–15 mg/kg IV (dog or cat) given to effect (not total dose). If seizures continue, consider CRI at 0.5–5 mg/kg/h IV. Gradually reduce over 24 h. Patient will most likely require *intubation*.

The clinician will rarely need to go beyond *level one*.

- *Perform a physical and neurological exam*. Clear the airway of saliva or debris (i.e., vomitus). The most common type of seizure during SE in a dog is the generalized tonic–clonic (i.e., a sequence of a tonic followed by a clonic phase), generalized clonic (i.e., rhythmic myoclonus, usually involving the same muscle groups, repetitive contractions at ~2–3 cycles/s), or generalized tonic (i.e., sustained increase in muscle contraction lasting a few seconds to minutes see videos 1–4). Cats are more likely to have focal seizures with or without dyscognition (see Appendix 1). These are obvious; however, extreme neck pain, a vestibular event, or choking could also be mistaken for an epileptic seizure. Assess patient for indications of elevated ICP. These may include anisocoria, miosis, mydriasis, abnormal posturing (e.g., decerebrate), or altered respiratory patterns (e.g., Biot's breathing, Cheyne–Stokes, apneustic., etc.) (Figures 8.3 and 8.4).
- *Place a catheter*. While the patient is being assessed and the drugs are being retrieved, IV access should be obtained through the placement of an IV catheter if not already done. Collect blood for hematological and biochemical analysis, antiseizure drug concentrations (do not use a serum separator tube), arterial blood gas, glucose, and electrolytes. Place a central line. Monitor ECG and pulse oximetry.
- *Provide supportive care*. Ensure a patent airway. Administer oxygen and ventilator support (if necessary) through face mask or endotracheal tube. Raise the patient's head to between 15° and 30° and try to keep the patient *sternal* to avoid any dependency in a lung field. Do not occlude jugular veins with towels used to prop up the head, placed under the neck (this will

increase ICP). If hyperthermic (common with sustained generalized tonic–clonic seizures lasting more than 5 min), apply active cooling such as ice packs, wet towels, and fan. To avoid hypothermia, active cooling should be stopped once the temperature drops to 39 °C (103 °F) unless the clinician's goal is to make the patient hypothermic (see Chapter 10). Therapeutic hypothermia temperature ranges for dogs in the refractory phase of SE are reported as 33–35 °C (one case) and 36.7–37.7 °C (three cases) (Hayes, 2009; Gioeni *et al*., 2020). Start fluids with appropriate crystalloids or colloids to maintain hydration and normal blood pressure.

- *Get an accurate history from the owner*. Ask about exposure to toxins or illicit substances (common and uncommon), recent vaccinations, travel history, medical history, and any current medications the patient or any family members are taking that the patient may have had access to.

CONTINUED SUPPORTIVE CARE AND PREVENTION OF SEIZURES

At this point, the patient has stopped actively having the seizure, an IV catheter is placed (ideally a central line and at least one peripheral line), fluids are running, blood work is being processed, and the pet's owners have been informed as to the status of the pet. While the nurses are monitoring the patient, the doctor is finalizing a physical/neurological exam, reading through notes on history and asking more questions if necessary. A neurological exam should have been performed to determine if ICP is elevated. State of consciousness, pupil changes, respiratory patterns, and posture are important determinants of impending or current brain herniation. A *complete physical exam* is essential to identify abdominal masses, cardiac arrhythmias, pulse deficits, perfusion, etc. If anisocoria, bilateral miosis or mydriasis, or decerebrate posturing is present, administer hypertonic saline or mannitol (Table 8.1).

INTRACRANIAL PRESSURE (ICP)

Detailed descriptions on the underlying pathophysiology of elevated ICP and its treatment are available (Bagley, 2005; Dewey, 2008; Sande and West, 2010).

The brain is encased in a rigid structure (i.e., the skull). Within the skull, there are three main components consisting of the brain parenchyma, the blood volume (venous and arterial), and the CSF. To maintain ICP (typically between 5 and 15 mmHg), any increase of one component or the addition of any other component (i.e., edema, inflammatory cells, tumor, etc.) must be countered by a reduction in the other components or ICP will increase. This is known as the *Monro–Kellie doctrine*. A state of equilibrium exists in normal brain. Intracranial compliance through fluid shifts between the brain vasculature and CSF maintains this state of equilibrium. If compliance fails, ICP will increase, which can lead to altered cerebral perfusion and ischemic damage to the brain. A relationship exists defined as

$$CPP = MAP - ICP$$

This simple equation relates cerebral perfusion pressure (CPP) to the mean arterial pressure (MAP) minus the ICP. Mean arterial pressure "pushes" blood into the brain and ICP "pushes" blood out of the brain. In order for the brain to be adequately perfused, the MAP must be greater than the ICP. If ICP is increased or MAP is decreased, brain perfusion is decreased. A target CPP of 60–70 mmHg has been established by the Brain Trauma Foundation (Carney *et al*., 2017). CPP is a critical determinant of cerebral blood flow (CBF). Other factors which may also reduce CPP include:

- Hypotension
- Hyperthermia
- Hypoxia/anoxia
- Hyper- or hypoglycemia
- Hyper- or hypocapnia

CBF is maintained through an autoregulatory process. If MAP is maintained between 50 and 150 mmHg, CBF will be consistent and constant. If MAP is outside of the autoregulatory zone, small changes to blood pressure can result in increased ICP and subsequent brain herniation or decreased cerebral perfusion and subsequent ischemic damage to the brain (Figure 8.2).

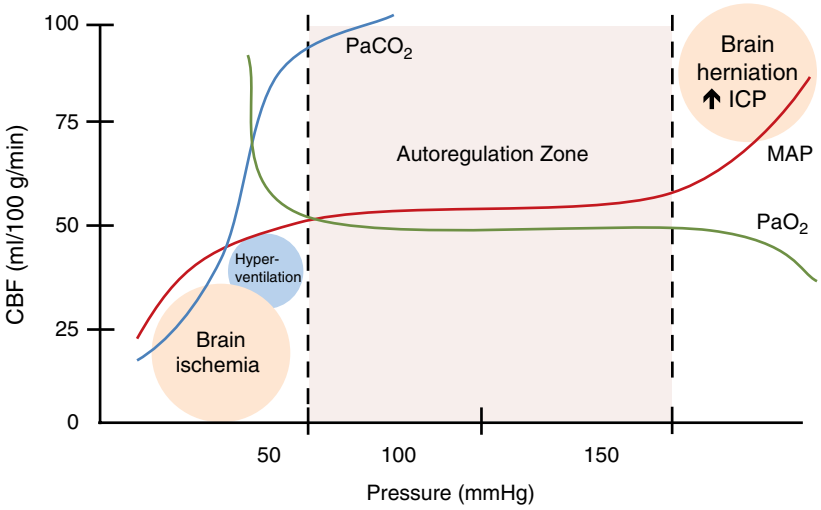


FIGURE 8.2 Diagram of cerebral autoregulation *in a normal brain*. As long as systemic blood pressure (MAP—red line) is maintained between 60 and 150 mmHg, cerebral blood flow (CBF) is constant and consistent. Small changes in blood pressure outside of the zone of regulation will cause dramatic changes in intracranial pressure (ICP), potentially leading to brain herniation or decreased brain parenchyma perfusion leading to ischemic damage. The partial pressure of CO_2 (blue line) also plays an important role in cerebral autoregulation. With hyperventilation, the $PaCO_2$ drops significantly causing the cerebral vasculature to constrict. This constriction reduces intracranial pressure by restricting the amount of blood getting into the brain. Hyperventilation can be a useful tool when there is impending herniation secondary to increased ICP, however, it is a fine balance between lowing ICP and cerebral ischemia. Target end tidal CO_2 ($ETCO_2$) in cases of increasing ICP should be about 35 mmHg (via capnograph). A short-term (minutes) $ETCO_2$ of <30 mmHg is acceptable for cases of acute decompensation. Of greater importance is to make sure the $ETCO_2$ does not go to the high end of normal (or higher) as this may significantly increase CPP exacerbating an increase in ICP. Let's also look at PaO_2 (green). The total amount of oxygen getting into the brain is fairly high, probably 3× more than is actually needed. Because of this, a substantial decrease in arterial O_2 levels is needed before cerebral vasculature steps in and dilates (to increase blood flow to the brain). Vascular resistance does not drop (blood vessel dilation) until PaO_2 levels fall below ~50 mmHg and then the body shifts into overdrive to get as much oxygen to the brain as possible. Generally, one can assume, supplemental oxygen is *not* necessary in this particular situation. Note: on this graph, I am using a common *x*-axis of pressure but there are no corresponding relationships between MAP, $PaCO_2$, and PaO_2. They just happen to plot out in this manner. Any intersectionality is only coincidence.

The *Cushing reflex* (i.e., cerebral ischemic response) is a sympathetic-mediated, systemic vasoconstriction (to increase systemic blood pressure) in response to an increase in ICP. As ICP increases, there is a reduction in CPP and CBF. The response, reflex, or effect (take your pick) is an effort to overcome the increase in ICP to prevent further ischemia to the brain. The vasomotor center of the brain (located in the medulla oblongata) senses increased CO_2 concentrations in the vasculature due to reduced tissue oxygenation. A systemic sympathetic response to increase MAP to increase CPP is generated. A *reflex bradycardia* develops, either mediated through baroreceptors in the carotid arteries and the aortic arch, which sense the systemic hypertension and trigger the *bradycardia,* or through compression of the intracranial vagal nerve (Tsai *et al*., 2018). There is a widened pulse pressure (increased systolic and decreased diastolic) and irregular respirations (Dinallo and Waseem, 2023). The irregular respirations occur in the later stages of the reflex. Once brainstem respiratory centers start to become compromised, either due to the increase in ICP or herniation/compression, shallow breaths with periodic apnea will eventually lead to agonal breathing if ICP is not lowered. If you see the Cushing Reflex, it implies brainstem herniation is soon to follow. Ideally, we are managing ICP, as best as we can, prior to the Cushing reflex developing. Altered levels of consciousness, hypertension, and tachycardia are important to watch for as they usually precede the Cushing reflex.

The effect of ischemia on the brain results in primary tissue damage and secondary damage to surrounding tissues through the generation of reactive oxygen species (ROS), production of proinflammatory cytokines, and activation of the arachidonic acid and coagulation cascades. ROS (i.e., free radicals) damage cellular membranes and promote further inflammation. Progressive hypoperfusion of brain tissue and subsequent acidosis, along with the effects of increased excitatory neurotransmitter activity (i.e., glutamate), may result in the generation of ROS. The excessive brain activity through the action of excitatory neurotransmitters (particularly glutamine) results in the depletion of ATP. As ATP is the cellular "fuel," membrane ion pumps begin to fail, leading to a disruption of ion homeostasis resulting in an influx of sodium and calcium ions into neurons and glial cells. Calcium influx leads to further cellular depolarization, release of more excitatory neurotransmitters, intracellular damage, and death. The culmination of this activity leads to cytotoxic (i.e., cellular) edema.

If we recall the Monro–Kellie doctrine, edema and inflammation of the brain can lead to increased ICP. Therefore, treatment of intracranial edema to lower ICP would be beneficial to the patient.

ASSESSMENT OF ICP

Lowering ICP, if necessary, is paramount to a successful outcome in the treatment of SE. The administration of hyperosmolar fluids such as hypertonic saline and mannitol is an established treatment. Hyperventilation, patient position, treatment to reduce spinal fluid production and vasogenic edema may also be considered. Indications of impending brain herniation or increases in ICP include anisocoria, miosis, mydriasis, decerebrate posturing, and alterations in respiratory patterns. Changes to pupil reactivity along with altered consciousness indicate diffuse forebrain disease, thalamic disease, or potential brain herniation (Figure 8.3). As ICP increases, the brain may herniate under the tentorium cerebelli or falx cerebri, leading to compression of the oculomotor nerve (CN III) or the oculomotor nuclei (rostral mesencephalon), causing pupil constriction and/or disruption of sympathetic fibers responsible for pupil dilation. The interruption of parasympathetic innervation to the eyes (CN III) will cause various degrees of mydriasis. Compression of the diencephalon, hypothalamus, or tectum (i.e., dorsal mesencephalon—rostral and caudal colliculi) may also disrupt sympathetic input to the pupils leading to miosis. As the midbrain is compressed upper motor neuron influence from the prosencephalon is reduced, leading to a release of lower motor neurons from the oculomotor nucleus (less

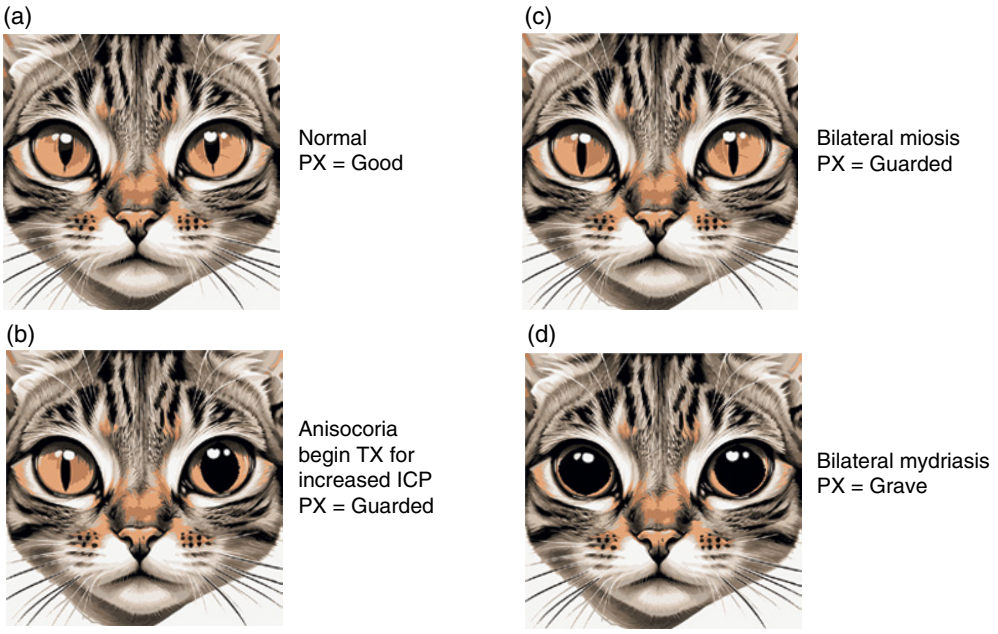


FIGURE 8.3 Representation of various pupil changes as intracranial pressure increases. (a) Normal. (b) Anisocoria. Implies compression of the oculomotor nucleus (rostral mesencephalon at the level of the rostral colliculi) or an individual oculomotor nerve. (c) Bilateral miosis. Progressive compression of the midbrain causing the oculomotor neurons to be released from inhibitory influence from upper motor neurons coming from the prosencephalon. (d) Bilateral mydriasis due to continued compression of the midbrain. Treatment for increased ICP should begin the moment anisocoria develops. Changes occur rapidly. Frequent monitoring of pupil size is recommended. In addition to the pupil changes, the patient's mental status will correspondingly decline. Adapted from de Lahunta, A., Glass, E., Kent, M. 2021. Veterinary Neuroanatomy and Clinical Neurology. 5th ed. St. Louis, MO: Saunders Elsevier. With permission of Elsevier.

inhibition = more constriction). Pupils tend to become fixed and unresponsive in a midrange state when the brainstem is compressed either through tentorial herniation or by the cerebellum as it herniates through the foramen magnum. This reflects disruption of both sympathetic and parasympathetic innervation to the eyes, although it can occur with oculomotor compression alone (de Lahunta *et al.*, 2021).

Compression of the brainstem and diffuse cerebral or diencephalic disease may also lead to altered respiratory patterns (Figure 8.4) (Bagley, 2005). *Biot's breathing* is characterized by irregular periods of apnea followed by 4–5 breaths of identical depth from a lesion in the area of the pons. A *Cheyne–Stokes* respiration is a repeating pattern of progressively deeper and occasionally rapid breathing, followed by a gradual decrease in respiration culminating in apnea due to bilateral cerebral hemispheric disease or diencephalic disease (or both). Other patterns such as tachypnea (central neurogenic hyperventilation) and *apneustic* breathing (one–two small breaths followed by apnea in a regular and repeating pattern) may also be indicative of damage or compression to the brainstem. An *ataxic* breathing pattern that is completely irregular is occasionally seen with compression of the medulla oblongata. These patterns may indicate forthcoming cardiac arrest. *Decerebrate posturing* is a combination of opisthotonus (head and neck extended dorsally) along with rigid extension of all four limbs (Figure A2.4). Compression of the midbrain (interruption of descending prosencephalic input to the pontomedullary reticular formation) results in a "release" of alpha and gamma lower motor neurons, which innervate extensor muscles, from their inhibitory upper motor neuron influence, resulting in extension of all limbs (along with being stuporous or

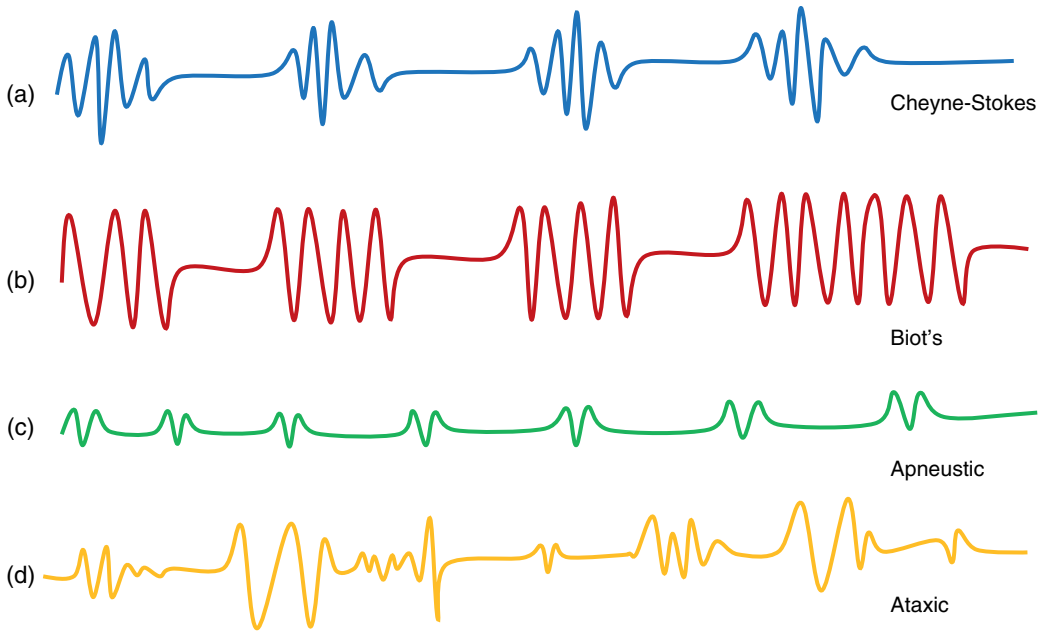


FIGURE 8.4 (a) Cheyne–Stokes breathing is characterized by progressively deeper and occasionally rapid breathing, followed by a gradual decrease in rate culminating in apnea. Usually caused by bilateral cerebral disease or compression of the diencephalon. (b) Biot's breathing is characterized by 4–5 breaths followed by irregular periods of apnea due to compression of the medulla. (c) Apneustic breathing pattern characterized by 1–2 small breaths followed by apnea in a regular and repeating pattern caused by lesions in the area of the pons. (d) Ataxic breathing characterized by a completely irregular breathing pattern from a lesion in the medulla oblongata.

comatose), similar to the release mechanism of the oculomotor neurons. Experimentally, a lesion between the rostral and caudal colliculi will create the same effect (de Lahunta and Glass, 2009). The facilitatory centers of the pontomedullary reticular formation and the vestibular system will function autonomously resulting in the extension of axial postural and limb muscles, whereas the inhibitory centers of the pontomedullary reticular formation require constant forebrain input to exert an inhibitory influence over muscle extension. The ascending reticular activating system of the brainstem is also involved, resulting in a severely altered sensorium or lack of consciousness (i.e., coma). The prognosis associated with this posture is grave, and emergency attempts to lower ICP should be undertaken. Decerebrate posturing should not be mistaken for *decerebellate* or *Schiff–Sherrington* posture (Figures A2.5 and A2.6). Decerebellate posture may look very similar to decerebrate, although the pelvic limbs may be flexed along with extended forelimbs (but not always). A lesion in the rostral cerebellar vermis or adjacent cerebellar hemispheres may create this posture. With Schiff–Sherrington posture, there is rigid extension of the forelimbs and flaccid paralysis of the rear limbs. This results from severe spinal trauma to the T3–L3 segments of the spinal cord, resulting in a disruption of inhibitory influence on thoracic limb extensors from a collection of interneurons located in the gray matter of the L1–L7 spinal cord segments (concentrated between L1 and L4). These interneurons, known as *border cells*, send their axonal processes cranially to innervate thoracic limb extensor lower motor neurons in the C6–T2 spinal cord segments. A significant differentiating feature between decerebrate posture and *decerebellate* or *Schiff–Sherrington* posture is the lack of consciousness *always* associated with the decerebrate posture.

TREATMENT OF INCREASED ICP

Hyperosmotic Agents

One of the most important elements of a successful outcome in the treatment of SE is the maintenance of normal blood pressure and adequate fluid resuscitation along with the reduction of ICP if it is elevated. Hypertonic saline and mannitol have both been shown extensively to reduce ICP when used appropriately. Both of these treatments *also* have the ability to expand systemic fluid volume. Hypertonic saline is well recognized as having the potential to rapidly reduce ICP *and* provide fluid resuscitation with a small volume (Kreimeier and Messmer, 2002; Lewandowski-Belfer *et al*., 2014). Using 7.5% hypertonic saline combined with 6% dextran solution has been shown to be more effective in lowering ICP, having a more rapid effect and lasting longer than mannitol alone (Battison *et al*., 2005). The blood–brain barrier is relatively impermeable to sodium ions. The hyperosmolar saline solution rapidly creates a shift (i.e., "pull") of intracellular and interstitial water into the cerebral vasculature resulting in a rapid decrease of ICP by reducing brain water content, within minutes of its infusion. Other positive effects of hypertonic saline to the brain include (Sande and West, 2010):

- Improvement of regional CBF by decreasing endothelial cell edema, thereby causing vasodilation, improved CBF, enhanced delivery of oxygen to tissues, and reduced ICP.
- Modulation of the inflammatory response in the brain by decreasing adhesion of polymorphonuclear cells to the microvasculature.
- Promotion of glial uptake of excitatory amino acids, thereby decreasing brain excitotoxicity.

The volume expansion created (fluid resuscitation) is far greater than the amount of hypertonic saline infused. Because it is a crystalloid and will redistribute rapidly to other fluid compartments, the effect of hypertonic saline at volume expansion is short lived, only lasting up to 75 min although the effect of decreasing ICP lasts much longer (Smith *et al*., 1985). If added to a synthetic colloid (e.g., hetastarch), the effect of hypertonic saline is prolonged for several hours, by retaining the solution within the vasculature and maintaining an osmotic gradient, through prevention of redistribution. Hypertonic saline should only be given to normonatremic patients (i.e., do not give if hyponatremic or hypernatremic). A hyponatremic patient treated with hypertonic saline has a risk of developing central or extra-pontine myelinosis (Laureno *et al*., 2018). With a hypernatremic patient who is made even more hypernatremic, there is a risk of creating an additional pathology that could result in seizures (encephalopathy secondary to hypernatremia). A recommended dose is 4 ml/kg of 7-7.5% or 5.3 ml/kg of 3% hypertonic saline given over 2–5 min. Additionally, a solution of 1 part 23.4% hypertonic saline combined with 2 parts 6% hetastarch and dosed at 4 ml/kg is recommended to provide long-lasting volume expansion and reduction of ICP (Sande and West, 2010). Repeated doses of hypertonic saline alone can have beneficial effects, and it can be alternatively dosed along with mannitol (Surani *et al*., 2013). Monitor sodium levels and serum osmolality. Prevent dehydration by providing maintenance isotonic crystalloids.

Mannitol has been used for decades, *safely* and with demonstrated efficacy in decreasing ICP although there are concerns about possible complications associated with its use (i.e., exacerbation of intracranial hemorrhage in cases of traumatic brain injury) have led to a shift toward the more common practice of using hypertonic saline in its place (Wakai *et al*., 2013). Many of the concerns regarding intracranial hemorrhage are unfounded and the potential benefits would outweigh the risks; however, hypertonic saline may possess more benefits. The mechanism of action of mannitol is suspected to be the reduction of blood viscosity through transient plasma volume expansion, in addition to promoting a shift of intracellular and interstitial water to the vasculature, thereby reducing ICP and increasing systemic blood pressure (Muizelaar *et al*., 1983). A reduction of blood viscosity leads to cerebral vascular vasoconstriction to maintain CBF. Cerebral blood volume is

decreased, leading to reduced ICP while still maintaining adequate CBF. The effect of mannitol at volume resuscitation will last for approximately 75 min like hypertonic saline alone; however, it takes 15–30 min after administration to exert its effect as opposed to the almost immediate effect of hypertonic saline. The effect of mannitol at lowering ICP may last for hours. Mannitol is also a free radical scavenger and may help prevent cellular damage due to oxidation. High-dose mannitol (~1.4 g/kg) has been shown to be more beneficial than low-dose (~0.7 g/kg) in reversing clinical signs associated with impending brain death in humans (Cruz *et al.*, 2004). Mannitol should be used with caution in hypovolemic patients as it has a profound diuretic effect, potentially leading to further volume depletion. Both mannitol and hypertonic saline should be combined with appropriate crystalloid therapy to maintain adequate hydration. The use of furosemide combined with mannitol has been shown to *not* have any additive effect, and because it may further precipitate hypovolemia through diuresis, the use of furosemide is *not recommended* by the Brain Trauma Foundation concurrently with mannitol to reduce ICP (Bratton *et al.*, 2007a). Mannitol should be given at 1.5 g/kg (7.5 ml/kg of a 20% mannitol solution) as a slow IV bolus over 15–20 min.

Hyperventilation

Cerebral blood vessel diameter is controlled in part by plasma CO_2 tension, as well as hydrogen ions and oxygen tension. Cerebral blood vessels respond to intravascular CO_2 concentrations in a normal brain with intact autoregulation. As $PaCO_2$ increases (hypoventilation), cerebral blood vessels dilate to increase blood flow to the brain. Increased blood flow to the brain leads to increased ICP. This *chemical* portion of autoregulation allows CBF to be maintained at a relatively constant rate despite fluctuations in blood pressure (i.e., *pressure* autoregulation) or CO_2 concentration. As $PaCO_2$ decreases (i.e., hyperventilation), cerebral blood vessels constrict, leading to a decrease in cerebrovascular volume and associated decrease in ICP (Bagley, 2005). A capnograph can be very useful if the patient is intubated. A targeted end-tidal CO_2 ($ETCO_2$) of 35 mmHg is a reasonable goal. A short-term (i.e., minutes) $ETCO_2$ of <30 mmHg may be used in acute decompensating patients; however, it is not recommended to be sustained as continued cerebral vascular vasoconstriction may lead to dangerously low CBF and subsequent further ischemic damage to the brain (Figure 8.2) (Bratton *et al.*, 2007b). If patients are not intubated, supplemental (i.e., mask or nasal cannula) oxygen should be provided with a targeted SpO_2 of >95%. Oxygen cages are not recommended as they prevent adequate evaluation of the patient. In a rapidly decompensating patient, intubation and mechanical ventilation may be necessary to transiently lower ICP while waiting for other methods to take effect (i.e., hypertonic saline or mannitol).

Other Considerations to Lower ICP

- Elevation of Head—Patient sternal
- Proton Pump Inhibitors—Omeprazole and Pantoprazole
- Carbonic Anhydrase Inhibitors—Acetazolamide

Care should be taken to make sure the jugular veins are not occluded while treating a patient in SE, this can be done by placing the patient on a stiff board and elevating the entire patient (Sande and West, 2010). Proper elevation of the patient's head between 15° and 30° from the horizontal axis of the treatment table will also help to maximize venous drainage of the brain. The patient should be in sternal recumbency in order to equally ventilate all lung fields.

The proton pump inhibitor *omeprazole* has been shown to experimentally decrease CSF production in rabbits and in normal dogs (dogs by 26%) (Lindvall-Axelsson *et al.*, 1992; Javaheri *et al.*, 1997). The mechanism of action is unknown but not related to proton pump inhibition (Lindvall-Axelsson *et al.*, 1992). Omeprazole has been successfully used combined with prednisone

and as a sole therapy, to medically treat hydrocephalic dogs (Amude *et al*., 2013; Pelegrini *et al*., 2019). Considering a patient in emergent need of ICP reduction is likely to not be able to take oral medications, it would be reasonable to use pantoprazole given IV during the initial course of treatment for dogs and cats (10 mg/kg IV over 15 min). Once the patient has recovered from SE and is able to take oral medications, omeprazole may be used as a gastroprotectant with additional effects of lowering ICP through attenuation of the production of CSF, if needed (10 mg/kg PO q 24 h for animals <20 kg and 20 mg/kg q 24 h for animals >20 kg) Amude *et al*., 2013; Dewey and da-Costa, 2016; Pelegrini *et al*., 2019). Only short-term therapy (or even just a single IV dose) should be necessary at the 10 mg/kg q 24 h dose (1–2 days).

The carbonic anhydrase inhibitor *acetazolamide* has been used clinically to lower CSF production and therefore ICP in humans (Shinnar *et al*., 1985; Carrion *et al*., 2001). There is limited evidence of clinical use in veterinary patients, with the exception for the treatment of glaucoma. The most common neurological use in veterinary patients is associated with the treatment of syringohydromyelia and experimental data showing its effect on the reduction of CSF production and flow in cats and dogs (Watanabe *et al*., 1976; Vogh 1980). Long-term use for this disease to treat syringohydromyelia in dogs with Caudal Occipital Malformation Syndrome may be associated with lethargy, abdominal pain, and weakness (Rusbridge *et al*., 2006). Carbonic anhydrase inhibitors reduce CSF production via the noncompetitive, reversible inhibition of the enzyme carbonic anhydrase. This inhibition decreases the availability of bicarbonate and hydrogen ions from carbonic acid making them less available to bodily fluids. They reduce blood flow to the choroid plexus which reduces CSF production by 40–90% within 3 h of administration (Holloway and Cassin, 1972; Watanabe *et al*., 1976). A reasonable, short-term dose for dogs or cats to reduce ICP would be 10 mg/kg IV once or every 12 h for 1–2 days, if needed. In this application, long-term side effects of carbonic anhydrase inhibitors (which may be several) should not be of concern.

Corticosteroids

A discussion of the treatment of SE and therefore, neurological disease, would not be complete without mentioning the use of corticosteroids. It is a controversial topic but I will try to present an argument that at the very least may lessen your concerns about their use. Ultimately, it is up to the clinician *in the moment* to decide what is best for their patient. Medicine is a nice balance between evidence-based science and the art associated with judgment. I believe we can judiciously use certain corticosteroids and still "do no harm." Corticosteroid use is not recommended in cases of head trauma (Alderson and Roberts, 2005). The evaluation of the use of corticosteroids to reduce ICP in cases of SE should be considered on a *case-by-case* basis. As mentioned in the *2024 ACVIM Consensus Statement for the Management of Cluster Seizures and Status Epilepticus in Dogs and Cats*, the immunomodulatory effects of corticosteroids have been shown to suppress signal pathways associated with the maintenance of SE, especially those patients in the super-refractory category (SE that continues past 24 h despite being treated with anesthesia (Shorvon and Ferlisi, 2011; Charalambous *et al*., 2024). Glucocorticoids have been shown experimentally to reduce CSF production in adult, healthy dogs (Watanabe *et al*., 1976). Humans presenting with SE due to inflammatory disease of the brain may benefit from corticosteroids (Pantazou *et al*., 2019). When the patient is a known idiopathic epileptic, whose seizures are controlled with phase I, II, or III medications (the benzodiazepines, phenobarbital or levetiracetam), there is likely no benefit (or harm) to using corticosteroids. However, as the patient progresses through the various phases getting closer and closer to the super-refractory level 5 treatment, one could certainly argue the use of steroids in moderation for their anti-inflammatory and therefore anti-edema properties (preferably methylprednisolone sodium succinate—Solu-Medrol® at 0.5 mg/kg q 12 h) is a reasonable consideration. Foundational evidence does not exist to support this recommendation; however, a significant amount of observational data does exist and one to two anti-inflammatory

doses are generally considered safe, in the author's opinion. Caution should be exercised when a patient is on a propofol CRI, as there is an increased risk of developing propofol infusion syndrome when also treated with corticosteroids (Hemphill *et al*., 2019). Corticosteroids may act as a *primer* for the development of propofol infusion syndrome. We should try to avoid corticosteroids such as dexamethasone (while cheaper and easier to obtain) that are known to cause more significant side effects and avoid the large doses associated with immunotherapy (Levine *et al*., 2008). Most clinicians will admit corticosteroids play a major role in the treatment of intracranial disease, where there is an increase in ICP (e.g., space-occupying mass, encephalitis, hemorrhage, or edema). Undoubtedly, most clinicians have witnessed firsthand the remarkable turnaround a patient can have clinically after even one dose of corticosteroids used to reduce ICP (typically when treating complications from an intracranial mass). If a significant portion of patients presenting with SE have structural intracranial disease, then treating the inflammation or edema associated with the disease may help reduce some of the negative consequences of sustained SE or increased ICP *if it is performed judiciously and with caution*.

A relationship between a hyperglycemic state and negative outcome exists in cases of traumatic brain injury (TBI). Hyperglycemia potentiates neuronal injury through the generation of ROS, increased excitatory amino acid release, cerebral acidosis, alterations in cerebral vasculature, and increased cerebral edema. Because of complications associated with immunosuppression, gastric ulceration, delayed wound healing, and hyperglycemia, corticosteroids are contraindicated both in human medicine and veterinary medicine in cases of TBI (Syring *et al*., 2001; Alderson and Roberts, 2005; Bratton *et al*., 2007c).

If a patient in SE is suspected to have structural, progressive brain disease such as neoplasia or encephalitis, reasonable anti-inflammatory doses of corticosteroids may help reduce inflammation associated with the underlying disease and improve seizure control. Because many patients are already taking corticosteroids when they present in SE, one should use caution if they are already hyperglycemic. However, in the face of declining clinical status and refractory SE, the benefits of corticosteroid administration may outweigh the risks. The author will use a dose of 0.5 mg/kg every 12 h of methylprednisolone sodium succinate (MPSS) (Solu-Medrol®) IV or prednisone (prednisolone in cats) PO to help reduce ICP through the reduction in the production of CSF, increased absorption of CSF, and reduced inflammatory response in the brain. Additionally, corticosteroids are known to stabilize cell membranes and are free radical scavengers. Corticosteroids are also known to be *toxic* to neurons, although it is unclear if this is a direct effect or a secondary effect through altered intracranial metabolism. Corticosteroids are not benign and are tapered if the patient shows any evidence of gastrointestinal ulceration (e.g., hematemesis, hematochezia, melena, vomiting, anemia, etc.). The use of dexamethasone has been shown to have more severe side effects when compared to prednisone. Neither omeprazole nor misoprostol was shown to be effective in either healing or preventing gastric ulcers in recumbent dogs (Neiger *et al*., 2000). However, gastroprotectants are advised with famotidine, omeprazole, and pantoprazole considered the safest (i.e., no inhibition of cytochrome P450) and the most effective at *increasing* gastric pH (Bersenas *et al*., 2005). Finally, just as an aside, the use of pulsatile, high-dose corticosteroids (dexamethasone) has been shown to be beneficial in treating children with infantile spasms and genetic pharmaco-resistant epilepsy (Schiller *et al*., 2024). Ultimately, when faced with a patient in the super-refractory state, you may have nothing to lose (see also Chapter 7).

NONEMERGENCY SEIZURE CONTROL (HOSPITAL)

Antiseizure Drugs

The patient may experience a second seizure or be actively having cluster seizures in the immediate postictal time period or shortly after the seizure (i.e., hours). If the patient presents with its first seizure or is not on any current antiseizure medication, the patient should be given a loading dose

of either phenobarbital (assuming liver function is adequate) at 10–15 mg/kg (diluted 1:2 with sterile saline) and injected IV over 10 min or levetiracetam at 30–60 mg/kg IV over 10 min. For cat use, a loading dose of 5–10 mg/kg of phenobarbital (as high as 20 mg/kg) or 30 mg/kg of levetiracetam. If the patient is unconscious, care should be taken to monitor closely for reduced gag reflex or the need to be intubated. Use your best judgment. If the patient is unconscious following the administration of the drugs used to stop the active seizure, the clinician may consider waiting to see if the patient becomes more responsive before giving a loading dose of another antiseizure drug. It takes approximately 5–30 min for phenobarbital concentrations to reach the brain; therefore, the patient should be monitored closely and assessed frequently.

If the patient is currently being treated for epileptic seizures with a prophylactic antiseizure medication, prior to presentation, increase the dose by 25% as soon as the patient can take oral medications and start a *bridge* therapy. Options include midazolam, diazepam, levetiracetam, or the longer-acting oral benzodiazepines such as clorazepate, or clonazepam to temporarily prevent seizures while waiting for a new steady state of the prophylactic drug to develop. As always, exercise caution when using an oral benzodiazepine in cats. This strategy may be used for a few days to several weeks depending on the drug (see Chapter 6 under Strategies). If the patient is already at maximum therapeutic levels or dosages, a second or third antiseizure medication can be considered (Figure 6.8). Loading doses of both potassium bromide and levetiracetam can be given to dogs rectally. For potassium bromide, a loading dose may be given by administering the calculated maintenance dose (30 mg/kg) every 4–6 h for a total of 10–15 doses (Table 7.3—Appendix 3). This may cause excessive sedation, ataxia, and transient diarrhea. Sodium bromide may also be given IV; however, the availability is limited in an emergency, and other alternatives are available (Tables 6.6 and 6.7). The injectable form of levetiracetam (100 mg/ml) may be given rectally at a dose of 40 mg/kg, with serum therapeutic concentrations being reached within 10 min of dosing (Peters *et al.*, 2014). There are no studies in the literature looking at the use of levetiracetam rectally in cats. One would assume it to be safe and effective, however, other methods of short-term control would be more reasonable to consider, unless the cat was already being treated with levetiracetam as a prophylactic.

If seizures resume, stop them as before using similar if not identical protocols used to stop the initial seizure event and consider constant short-term seizure control using one of the following methods in order (note: there is significant variability in dosing recommendations, especially for the benzodiazepines. Please refer to a veterinary formulary for ranges):

- Lorazepam or midazolam IV (repeated boluses). Lorazepam should have an activity of approximately 4–6 h and can be given multiple times during a hospitalization stay to prevent continuous seizures. Midazolam may also be used in this manner. Once the patient is awake and able to take pills, oral clorazepate, clonazepam, or levetiracetam may be started as *bridge therapy*. Clorazepate is the weakest benzodiazepine and clonazepam is the strongest (Figures 7.1 and 7.2).
- Diazepam CRI. If a central line is placed, diazepam is given as an infusion with a syringe pump. The IV tubing should be covered to protect the diazepam from light (white tape or aluminum foil). The IV lines should be flushed with diazepam solution to saturate the binding sites on the plastic tubing (MacKichan *et al.*, 1979). The dose is 0.5–2.0 mg/kg/h; however, you can simply give the total amount used to stop the seizure over 1 h, as this dose often works well. If a central line is not placed, the diazepam should be diluted in 5% dextrose (D5W) to avoid precipitation. The author recommends continuing the diazepam CRI at 100% strength for 4 h and then reducing the dose by 25% every 4 h. If seizures return during the weaning period, the patient is given the previous dose, as a bolus, used to stop the seizure and returned to the last level of diazepam given as a CRI prior to the return of seizures. Diazepam should be used cautiously in cats due to the potential to develop fulminant hepatic necrosis, although this complication has only been reported with oral forms (Center *et al.*, 1996).

- Ketamine IV (dogs and cats) at 5 mg/kg followed by a 5 mg/kg/h CRI if seizures return (Serrano *et al*., 2006). Use caution, however, as ketamine may cause CNS stimulation. Benzodiazepines tend to become less effective in the later stages of seizures as GABA receptors become internalized within cell membranes (Kapur and Macdonald, 1997). NMDA receptor antagonism has been shown to be effective in treating prolonged SE and to have neuroprotective effects (Fujikawa, 1995; Borris *et al*., 2000). NMDA receptor activation is present in the later stages of SE but not in the early stages (Kapur and Lothman, 1990).
- Dexmedetomidine IV (dogs or cats) as an IV bolus followed by a CRI in combination with ketamine has been reported to treat SE successfully *in dogs* combined with hypothermia (Gioeni *et al*., 2020). In this report, ketamine was given at 1 mg/kg IV over 5 min followed by a dexmedetomidine bolus of 3 µg/kg IV over 5 min. These boluses were immediately followed by a ketamine CRI at a rate of 1 mg/kg/**h** for 12 h and a dexmedetomidine CRI at a variable rate of 3–7 µg/kg/**h**. The patient's body temperature was maintained at 36.7–37.7 °C.
- Propofol. A propofol infusion at 6–10 mg/kg/h may be used like diazepam, *titrated to effect*, and weaned by 25% every 4 h. Caution should be used when given chronically in cats due to the possibility of developing Heinz body anemia and in patients who are being treated with steroids (to lessen the risk of propofol infusion syndrome). Patients should be intubated.
- PENTObarbital IV as a bolus at 3–15 mg/kg slowly to effect or a CRI if needed at 1–3 mg/kg/**h**. Patients should be intubated. Monitor closely for cardiac and respiratory depression, hypothermia, and hypotension.
- Gas anesthesia. In the first edition of this book, I recommended against the use of gas anesthesia to control seizures. Gas anesthesia will increase ICP (through its vasodilatory mechanisms) and should be avoided as pre-existing increases in ICP are likely to be present and near or above those levels associated with natural compensation. This may be due to existing structural brain disease or secondary to the pathology associated with SE. Gas anesthesia will increase ICP in *normal* animals, albeit still within the compensatory range (generally considered to be between 13 and 20 mmHg for a short amount of time). Cerebral perfusion pressure (CPP) is also reduced in a dose-dependent manner with isoflurane or sevoflurane anesthesia (Chohan *et al*., 2013). Animals at the edge of decompensation may be pushed over the edge by inhalant anesthesia. *However*, inhalant anesthesia may be considered as a *last resort* when all other options have been exhausted (Charalambous *et al*., 2024).
- Weaning a patient off either a CRI or anesthesia should be done gradually. Many factors may shape your decision timeline (cost of daily hospitalization, owner's pressure, availability of medications, etc.). I personally like to go a minimum of 4 h with subsequent reductions of medications by 25% every 4 h thereafter, as long as seizures do not return. If they do return, go back to the last effective dose and start the weaning period again but with a longer initial time course. Suggestions of waiting a minimum of 12 h and often 24–48 h prior to initiating the weaning protocol have been made in the ACVIM consensus statement on treating status epilepticus and cluster seizures (Charalambous *et al*., 2024).

If the patient presented in SE or had a seizure lasting longer than 5 min, consider treatment with an agent directed at *decreasing* ICP (see preceding text).

Corticosteroids

The use of corticosteroids in neurological patients in the post-emergency time frame tends to be less controversial but still creates significant debate among clinicians enthusiastically arguing about the advantages and disadvantages of corticosteroid use. Individual experience and preference will dictate

their use. Currently, there is no conclusive evidence steroids are beneficial for the treatment of epileptic seizures, although as previously mentioned, the immunomodulatory effects of corticosteroids may have benefit along with the potential for reducing ICP through the reduction of CSF production (Charalambous *et al*., 2024). I tend to approach novel cases, where I do not know the underlying cause of the seizures, as if anything is possible and therefore consider I am treating a potential case of inflammatory or structural brain disease, where corticosteroids, used carefully, may have a benefit and rarely cause harm. We also have significant evidence of cerebral edema secondary to seizure activity in dogs and cats through MRI examination in the post-seizure state. With known cases of traumatic brain injury (TBI), corticosteroids *should not be used*. A significant amount of shared pathophysiology exists between the TBI and SE. TBI may include blunt trauma, vascular accident (i.e., stroke or hemorrhage), and to some degree tumor or encephalitis, as all etiologies have the potential to *traumatize* the brain but for the most part, we are referring to blunt force trauma to the brain when we avoid corticosteroids. Numerous studies have demonstrated pathological damage to the brain (particularly the hippocampus) in both experimental animal models of SE and naturally occurring SE (Aroniadou-Anderjaska *et al*., 2008). Understandably, postmortem evidence of human brain damage following naturally occurring SE is scarce. Chronic unremitting epilepsy in humans may lead to memory loss and altered cognition, although these consequences are not common and brain damage secondary to naturally occurring seizures is generally regarded as inconsequential. In cats, however, there is sufficient evidence to warrant concern, as it appears many cats with epilepsy do suffer from pathological changes to the hippocampus and piriform lobe (Fatzer *et al*., 2000). Some of these changes may be related to autoimmune destruction of the hippocampus (Bien *et al*., 2007; Tüzün and Dalmau, 2007; Podell, 2008). Antibodies directed at leucine-rich glioma inactivating factor 1 (LGI1), which is a component of the voltage-gated potassium channel (VGKC) complex of cats, have been identified (Pakozdy *et al*., 2013). A cat confirmed to have epileptic activity on EEG along with magnetic resonance imaging (MRI) changes to the hippocampus bilaterally tested positive for the VGKC-complex/LGI1 antibody and was successfully treated with antiseizure medications and corticosteroids (Pakozdy *et al*., 2014a). An association has been made between this form of *limbic encephalitis* and human limbic encephalitis. Corticosteroids may unknowingly or *knowingly* treat many inflammatory or autoimmune forms of epilepsy. Animals with underlying structural brain disease are more likely to have pharmacoresistant episodes of SE or refractory SE. Using corticosteroids in the early stages of treatment may reduce inflammation resulting in more successful management of SE. Additionally, concern is raised because of the potential of reactive seizures leading to pathological brain damage and the subsequent development of epilepsy (i.e., spontaneous reoccurring seizures). However, several studies have demonstrated dogs suffering from reactive or metabolic seizures are highly *unlikely* to go on to suffer from chronic epilepsy once they recover from their toxicity (Zimmermann *et al*., 2009; Gommeren *et al*., 2010; Jull *et al*., 2011). This fact is contradictory to experimental rodent models of toxin-induced seizures, where a clear connection is made between toxin-induced brain damage and the subsequent *kindled* development of an epileptogenic site (Cavalheiro *et al*., 1991). A link between reactive seizures and spontaneous reoccurring epilepsy has not been made in cats although long-term prognosis for cats suffering from unknown (i.e., idiopathic) epilepsy is good (Pakozdy *et al*., 2014b). *Epileptogenesis* is the process by which injured neurons, surviving the acute insult, go on to form hyperexcitable, epileptic neuronal networks with neurons not injured. Excessive glutaminergic activity, alterations in calcium homeostasis, and deranged GABAergic mechanisms are all known to play a role. The development of an epileptogenic site may be delayed by months to years after an acute brain injury (i.e., head trauma). The time between the initial insult (which may include an episode of SE) and the development of epilepsy may provide a target for therapy to intervene and prevent the onset of an epileptogenic site. As stated previously, judicious, temporary use of prednisone or prednisolone at a dose of 0.5 mg/kg q 12 h and then tapered over several weeks is reasonable and in the author's experience, very safe.

TRAUMATIC BRAIN INJURY (TBI)

Several excellent reviews on the emergency treatment of TBI to dogs and cats are available (Syring, 2005; Sande and West, 2010; Dewey and da-Costa, 2016). The development of epilepsy (i.e., spontaneous reoccurring seizures) occurring months to years after TBI is estimated at approximately 5–19% of the human population (Bushnik *et al*., 2004; Ferguson *et al*., 2010). Dogs suffering from TBI have a similar incidence of the development of epilepsy later in life following TBI (6.6% compared to 5.4% for humans in the Ferguson study); however, they tend to present to the hospital actively having seizures or having their first seizure within the first 48 h of TBI (Friedenberg *et al*., 2012; Steinmetz *et al*., 2013). Causes of traumatic head injury in dogs and cats vary; with the most common reported causes being struck by a moving vehicle, acceleration–deceleration injuries (i.e., running into a fixed object), bite wounds, being kicked by livestock, and, sadly, punches to the head by a sad human (Steinmetz *et al*., 2013). Crush injuries are the most common causes of TBI to cats (Syring *et al*., 2001). The mortality rate of dogs having seizures in the acute time frame following TBI is significantly higher than those who have their first seizure in the subacute and chronic time frames. As expected, the more severe the brain injury (open vs. closed), the more likely the patient is to die or be euthanized and the more likely they are to develop seizures following the injury. Like humans (3.1 increased chance), the chance of a dog developing epilepsy following TBI is 3.4 times greater than a dog in the general population who does not suffer from TBI, and the development of epilepsy is usually within the first 2 years following the injury (Annegers *et al*., 1998; Steinmetz *et al*., 2013). Dogs and cats may not present with seizures following a TBI, however, pet owners should be cautioned regarding the possibility of epilepsy occurring in the post traumatic state (up to several years following the injury). Since brain surgery is a form of brain trauma, I also caution pet owners contemplating intracranial surgery for their dog or cat, epileptic seizures are a remote but possible consequence of the surgery.

In humans with TBI, there is a significantly higher mortality rate in those treated with steroids compared to those individuals not treated with steroids (Bratton *et al*., 2007c). The primary *advantages* of the use of steroids are:

- Reduction of ICP through alteration of CSF kinetics (see discussion on Monro–Kellie doctrine earlier in the chapter). Decreasing the production of CSF and/or increasing its absorption may reduce ICP.
- Stabilization of neuronal membranes.
- Free radical scavenger.
- Many other potentially beneficial, although not conclusively documented, benefits of steroids (i.e., immunomodulatory, regulation of DNA synthesis, etc.).

The disadvantages of steroids are numerous and include increased risk of gastrointestinal ulceration and hemorrhage, hyperglycemia, and immunosuppression. That being said, the author uses steroids but with caution and a few rules. Individual training and experience will dictate what the clinician is most comfortable with. Our decisions whether or not to use corticosteroids may be weighted to what the literature tells us, but we are bound to look to our own empirical experiences, as well. The question will continue to be reviewed as we gain new methods of evaluation its use. Diffusion tensor imaging MRI (DT-MRI) was used to look at the effect of dexamethasone to influence peri-contusion (vasogenic) edema in humans following a TBI. Those patients who received a taping dose of dexamethasone (at what are considered low doses for a human) had a median *reduction* of intracranial vasogenic edema from 22 to 19 ml, whereas those patients who did not receive dexamethasone had a median *increase* of vasogenic edema from 11 to 15 ml (Moll *et al*., 2020).

The author only uses methylprednisolone sodium succinate (MPSS—Solu-Medrol®) in neurological patients who cannot take oral prednisone or prednisolone. The dose the author uses

is considered an *anti-inflammatory* dose of 0.5 mg/kg every 12 h. While I may personally avoid dexamethasone (for any use), many clinicians use it regularly and are very comfortable with its safety and efficacy profile. Dexamethasone is demonstrated to have more potential for inducing gastrointestinal mucosal lesions when compared to prednisone (Bagley, 2005; Levine *et al.*, 2008), although others report no difference (Neiger *et al.*, 2000). There is no doubt, when using corticosteroids in any form, an increased risk of gastrointestinal complications exists. Previous studies have shown no benefit to treatment with omeprazole in preventing the development of gastric ulcers (Hanson *et al.*, 1997; Rohrer *et al.*, 1999; Neiger *et al.*, 2000). However, in a double-blinded, placebo-controlled, randomized trial, there was a demonstrated protective effect of treatment with omeprazole (Rak *et al.*, 2023).

Previously, MPSS was advocated at a "trauma" dose of 30 mg/kg IV initially followed by 15 mg/kg IV at 2 and 6 h after the first dose. This dose was extrapolated from the human literature looking at the use of steroids in spinal trauma. Recognizing a significant number of patients who have MRI of the brain following episodes of SE and the identification of periventricular edema, the author considers it reasonable to use MPSS or prednisone (prednisolone in cats) at a dose of 0.5 mg/kg every 12 h for 3–14 days and then taper at once a day for 5–14 days and then every other day for 5–14 days. Anti-inflammatory doses (up to 2 mg/kg/day for 7–14 days) of prednisone in dogs or cats does not significantly increase plasma glucose concentration (Masters *et al.*, 2018; Khelik *et al.*, 2019; Tinklenberg *et al.*, 2020). There are no distinct rules as to how long to dose the medication; rather, a clinical judgment is made based on the underlying disease pathology, the recovery from the seizure event, your own "Spidey" senses, and the family's disposition regarding tolerating the side effects of steroids. Very few negative side effects will be encountered if used at a low dose (0.5 mg/kg q 12 h for less than 7 days) in most dogs. Steroids are more likely to be used in the event of SE and multiple cluster seizures or when seizures are known to occur (or suspected to occur) secondary to structural brain disease (e.g., brain tumor and encephalitis), during the recovery period of the emergency event. Ultimately, the clinician should use their best judgment when deciding to include or exclude corticosteroids in their treatment plan. Judicious use of gastroprotectants must also be considered, if not just to cover your base, despite the small amount of evidence they may help (Rak *et al.*, 2023).

CONTINUED MONITORING AND CARE

If a patient is placed on a CRI of antiseizure medications, especially an anesthetic, careful attention and monitoring is necessary. Adequate hydration with crystalloids, maintenance of blood pressure, and attention to the patient's position and environment are essential, especially if previously treated with hypertonic saline or mannitol. Do not ignore the obvious needs for excellent patient care and monitoring. The patient should be kept on a well-padded bed with absorbent pads to wick away urine from the body. The patient should be kept sternal with the head elevated at 30°–45°, and the rear limbs should be rotated every 4 h. If the patient is laterally recumbent, the whole body should be rotated every 4 h and assessed for urination, defecation, and pressure sores. The patient's bladder should be routinely palpated every 4 h and expressed gently or catheterized as necessary (in lieu of an indwelling catheter). The patient should be kept, clean, warm (unless hypothermia is your intent), and dry. Lubricate the patient's eyes with sterile ophthalmic ointment every 4 h. Provide mouth care. Mouth care entails keeping the oral cavity free from the accumulation of excessive saliva and mucus. A gentle swab with a moist gauze sponge at least every 4 h is recommended. Active cooling may be necessary if the patient is hyperthermic but should be stopped once body temperature drops below 39 °C (103 °F). This is more common with metaldehyde (slug-bait) toxicity and other reactive seizures or refractory SE (SE that does not respond to treatment with benzodiazepines and one AED). Adequate patient care and monitoring is essential for a successful outcome.

EMERGENCY HOME TREATMENT

STRATEGIES

Chronic Therapy

The veterinarian should direct chronic or prophylactic antiseizure therapy (see Chapter 6). The client is responsible for keeping a seizure diary (see Chapter 4 and Figure A2.16). This will allow the client to notice changes in seizure frequency and intensity as it relates to the natural progression of disease and ineffective antiseizure medications and is relative to changes in the environment (e.g., stressors) or antiseizure medications. For example, a client may notice a pattern of increasing frequency of seizures coinciding with some external influence. By recognizing this pattern, the client may be able to *predict* when a seizure will come and use a temporary *bridge medication* such as clorazepate, clonazepam, or levetiracetam (see Chapter 6). The client may notice a change in pattern warranting an increase in chronic or prophylactic medications. Side effects, especially as they relate to dose modifications, can be helpful to report, as it gives the veterinarian guidelines on how to increase or decrease medications. Of greatest importance, however, is the response to medications. Veterinarians often find themselves treating a patient who is taking multiple medications. By knowing the efficacy of the individual medications, it allows the veterinarian to determine which one may be reduced over time or which medications should be left alone, due to a *presumed* beneficial effect. Untangling an ineffective polypharmacy situation can be very complicated and time-consuming.

Bridge Therapy

Bridge therapy can often be adjusted at the discretion of the owner. They should be working within clear and distinct guidelines set forth by the veterinarian. Abuse of bridge therapy can lead to a reduction in long-term efficacy due to the development of tolerance (in dogs, usually not cats). Furthermore, many of the medications prescribed for bridge therapy have the potential for human abuse, and the government takes drug diversion very seriously. The veterinarian should always be in control and keep meticulous records regarding the dispensing and recommended use of controlled substances such as benzodiazepines and barbiturates.

Developing trust is an essential component of the veterinary–client relationship. If comfortable, the veterinarian may prescribe medications to be used as bridge therapy stored at the pet's home for periodic use. A client may recognize a stressor (seizure precipitating event), which tends to induce seizures in their pet, or the pet may behave in a manner signaling an imminent epileptic seizure. A medication such as clorazepate or clonazepam may be given orally if the owner feels they have approximately 30–60 min before the seizure is "scheduled" to happen (Figure 6.13). If there will not be enough time for clorazepate or clonazepam to have an effect, oral lorazepam, oral midazolam, IN lorazepam, IN midazolam, or rectal diazepam may be used as a bridge therapy. The medication is typically dosed several times throughout the day to provide a temporary increase in seizure coverage and potentially for several days if the patient is historically at risk for cluster seizures. Diazepam should not be used chronically in this manner as it will only be effective for 1–2 h in a dog and they will develop tolerance. It can be used chronically in cats, although oral diazepam carries the potential risk of acute fulminant hepatic necrosis, and its use in cats is discouraged, especially since there are safer alternatives (Center *et al*., 1996). If an owner suggests oral diazepam is effective, the patient is likely benefiting from the active metabolites of oral diazepam and may do even better (with less risk of developing tolerance) with another benzodiazepine (lorazepam, midazolam, clorazepate, or clonazepam). The shortest amount of bridge therapy should be used to avoid the development of tolerance. It is important clients understand this.

Pulse Therapy

Most patients will continue to have periodic or breakthrough seizures, despite having adequate therapeutic levels of drug in their bodies. This is especially more likely to occur with patients who are suffering from structural brain disease (e.g., brain tumor, encephalitis, or previous trauma). The use of *pulse* therapy was designed to help alleviate some of the complications associated with periodic seizures including hospitalization visits and emergency costs (Podell *et al*., 1995). This single strategy can be very helpful in preventing premature euthanasia due to economic reasons or feelings of helplessness, which often translate into "my pet is suffering." The *helpless* owner can become excessively worried about leaving their pet at home unattended, taking their pet away from the home, and most of all not having the ability to do anything when their pet is having a seizure at home. Pulse therapy can help in these situations and goes a long way in giving pet owners some control.

With this strategy, a single dose or *pulse* of medication is given prior to a seizure (assuming predictability), during a seizure (to help prevent SE), or after a seizure to prevent clustering. Drug options include:

- Rectal diazepam. A dose of 1–2 mg/kg of the injectable solution is given rectally. The dose should be increased if the pet is receiving chronic phenobarbital therapy by 25–50%. To prepare the rectal medication, the dose of diazepam is placed in a red top blood tube (Figure 6.14). The client is sent home with several individual vials, each containing a single dose. An appropriately sized syringe is fitted with a short piece (dependent on size of pet) of a red rubber feeding tube. The tube should be cut at the *proximal* location to allow it to fit the tip of a syringe. The cut *distal* end should be carefully melted to prevent a sharp edge from being created and damaging the rectal mucosa (Figure 6.14c and d). The tube should be placed on the end of the syringe for the owner. The owner is instructed to withdraw the entire contents of one vial into the syringe, through the red tube. The tube is then inserted rectally approximately 4–6 in., and the entire contents are injected as the tube is slowly withdrawn. This allows for greater rectal mucosal surface area contact and makes it less likely the client will inject the contents into feces. If the seizure does not follow its normal pattern of cessation within 10 min of giving the rectal diazepam (*for that particular patient*), the pet should be given another dose and taken to the nearest emergency veterinary facility. The client should make sure that the attending emergency veterinarian knows how much diazepam was given, by which route, and when it was given. Diazepam should not be dispensed in preloaded syringes as it may bind to certain plastics and become less effective (MacKichan *et al*., 1979). See Table 6.9 for a comparison of home dispensing benzodiazepine shelf times.
- IN lorazepam. A dose of 0.2 mg/kg is given by nasal drop method or with an attached atomizer to create a "stream" of lorazepam (Figure 6.15). This dose should attain rapid brain concentrations within 3–9 min and maintain at antiseizure levels for longer than 60 min (Mariani *et al*., 2003). The advantage over rectal diazepam is a faster onset of action, and lorazepam is significantly more potent than diazepam with a longer duration of action (see Figures 7.1 and 7.2) (Leppik *et al*., 1983; Appleton *et al*., 1995). Lorazepam may also be more successful in treating acute seizures due to its persistence in the nervous system compared to serum levels, which decline more rapidly (Walton and Treiman, 1990). While diazepam can also be used with the IN route, it is a much larger volume (a 10 kg dog would need 1–2 ml of diazepam as opposed to 0.5 ml of 4 mg/ml lorazepam given IN). Lorazepam is also well absorbed through the oral mucosa. The injectable form used for the IN route may be given orally; however, this is not advised if the patient is actively having a seizure, as active hypersalivation may prevent the medication from contacting the oral mucosa (i.e., the absorption is transmucosal). Lorazepam is also available as an oral *tablet*, which is rapidly disintegrating and reported to be tasteless (Plumb, 2011).

Lorazepam should *not* be given rectally as its absorbance is erratic and unpredictable (Podell *et al*., 1998). This is contradictory to the human experience, in which rectal lorazepam has been reported to be extremely effective in stopping epileptic seizures (100% effective as a single dose with no complications) (Appleton *et al*., 1995).

- Midazolam is 2 times stronger in binding to the benzodiazepine receptor when compared to diazepam and 3 times more potent (Reves *et al*., 1985). Midazolam may be given via the *IN* route at a dose of 0.2 mg/kg and will achieve therapeutic concentrations in dogs like that reported for humans (Eagleson *et al*., 2012). Peak serum concentration is attained twice as fast with IN dosing compared to oral dosing in dogs. Additionally, serum concentration is 3 times greater and 2.5 times more midazolam is absorbed through the IN route when compared to oral dosing (Lui *et al*., 1991). A drawback of the parenteral preparation when compared to diazepam or lorazepam is the shelf life of midazolam. Because it is an aqueous preparation (allowing it to be given IM) resulting in less irritation, the injectable formulation does not contain adequate preservatives, and the medication is only stable for 30 days once opened according to the package insert. However, other studies have shown it to be shelf-stable for up to 60 days (at least) both at room temperature and refrigerated (see Table 6.9). The use of bio-adhesive gels theoretically will improve the efficacy of midazolam and allow for smaller, more concentrated doses to be given through the IN route (Eagleson *et al*., 2012). Midazolam should *not* be given rectally as its absorbance is erratic and undetectable (Eagleson *et al*., 2012; Schwartz *et al*., 2013). Midazolam for home use can be prepared similar to lorazepam (Figure 6.15).

The use of at-home *bridge* therapy and *pulse* therapy can assist the pet owner significantly in the management of epileptic seizures. These strategies can help to attenuate the feeling of "helplessness" many pet owners will experience. They also significantly reduce the overall number of emergency room visits and costs associated with the management of epilepsy. Finally, by involving the pet owner in the treatment and management process, the veterinarian gains a valuable ally to help monitor for effectiveness and side effects. All these components will help to prevent *economic* and *unawareness*-associated euthanasia, as well as improved quality of life for the pet and its family. Thanks Dr Podell!

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Alternative, Integrative, and Complementary Therapy

CHAPTER 9

KEY TAKEAWAYS

Just because something is natural does not mean it is safe.

Don't forgo a known-to-be-effective treatment over an unknown treatment (use what works).

Look at the literature. MCT, Omega 3, and CBD may be helpful in the management of epilepsy

QUICK JUMP

MCT calculation for Diet Table 9.1

Diet and supplementation summary Table 9.2

Cannabidiol and THC (Δ^9–tetrahydrocannabinol) page 404

Introduction 383
Diet 386
The Ketogenic Diet 386
Other Dietary Considerations 389
Complementary, Alternative, and Integrative Medicine 393
Acupuncture/Acupressure 393
Herbal- and Plant-Based Remedies 394
Aromatherapy 410
Ayurveda 413
Homeopathy 414
Other Modalities 417
A Note on Safety 417

Myelominutia: Up to 1% of Valerian root may be converted to isovalerate, which is structurally similar to valproic acid, a potent anticonvulsant used in humans.

INTRODUCTION

In 2012, nearly 20% of Americans spent over 30 billion dollars, out of pocket on complementary and alternative medicine (CAM) visits to practitioners and products related to the treatment of human disease (Nahin *et al.*, 2016). No real data exists for money spent on pets in the category of CAM, however, out of the $136 billion spent in the USA alone in 2022, we can bet a significant amount of that was on CAM. The popularity of CAM has grown tremendously

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Companion website: www.wiley.com/go/sanders/seizures2e

since the 1970s, partially motivated by a more open-minded culture in the USA but also attributed to dissatisfaction with conventional or mainstream allopathic medicine. As of 2024, 47 US states allow marijuana to be used for medical reasons. In the last decade, research into the possible medical effects of hallucinogens (psilocybin, LSD, mescaline, DMT, MDMA, etc.) has had a quiet resurgence. In one study, 67% of respondents reported giving their dogs nutritional supplements with the goal of improving their general health, helping with behavior changes or influencing age-related diseases (Haake *et al*., 2023). There may be many motivating factors why a pet owner or clinician would look to alternative, integrative, or nontraditional therapies. Some pet owners may be motivated because they themselves use these modalities. Some may be motivated by a lack of success or failure using traditional modalities, and others may be motivated by curiosity. Separating *science-based* from *pseudo-science* or even *fantasy-based science* is the trick. Generally speaking, "seizure control" is more successfully attained in dogs and cats compared to humans. "Control" is a relative term, however, and may have different meanings to different individuals and species (dogs and cats vs. humans). It is estimated that 15–33% of human epileptics are refractory to pharmacological treatment (Sander, 1993; Picot *et al*., 2008; Walker and Köhling, 2013). The variability in determining pharmacoresistance in the literature stems from the lack of a consensus on the *definition* of what pharmacoresistance is. In dogs, it is estimated that 25–30% are not well controlled with medical management and therefore considered pharmacoresistant. (Farnbach, 1984; Schwartz-Porsche *et al*., 1985; Podell and Fenner, 1993; Fischer *et al*., 2022). The ketogenic diet is the only complimentary or alternative therapy which has been shown to be effective in humans for the treatment of epileptic seizures in multicenter, double-blind, and controlled clinical trials (Kwan *et al*., 2011). Certainly, many variables are considered, and cross-species comparison can be difficult and should not be overinterpreted. However, a fundamental similarity exists; portions of the population we treat are refractory to conventional (pharmacological) therapy.

Pharmacoresistant human patients are more likely to suffer from premature death, injuries, and reduced quality of life (Lawn *et al*., 2004; Mohanraj *et al*., 2006). When considering polypharmacy, only 10% of humans who are labeled as "pharmacoresistant" will benefit from a second drug trial and only 3% from a third (Mohanraj and Brodie, 2006). As many previous studies have shown, if you fail one drug, you are likely to fail other drugs (Forsgren *et al*., 2005; Gazzola *et al*., 2007). We may assume the same for veterinary patients. The desire to investigate alternative, complementary, or unconventional treatment modalities is therefore well justified. We should not judge a therapy modality by its name or label (e.g., conventional vs. *unconventional*) but by whether it *works*. However, there are some significant aspects of alternative methods to account for when considering these modalities:

- Just because it is safe for humans does not mean it is safe for dogs and cats.
- Just because it is safe for a dog does not mean it is safe for a cat (and vice versa).
- Do no harm.
- Do not supplant or disregard a known or effective modality with an unknown modality.
- Look at all the results with a clear unbiased eye.
- Before labeling a patient as *pharmacoresistant* make sure it is not *pseudoresistant*.

A study showed approximately 1/3 of canine patients, who were diagnosed as having pharmacoresistant epilepsy, had other essential causes for their "drug resistance" (Kajin *et al*., 2023). One of those seemingly easy elements to correct is making sure the patient is actually getting their medication. Another study demonstrated that only 21% of the study population of dogs had a 100% compliance in getting their medications from their caregivers (Booth *et al*., 2021). So, before you

give up on what is known to work, make sure it is *allowed* to work. Other factors which may lead to pseudoresistance include (Kajin *et al.*, 2023):

- Misdiagnosis—actually, not epileptic seizures or *reactive* seizures
- Misclassification—structural cause of seizures as opposed to idiopathic
- Low serum antiseizure medication levels (underdosed)
- Inappropriate choice of drug or dosage

An *alternative* therapy suggests a therapeutic modality that is used in lieu of a traditionally accepted therapy. A traditionally accepted therapy may vary depending on cultural, historical, geographical, emotional, financial, and anecdotal factors. For the focus of this chapter, the traditional therapy accepted for the treatment of epileptic seizures in dogs and cats is pharmaceutical treatment based on allopathic medicine. *Integrative* therapy implies the modality is used in combination with an allopathic therapy. It is therefore interwoven or *integrated* with the treatment in a *complementary manner*. A *nontraditional* therapy may be a modality that is uncommonly used in allopathic medicine. Acupuncture, for example, is a traditional therapy in many parts of the world. All medicine or therapeutic intervention, at some point, was novel, untried, experimental, and for the time, *state of the art*. From the discovery of plant extracts, which provide a therapeutic benefit, to the most technologically advanced targeted treatments, experimentation has been necessary to develop consistent beneficial treatments. All success begins with anecdotal reports of empirical therapy. The ancient Greeks and Egyptians realized a tea prepared from willow bark helped to reduce fever and inflammation. Thousands of years later, we still use aspirin to treat the same maladies. As scientists, we should be cautious of alternative treatments but at the same time have an open mind to consider the possibilities and discovery. We should be skeptical but curious. We should not be dogmatic in our views. Veterinarians should be a resource to help pet owners find the safest, most effective method for controlling epileptic seizures. If we do not provide guidance down the treatment path, many pet caregivers will forge their own way. Pet owners should be able to develop trust in their veterinarian's recommendations. Ultimately, it is the responsibility of the pet owner to seek out advice and follow recommendations based on sound medical judgment and experience. Consider this: if veterinarians are not there to help the client, they will often look for and experiment on their own, potentially causing harm to their pet. In a human study, those people whose general practitioner physicians had knowledge of complementary medicine tended to have lower healthcare costs and morbidity rates (Kooreman and Baars, 2012). There are many explanations for this finding including:

- A patient population that is healthier and better educated, seeking out complementary medicine.
- Patients who seek out complementary medicine tend to have longer-lasting chronic conditions and are typically *undertreated*. This would naturally lead to a population with lower mortality rates and lower healthcare costs.
- There may be a stronger focus on preventative healthcare and attention to the patient (i.e., discovery of problems early in the course of disease). The focus of complementary medicine tends to be self-healing and self-management of disease with less dependence on pharmacology, laboratory tests, and procedures. This also results in undertreatment.
- People may have more out-of-pocket expenses (i.e., traditional insurance may not cover complementary medicine), leading to an artifactual underreporting of healthcare costs.
- It works.

Skepticism and mistrust surround complementary medicine. Those who embrace CAM tend to do so wholeheartedly and will defend its application with testimony after testimony, personal

experience, and dump trucks of anecdotal reports. This is fine, as no one person's personal experience should be discounted. However, an inherent confirmation bias exists for those who support it. Any interpretation of presumptive effect or misinterpretation regarding possible side effects must be made based on an inherent measurable knowledge of the chemical composition of the remedy (e.g., homeopathy) or behavior of the applied remedy (e.g., energy healing). For this reason, a disregard to possible safety issues stems from the lack of being able to even apply a methodical research protocol to the underlying *science*. Maybe it is simply enough to only *believe* it is working. Again, that would be perfectly fine if you do no harm (. . . and it works).

While we may not understand the modality, we can help direct the pet owner to those who do. Many traditionally trained Western veterinarians have developed an interest in alternative and nontraditional forms of medicine. This interest is often fueled by an intense passion either through personal experience or curiosity. Look for professionals who focus on the modality and assimilate it with allopathic medicine or work with other professionals to create a synergistic, *integrated* treatment plan. You can be skeptical and "open-minded" at the same time. Look at results cautiously, and above all, consider the health of the patient first. Do not exclude a known and effective treatment for the pursuit or application of the unknown. Use the knowledge you have gained through your education and experience to help guide your judgment. It also never hurts to ask the question, "What would I do if this were my own pet?"

DIET

THE KETOGENIC DIET

The most well-known diet used to treat epilepsy in humans is the *ketogenic diet*. The underlying foundation of why the ketogenic diet should work *is* rooted in basic science. Hippocrates (ca. 400 BCE) noted seizures (and many other illnesses) could be altered with fasting as a treatment modality (Wheless, 2008). The modern ketogenic diet, developed in 1921 by the Mayo Clinic physician RM Wilder specifically for the treatment of epileptic patients, was based on the historical therapeutic results of a fasting state. The premise was constructed on the idea a diet low in carbohydrates and protein but rich in fats could *mimic* a fasting state by creating ketonemia. Fasting children with epilepsy, was known to be beneficial, and the diet, which mimicked a fasting state, was a better long-term solution. The level of ketosis, in children, recognized as being optimal for seizure control is >4 mmol/l of β-hydroxybutyrate (Worden *et al*., 2020). A traditional American diet typically consists of 50% carbohydrates, 15% protein, and 35% fat. A ketogenic diet is composed of typically very high fat (75–90% fat), low carbohydrates (5% carbohydrates), and low protein (10–20%). While originally used to treat children with specific epileptic syndromes, it is also used to treat adolescents and adults with medically intractable epilepsy. The diet is usually recommended in children after two unsuccessful attempts at pharmacotherapy (Kossoff *et al*., 2009). The literature claims a 90% reduction in the frequency of seizures in one-third of the human patients who use it (Henderson *et al*., 2006). However, other studies conclude there are no benefits. No one knows for sure why the diet works; however, many hypotheses exist including (Caraballo and Vining, 2012):

- The anticonvulsant effects of ketone bodies
- Cerebral acidosis as a secondary effect of ketosis
- Cellular and extracellular dehydration
- Hypoglycemia

- Modulation of membrane potential and ion channels
- Alterations of neuronal firing
- Alterations of synaptic function
- Changes to neurotransmitters
- Effects on lipids and neuronal excitability
- Changes in cerebral energy utilization
- Neuroprotection via inhibition of the production of *reactive oxygen species*
- Alterations in mitochondrial metabolism

Ketone production does not correlate well with the antiepileptic effect of the diet. Another possible hypothesis is an ingredient used in the ketogenic diet is contributing to the antiepileptic effect, as opposed to the ketones themselves. Coconut oil is used as a basis for *medium-chain fatty acids*, which is a major component of the ketogenic diet, and as we will see later, may have its own ant-epileptic effects. *Decanoic* acid is a significant component of coconut oil and has been identified as a possible antiseizure element (Walker and Williams, 2013). The brain utilizes glucose as an obligate energy source. In a hypoglycemic state, ketone bodies, derived from fats, are oxidized instead of glucose derived from carbohydrates. The altered energy metabolism due to the utilization of ketone bodies may create a functional change in the cerebral energy state. An increase in the expression of brain mitochondrial uncoupling proteins translates to neuroprotection through reduced production of reactive oxygen species. The multiple effects of altered cerebral energy metabolism are thought to create resistance of cerebral tissue to metabolic stress. The core theme of the hypothesis centers around the notion that altered energy states may compensate for deficiencies in other, naturally, inhibitory mechanisms of the brain such as GABAergic function. The ketogenic diet increases glial cell conversion of glutamate to glutamine, which is a precursor for GABA synthesis, while at the same time decreasing the conversion of glutamate to aspartate (an excitatory amino acid) (Yudkoff *et al*., 2001).

Children likely benefit from the ketogenic diet preferentially compared to adults because of altered cerebral energy utilization and metabolism. Suckling rats in a hypoglycemic state are naturally resistant to experimental induction of seizures, and there is an age-related switch in the expression of brain nutrient transportation in rats and humans (Vannucci and Simpson, 2003). By mimicking a fasting state, the ketogenic diet provides some of the seizure-protective elements while still allowing the organism to attain calories. The immature brain of rats and humans utilizes a combination of glucose, lactate, and ketone bodies for energy. In normal development of the brain, there is a switch to glucose as a primary energy source (Cremer, 1982).

The ketogenic diet does not come without side effects. The diet is challenging to maintain, and common side effects include hypoglycemia, dehydration, acidosis, gastrointestinal upset, anorexia, nausea, vomiting, and constipation (Wheless, 2001; Caraballo and Vining, 2012). Other possible side effects include cardiomyopathy, renal tubular acidosis, nephrolithiasis, and even death (Stewart *et al*., 2001). If there is any doubt as to the intense patient compliance, constant monitoring, supplementation, and concern for the development of side effects, one only needs look to the parents of human children who dedicate much of their lives to compliance with the ketogenic diet (Vogelstein, 2010). Many of the side effects of the ketogenic diet, which traditionally relied on long-chain fatty acids as the source of fat, have been offset with the use of medium-chain triglycerides, which produce more ketones and allow for an increased amount of protein and carbohydrates in the diet, consequently reducing many of the vitamin and mineral deficiencies associated with the traditional diet (as well as, increasing its palatability). As veterinarians, we often select drug therapy alone based on the convenience of dosing (e.g., every 12 h as opposed to every

8 h). Certainly, the degree of compliance and monitoring would not impede many of our devoted clients. However, the ketogenic diet, in its original form, when applied to dogs, simply does not work.

The Ketogenic Diet for Dogs

There is very little in the veterinary literature regarding the ketogenic diet, however, a review is available (Vendramini *et al.,* 2024). An online survey found over *67%* of surveyed dog owners, changed their pet's diet after they received a diagnosis of idiopathic epilepsy (Berk *et al*., 2018). Dietary supplements have the potential to alter the absorption, bioavailability, efficacy, and clearance of anti-epileptic drugs. Pet owners should be encouraged to disclose the use of any dietary supplements with their pet's veterinarian. In dogs fed with a modified ketogenic diet (57% fat) compared to control diet in a multi-institutional, prospective, double-masked, placebo-controlled study, there was no statistical difference in seizure frequency, despite elevated concentrations of beta-hydroxybutyrate in those dogs receiving the modified ketogenic diet (Patterson *et al*., 2005). One possible explanation is the low-fat content of the diet fed to the dogs compared to the traditional formulation containing 90% fat. Twelve dogs completed the study and power calculations determined 22 dogs would need to participate in each diet group to show a significant difference. In rats fed a diet with a 6:1 ratio of fat to carbohydrates, there was improved seizure protection when compared to those fed the traditional 4:1 ratio (Bough *et al*., 2000). The dogs in the Patterson study may have needed a higher percentage of fat in their diet; however, the naturally increased capacity of ketone utilization of dogs, when compared to humans, may offset even higher amounts of fat (Puchowicz *et al*., 2000). Dogs have not evolved to rely on carbohydrates as an energy source. Dogs rely primarily on fat and protein as energy sources. Dogs do not develop significant ketosis during long-term fasting and rarely become ketotic (Crandall, 1941). Ketosis in dogs is achieved when the concentration of β-hydroxybutyrate is between 0 and 1.9 mmol/l (Feldman *et al*., 2015). Dogs have evolved to consume a large meal separated by extended periods of time without eating (i.e., wolves getting an occasional "kill"). This adaptation to extended periods of fasting is made possible through an efficient and high capacity for ketone body utilization when compared to humans (de Bruijne and van den Brom, 1986). Dogs achieve this through a well-developed glucohomeostatic system. In times of fasting, a dog's body will adapt through increased glucogenesis and decreased glucose utilization in the body. Glucagon levels remain normal and there is only a slight elevation in ketone bodies, the very mechanism thought to confer a higher seizure threshold in children (de Bruijne *et al*., 1981). During fasting states, the dog's glucohomeostasis is maintained by glycogenolysis in the liver. Once the liver stores are exhausted, amino acids from the breakdown of muscle proteins, glycerol and lactate can be used as substrates for gluconeogenesis. Furthermore, free fatty acids and ketones can be utilized as an energy source by peripheral tissues with glucose being *shunted* to the brain. Therefore, it is difficult to initiate or *mimic* a fasting state in dogs (de Bruijne *et al*., 1981). This protective adaptation to times of reduced energy access (e.g., starvation) prevents the ketogenic diet from being a useful tool in normal dogs. Young toy breed dogs, who commonly suffer from episodes of hypoglycemia due to inadequate gluconeogenesis, may be candidates for a ketogenic diet, provided the cause of their epileptic seizures is not due to hypoglycemia alone (e.g., hydrocephalus and encephalitis) (van Toor *et al*., 1991).

The Ketogenic Diet for Cats

The metabolic situation of the cat in response to a fasting state is significantly different from a dog. A ketotic diet is one where the primary energy source is eliminated. For cats, this would be protein. In the cat, fat accumulates in the liver during times of anorexia leading to the development of feline hepatic lipidosis (Blanchard *et al*., 2002). This clinical disease entity, somewhat unique to cats, can be fatal. Cats, in contrast to humans, do not efficiently utilize fats during a state of

starvation (Cornelius and Jacobs, 1989). Although the ketone, β-hydroxybutyrate is increased in cats with hepatic lipidosis, there appears to be an imbalance between the amount of ketosis and the amount of fatty acid storage in the liver (Day, 1994). Considering the incidence of epileptic seizures is far less in cats compared to dogs and the response to conventional therapy tends to be greater, the need to explore the efficacy of the ketogenic diet does not outweigh the possible risks associated with the induction of a ketotic state in the cat.

No studies have been reported evaluating the effects of MCT supplementation in the diet of cats, expressly for the benefit of seizure control or enhancing cognitive function. MCT supplementation has been used for cats with malabsorption or maldigestion disorders, exocrine pancreatic insufficiency, cardiac disorders, lymphangiectasia, weight loss, and chylothorax (Trevizan *et al*., 2010). MCTs are generally regarded as safe when oral supplementation is less than 15% of the caloric content of the diet. While cats may be averse to MCT added to their diet, a flavorless, odorless, and colorless product may be tolerated at the amount found to be beneficial for dogs (i.e., 10% of caloric needs). It would certainly be worth a try in an epileptic drug-resistant cat (Table 9.1).

OTHER DIETARY CONSIDERATIONS

Anecdotal accounts of diet changes to avoid supposed toxins or allergens for the management of epileptic seizures are occasionally reported and an epidemiological relationship exists in humans between allergic disease and epilepsy (Silverberg *et al*., 2014; He *et al*., 2021). No evidence exists, yet, there is an association between dogs and cats with epilepsy and allergic disease. There is a significant amount of interest regarding gluten-free diets for dogs and cats. Gluten, along with casein, soy, and corn, are suspected to be responsible for many of the chronic illness humans and animals experience, including epilepsy. Proponents of dietary change claim significant improvement regarding epileptic seizure control when pets are given an elimination diet (Symes, 2007). A gluten allergy (modified gliadin peptide immunoglobulin and tissue transglutaminase-2 immunoglobulin A) has been linked to paroxysmal dyskinesia in dogs (Lowrie *et al*., 2016; Polidoro *et al*., 2020; Rogers *et al*., 2023). Since some of these dogs may also respond to AED, it would be reasonable to assume (and certainly no harm could come from a dietary trial) that there may be a link between diet allergy and epilepsy in dogs and cats. A formal peer-reviewed study would be beneficial to evaluate the efficacy of the diet (Muñana, 2013). In a blinded, placebo-controlled trial of 15 dogs diagnosed with genetic (i.e., idiopathic) epilepsy and treated with essential fatty acid supplementation, there was no change in epileptic seizure frequency or intensity (Matthews *et al*., 2012). If a pet caregiver is providing a well-balanced and safe diet, there may be nothing to lose in trying dietary modifications; however, any dietary manipulation should be overseen by a veterinarian or qualified nutritionist. Even something seemingly innocuous as fatty acid supplementation can result in life-threatening illnesses to dogs and cats such as pancreatitis, if not dosed appropriately or obtained from a reputable manufacturer. The metabolism of dogs and cats is significantly different from humans. Human experience with various diet modifications may seem to translate to dogs and cats; however, care should be taken in formulating home-cooked or experimental diets as, oftentimes, supplementation of essential nutrients, which dogs and cats may be unable to synthesize, would be necessary, potentially leading to significant nutrient deficiencies and, ironically, secondary seizures (Hutchinson *et al*., 2012). To be safe, pet owners should consult with their veterinarian prior to making any diet changes. There are literally hundreds of dog and cat food choices. Not all pet foods are equal, and significant controversy surrounds the use of *raw* food diets. Raw food diets have been shown to pose a health risk for the public and to the animals themselves (Finley *et al*., 2007, 2008; Lefebvre *et al*., 2008; Taylor *et al*., 2009; Leonard *et al*., 2011). The American Veterinary Medical Association discourages the feeding of any diet

to dogs and cats that does not undergo a process to eliminate pathogens (AVMA, 2012). Investigation into the use of novel diet to alleviate epileptic seizures continues in this area (Volk and Davies, 2013).

Medium Chain Triglycerides

While not a true ketogenic diet, investigators have evaluated the use of medium-chain triglyceride supplementation in the diet of elderly and epileptic dogs. MCTs are better digested and absorbed compared to long-chain triglycerides. Furthermore, they have a better conversion rate to ketone bodies compared to long-chain fatty acids and their addition to a diet allows for the use of more protein and carbohydrates to provide a more nutritionally balanced and better-tasting diet. Medium-chain fatty acids can directly cross the blood–brain barrier and are oxidized within the brain (Oldendorf, 1971; Ebert *et al*., 2003). Dogs fed a diet supplemented with MCT showed an increase in γ-aminobutyric acid (GABA) and a significant shift in the GABA:glutamate ratio with a 50% increase on the GABAergic side along with other significant alterations to amino acid and fat metabolism (Berk *et al*., 2022). These changes are hypothesized by the Berk study to exert anticonvulsant effects by:

- Compensating for energy shortage
- Influencing the GABA:glutamate ratio via astrocyte metabolism
- Reduce oxidative stress through increases in ATP
- Neuroprotective effects through MCTs influence on metabolic pathways

In a prospective, randomized, double-blinded, placebo-controlled cross-over study, epileptic dogs who were fed a diet, supplemented with 5.5% MCT, showed a reduction in seizure frequency (Law *et al*., 2015). In this study, 3/21 dogs achieved seizure freedom and an additional seven dogs had a seizure reduction by ≥50%. Only 6/21 dogs showed no response. The same study group also demonstrated a reduction in signs of attention deficit hyperactivity disorder (ADHD—extrapolated from signs in human children with IE) of excitability, chasing behavior, and decreased trainability in dogs with IE (Packer *et al*., 2016). This effect may be attributed to a previously identified *anxietolytic* effect of a MCT-supplemented diet (Shihab *et al*., 2011). The beneficial effects of MCT in enhancing cognition and slowing down cognitive decline have been demonstrated in dogs along with measurement of β-hydroxybutyrate showing the subjects achieved adequate levels when fed a diet supplemented with 5.5 or 9% MCT (Pan *et al*., 2010, 2018; Berk *et al*., 2021). In a study looking at similar supplementation of MCT to IE dogs being treated with zonisamide, there was no significant effect when dogs were fed the control diet or the diet with added MCT, although the subject number in this study may have been too low to demonstrate an effect ($n = 7$) (Nakatsuka *et al*., 2023). Additionally, 5/7 of the dogs in the zonisamide study had cluster seizures which may have contributed to the reduced effect (Packer *et al*., 2014). In a study excluding dogs with cluster seizures (prospective, open-label, single-arm with no placebo), a commercial diet containing 6.5% MCT was given to 21 dogs with IE. Cluster seizures were defined as "more than one seizure per day." In this study, 16/21 dogs had fewer seizure days with the mean number of seizure days/month significantly reduced (by 42%), as was the number of seizures/month (32% decline). Three dogs had no change in seizure frequency and two dogs had an increase in seizure days. Five dogs in the study group experienced at least one cluster seizure and when excluded from the trial (because the intent was to see the effect without cluster seizures confounding the data), the mean seizure/month rate declined by 58% (Molina *et al*., 2020).

While many of the studies were funded by a commercial manufacturer of a diet specifically marketed as a "neuro care diet" and used that diet in their study protocol, other studies looked at pure dietary supplements using a combination of medium chain fatty acids (MCFAs) (octanoic—C8 or

decanoic—C10 fatty acids). In a 6-month, multicenter, prospective, randomized, placebo-controlled cross-over trial, 28 dogs were given a dietary supplement (added to their normal) food containing either a mix of MCFA or placebo (olive oil) (Berk *et al*., 2020). Seizure frequency was significantly reduced compared to the control diet when dogs were fed the MCFA supplement. Two dogs were seizure-free during the MCFA portion of the study, while 15 dogs had an overall reduction in seizures/month. During the period where the control supplement was fed (olive oil), none of the dogs experienced a seizure day reduction by more than 50%, 17 dogs actually had an increase in seizure frequency and no dogs experienced seizure freedom. Care should be taken with any fat supplement as epilepsy is a risk factor for developing pancreatitis in dogs and pancreatitis is recognized as often developing from ingestion of a high-fat-containing meal (Hess *et al*., 1999; Larsen *et al*., 2014).

Supplement dose of MCT (in this case, C8) is extrapolated to be 10% of a dog's caloric needs (Table 9.1).

Table 9.1 Medium-chain triglyceride supplement for epilepsy and cognitive dysfunction.

Dog	10 lb|4.5 kg	30 lb|14 kg	50 lb|23 kg	70 lb|32 kg	90 lb|41 kg
PUPPY (10 lb puppy growing to 33 lb at maturity)	15 ml				
ADULT INACTIVE DOG	4.5 ml	10.5 ml	15 ml	19 ml	23 ml
ADULT ACTIVE DOG	6 ml	14 ml	20 ml	26 ml	32 ml
PREGNANT DOG (4 weeks after mating to delivery)	8 ml	20 ml	30 ml	38 ml	48 ml
YOUNG ADULT ACTIVE DOG	7 ml	15 ml	22 ml	28 ml	34 ml
OLDER ACTIVE DOG	5 ml	11 ml	17 ml	21 ml	25 ml
Cat	**5 lb|2.3 kg**	**10 lb|4.5 kg**	**15 lb|6.8 kg**	**20 lb|9 kg**	
KITTENS (after weaning)	3 ml				
LEAN DOMESTIC CAT	2.5 ml	4.2 ml	5.4 ml	6.6 ml	
OVERWEIGHT DOMESTIC CAT	2.7 ml	3.6 ml	4.2 ml	4.6 ml	
PREGNANT/NURSING CAT	5 ml	9 ml	12 ml	16 ml	

Caloric needs calculations derived from The National Research Council of the National Academies (www.national-academies.org) (National Academy of Sciences, 2006).
MCT supplement at 10% of calculated calories.
C8 oil calculated at 100 cal/15 ml.
15 ml = 1 tbsp. = ½ oz.

Omega-3 Fatty Acids (DHA and EPA)

The omega-3 fatty acids (docosahenaenoic—DHA and eicosapentaenoic—EPA) may reduce inflammation associated with increased generation of prostaglandins, reactive oxygen species, and cytokines associated with epileptic seizures (Omrani *et al*., 2019; Krupa *et al*., 2024). Omega-3 FA are neuroprotective and help to prevent status epilepticus in an epileptic rat model (Ferrari *et al*., 2008). Young dogs (age between 2 and 6 months) fed a diet rich in fish fat were found to have less of an association with epilepsy later in life, compared to dogs who did not have a high fish fat diet (Hemida *et al*., 2023). In a very small (four dogs completed study) open-label, 6-month observational, clinical trial, dogs diagnosed with idiopathic epilepsy and given a DHA supplement (69–166 mg/kg/day), showed a decrease in seizure frequency (all dogs up to 50% or more seizure reduction, within 2–3 months) (Yonezawa *et al*., 2023). In the Yonezawa trial, three of the four dogs completing the trial had their seizure frequency reduced to 0-1/month

(pre-trial frequency was 4, 3, 45, and 6 seizures/month). The amount of DHA used was significantly higher than that reported in previous studies. The mechanism of action is unknown and may involve combatting inflammation, enhancing serotonin levels, increasing fluidity of cell membranes, affecting ion channel currents, prolonging the inactive state of cells after action potential generation, and enhancing effects of γ-aminobutyric acid on transmission and neurogenesis (Ferrari *et al.*, 2008; Yonezawa *et al.*, 2023). Fish oil is a rich source of omega-3 FA, as algae convert alpha-linoleic acid to EPA and DHA, which is then present within the aquatic food chain. The parent omega-3 FA (alpha-linolenic acid) derived from plant sources, such as flax seed may not have the same activity. It is important when supplementing omega-3 FA to give DHA and EPA, derived from fish oil. Fish oil supplementation has also been studied in dogs to treat conditions such as inflammatory skin disease, renal disease, cardiovascular disease, osteoarthritis and joint health, and hyperlipidemia (Bauer, 2011). Doses ranged from 115 to 310 mg/kg$^{0.75}$/day. The National Research Council's "safe upper limit" for EPA and DHA in dogs is 370 mg/kg$^{0.75}$/day. No safe upper limit has been established for cats. Possible negative consequences of over-supplementation include:

- Weight gain
- GI upset, diarrhea, pancreatitis
- Altered platelet function
- Delayed wound healing
- Altered immune function
- Lipid peroxidation
- Insulin sensitivity
- Drug–supplement interactions

Supplementation of FA in the correct amounts, end products, precursors, and ratios is a complicated subject and beyond the scope of this book. I have tried to provide literature suggestions based on applicability to epilepsy. Without specific evidence, it would be reasonable to supplement with known amounts verified to be helpful in other disease processes (such as inflammation or cardiac support) with the knowledge you will likely do no harm. Several excellent reviews are available (Bauer 2011; Burron *et al.*, 2024) (Table 9.2).

Table 9.2 Summary of dietary modifications for canine and feline epilepsy.

Modification	Benefit	Dose (if applicable)
Ketogenic diet dog	No	
Ketogenic diet cat	No	
MCT dog	Yes	10% of calculated daily calories
MCT cat	Maybe	10% of calculated daily calories
Hypoallergenic diet dog	Maybe	
Hypoallergenic diet cat	Maybe	
Omega-3 FA (DHA/EPA) dog	Yes	<370 mg/kg$^{0.75}$/day 69–166 mg/kg/day[a]
Omega-3 FA (DHA/EPA) cat	Maybe	600–700 mg/cat/day 102–130mg/kg$^{0.67}$/day[b]

[a] Yonezawa et al. (2023).
[b] Bauer (2011).

COMPLEMENTARY, ALTERNATIVE, AND INTEGRATIVE MEDICINE

ACUPUNCTURE/ACUPRESSURE

Acupuncture has been used for thousands of years to treat disease and illness. In the West, acupuncture started to gain popularity in the 1970s as the "alternative" treatment of human disease. The use of acupuncture to treat animals parallels its use in treating human disease in Eastern cultures as well. This therapeutic modality for the treatment of animal disease in the West became more popular in the late 1980s and has continued to gain acceptance and recognition based on sound, mainstream science showing a definitive effect of the treatment on physiology. Acupuncture is no longer considered *alternative*. Many now regard this therapy, among others, as being *integrative* and complementary. In this sense, the treatment is combined or integrated with traditional Western or *allopathic* (using drugs, radiation, or surgery) medicine. Reasons for trying acupuncture may include:

- Failure of traditional drug therapy
- Adverse side effects of drugs
- Personal experience with acupuncture
- A desire to avoid medications

In brief, the underlying Eastern explanation for epileptic seizures involves the closure of the portals from which the *spirit* flows from the body. A clouding of the spirit ensues resulting in convulsions, which are wind and phlegm signs. The acupuncture point, which is stimulated, is known as *shen-men*. It is located on the pinna or ear of the dog. This point is referred to as the *spirit gate*, and when stimulated, it opens the gate, once again allowing the spirit to flow (Panzer and Chrisman, 1994). Some may refer to this as a *mysticomagical* explanation, which by definition does not allow itself to be proven other than by testimonial or anecdotal results. The Western explanation for the results and benefits of acupuncture involves the stimulation of the secretion of cortisol and the natural release of endorphins (chemicals similar to opioids the body produces) to block pain. This topic is very broad and an explanation in this section alone would not do it justice. Nevertheless, clients may ask about acupuncture so a brief discussion is warranted. As with any unconventional therapy (by Western standards), caution should be taken in subverting traditional allopathic modalities, which are known to work through documented, proven scientific methods. Encourage your clients to explore all possibilities as long as the patient is not at risk. Acupuncture has little chance of harm when practiced by a trained professional. Many veterinarians are skilled in this methodology and combine it with traditional Western teaching and treatment in their practices. Several papers have been published regarding the use of acupuncture in dogs for the treatment of epileptic seizures.

One study looking at the use of acupuncture to treat epileptic seizures in dogs reported that 4 of 11 dogs were seizure-free with no drugs after acupuncture treatment. However, one of the dogs was seizure-free (being treated with primidone) prior to acupuncture treatment and remained seizure-free after acupuncture treatment *and* primidone withdrawal. Another 3 dogs of the 11 showed improvement, which allowed a dose reduction in medications, and the remaining 4 of the 11 showed little or no response. The authors did apply caution to the results, as they may have been coincidental. Of the 11 dogs treated, all tolerated the therapy, and no patients developed any adverse side effects except slight sensitivity at the acupuncture point (Janssens, 1993). For the treatment to work, the authors suggest the needles need to be in place for extended periods of time. Essentially, the needles need to stay in place *all of the time*. In another study, two of the five dogs became seizure-free for 4 months following treatment, one of the five had a significant reduction in seizure frequency,

and two of the five had no response or little response (Panzer and Chrisman, 1994). The authors speculated the two which did not respond because the needles fell out within minutes of their placement and the three that did respond had their needles in place for several hours. Another anecdotal report discusses a patient with suspected genetic epilepsy who became seizure-free after a single treatment with the needles in the shen-men point, bilaterally and left in place for 10 h. Prior to treatment, the dog had been weaned off its antiseizure medication due to high serum concentrations (van Niekerk and Eckersley, 1988). An uncontrolled study using gold wire implants measured seizure frequency and severity in dogs, along with EEG recording, before and after treatment. While no statistical significance was identified regarding the EEG recordings, 9 of the 11 dogs in the study achieved at least a 50% reduction in seizure frequency during the 15-week post-treatment follow-up period (Goiz-Marquez *et al.*, 2009). A human study looking at improvements in health-related quality of life for intractable epileptics did not find any difference between those treated with acupuncture and "sham" acupuncture (Stavem *et al.*, 2000). The most recent Cochrane review concluded that randomized control trials in humans were small, heterogeneous, and had a high risk of bias with no evidence to support the use of acupuncture in humans for treating epilepsy (Cheuk and Wong, 2014). It's also important to note that the review found acupuncture did not have any adverse effects and, in many studies, quality of life did improve. A prescription flowchart, using acupuncture to treat dogs with various diseases, including epilepsy is available (Jeong *et al.*, 2013).

The author also has an anecdotal experience. As a neurology resident, I was presented with a 16-week-old, female Pug Dog who had been experiencing epileptic seizures since birth (see Video 1). The seizures occurred without fail about 2–5 min after falling asleep, shortly after rapid eye movement (REM) began (which interestingly is considered a "seizure-resistant" state of sleep – but maybe not so much in young animals) (Herman *et al.*, 2001). The seizures were characterized as generalized tonic–clonic lasting approximately 15–20 s with a 2–5 min postictal time period. All diagnostic testing was considered normal (Tier III) and she was classified as an early-onset idiopathic epileptic. The dog was placed in a video EEG laboratory in order to attempt to better characterize the epilepsy. There, it was confirmed the seizures always began shortly after REM sleep began. A student, who had an interest in acupuncture and whose husband was a human acupuncture practitioner, asked if she could try it on the puppy. I reluctantly acquiesced (especially since I was not making any headway on AED therapy). The next day, during rounds, the student was holding the puppy who was fast asleep in her arms complete with an acupuncture needle coming out of the center of the pup's ear. I had never observed the puppy to sleep longer than 5 min. She said the pup had fallen asleep shortly after she placed the needles and had remained asleep for the last 15 min. I was a little surprised to say the least. Then she said, "watch this." She gently removed the needles, and within 2 min, the dog had a generalized tonic–clonic seizure. Over the next few months, seizures were controlled in a traditional manner using diazepam as needed and potassium bromide. The pup was adopted by a veterinary student and went on to live a fairly normal life.

When clients are faced with the emotional and financial burden of a pet who has seizures, they will often jump at any chance to stop the seizures. Clinicians should not turn a blind eye to integrative medicine; rather, they should help clients find safe and effective resources (or they will try to find them on their own).

HERBAL- AND PLANT-BASED REMEDIES

When it comes to plant and herbal-based remedies, the general impression is "all natural" equals "safe" with no side effects. National surveys show approximately 42% of people questioned have used at least one form of complementary, alternative, or integrative medicine. Most of these people do not report the use of these therapies to their physicians, 42% of people surveyed use herbal medicines concurrently with over-the-counter medication and 69% of people surveyed were also prescription medication users (Rashrash *et al.*, 2017). A substantial number of Americans

(~15 million) concurrently take *prescription medications* with unconventional therapies (Spinella, 2001). In 2023, sales of herbal products reached a total of $15.5 billion US dollars compared to 6 billion in 2013, which was a 4.4% increase compared to 2022 (Lindstrom *et al*., 2014; Smith *et al*., 2024). Of significant concern is the potential for unintentional side effects and drug interactions. Psychologically, we tend to assume if we can buy it at a grocery store, it is safe. Veterinary patients are potentially no different other than the fact they are not *choosing* to self-administer these therapies and they cannot self-report side effects. The human in charge of administering the remedy must *observe* a side effect. It is important to remember most drugs, toxic chemicals, and poisons are derived from plants, not the toxic by-products of industrial production and large chemical factories. Nature was the first chemical factory. The active chemical constituents of many of these compounds have been identified, allowing them to be tested in a laboratory setting. Many are known to directly affect the central nervous system (CNS) and other organs, specifically the liver. Interaction with the liver may alter its natural ability to metabolize drugs, place an extra burden on an already *stressed* liver, or even cause direct toxic organ damage. However, while possibly being deleterious, some of these compounds may have the ability to affect epileptic seizures. Furthermore, as many of the mechanisms of action of AED are unknown, compounding an unknown with an *unknown* should be avoided. An important distinction must be made between the differences in integrative therapy such as acupuncture and plant-based or herbal remedies. It is well accepted that the direct application of acupuncture will not hurt a pet (although this may be disputed by some) if it is not replacing or delaying a therapy that would otherwise help. However, it is possible the direct application of a plant or herbal remedy could hurt a pet. Furthermore, the FDA does not regulate herbal remedies and the quality/purity is always based on self-reporting by the manufacturer/distributer (kind of like the fox counting the chicken situation . . .). A person might feel sudden gastrointestinal upset after taking a plant-based or herbal remedy. This would encourage them to stop or seek medical care. A dog or cat may not be able to "tell" their owner they are feeling ill. More of the "medication" is given, and by the time the pet collapses or starts to vomit, the damage such as acute liver failure may already be well on its way. There is no way to monitor for the accumulation of tainted product with toxic levels of heavy metals present. Treat any potential remedy with caution and use common sense. A lack of solid science showing the benefits of any one product is overwhelmingly dismissed by anecdotal reports and testimonial accounts. Many of the "safe" products used by humans are toxic to other species, particularly cats and dogs. No herbal or plant-based remedy should be used for a dog or cat without verifying with the pet's veterinarian it will be safe. Any product should be used under the direct supervision of a veterinarian who is experienced with the modality. Some commonly used over-the-counter herbal or vitamin supplements may either be directly toxic to cats and dogs if not given in the correct amount (e.g., St. John's wort), interfere with the disposition of other medications (e.g., milk thistle), increase the side effects of antiseizure medications (e.g., valerian root), or, in some cases, even promote more seizure activity (e.g., rosemary, sage, and eucalyptus). Additionally, the results of a study using highly purified and carefully dosed chemicals may be worlds away from the practical application of an off-the-shelf preparation applied to the family pet. It is completely understandable why many people and pet owners would seek alternative therapies for the control of epileptic seizures for themselves or their pets. A significant portion of the human (~30–40%) and veterinary (~25–30%) epileptic population is pharmacoresistant. Some are truly not helped by multiple medications, given at the correct doses for appropriate amounts of time. However, many pets that do not have their epileptic seizures controlled *may not* have been given the appropriate medication, at appropriate doses, for the appropriate amount of time (a term referred to a "pseudo-resistant", see Chapter 6). Additionally, the number of newer antiseizure medications will continue to increase with time. Basically, there are more tools in the toolbox to try (i.e., conventional and science-based medications) before looking to untested, controversial, sometimes illegal, and potentially harmful alternatives. It is difficult to dispute testimonial accounts or anecdotal data. As

veterinarians, we should be providing our client/pet owners with safe, efficacious medical treatments. We should direct them to specialists in the area of interest or expertise. This may include veterinarians who either limit their practice to or are heavily involved in the use of alternative, integrative, homeopathic, naturopathic, Ayurvedic, herbal and plant-based, aromatherapy, color therapy, music therapy, energy healing, or even folk-based medicine. Some of these alternative therapies may be considered *conventional* medicine in the part of the world they originated from and may have been used "successfully" for centuries on people and animals. This does not mean they should be used without extreme caution on pets. As all veterinarians know, animal disease, while sharing extremely similar pathophysiology to human disease, is not always treated the same. Animals may metabolize human medications in very different ways. Even among traditional veterinary medicine-treated species (i.e., dogs and cats), the differences in drug and plant metabolism can be dramatic (e.g., potassium bromide, benzodiazepines, and corticosteroids). A veterinarian is trained to either recognize these differences, know where to look for specific information, or know who to talk to gain confidence in the proposed treatment.

While many ancient, traditional remedies and even more recent treatments may be effective, one thing almost all have in common is a lack of well-designed scientific studies looking at their efficacy and safety. Again, just to stress the point, this does not mean they will not work or will be dangerous, just there may be insufficient clinical evidence on their efficacy and safety. At no time should a client experiment with herbs and plants on their own pets. Even those commonly used and generally accepted as safe preparations, because of a lack of government regulation, may be produced with various methods, leading to inaccurate concentrations or the addition of harmful by-products. This can lead to disastrous consequences including severe sickness or death. To further complicate the matter, contradictory information is present in the literature and online regarding the use or avoidance of certain remedies (particularly marijuana and rosemary). Many of the recommended remedies use vague terms such as "tincture," which, in itself, does not provide for precise measurements by the layperson. A person who practices veterinary alternative, integrative, or complimentary medicine will undoubtedly have their own individual-preferred preparations and remedies just as veterinary neurologists who *may prefer* to use one drug over another. They may even prepare their own remedies for sale to the public, based on their experience, anecdotal accounts, and testimonials. The rest of this section will examine a few of the potentially therapeutic plant-based and herbal remedies, as well as, those which may lower the seizure threshold (i.e., move the patient closer to having seizures). This section is not meant to be a complete list. Hundreds of books are available on the subject and a gazillion opinions. Of utmost importance, no pet owner should experiment with botanicals, essences, extracts, or any preparation of a seemingly "safe" remedy on their pet. Even when reading about possible cures or treatments for epileptic seizures (including diets), a veterinarian should be consulted. There are hundreds if not thousands of possible plant, herbal, and botanical-based extracts and essential oil combinations that have been used to treat epileptic seizures, some for thousands of years. A comprehensive discussion is beyond the scope of this publication. However, we will look at some of the more commonly used and discussed remedies.

Potentially Harmful

Most information about both potentially harmful and helpful plant-based medications is derived from the human and experimental animal literature. There are sporadic accounts of experimental evidence showing certain compounds will lower seizure threshold in animal models and humans. The compounds a-pinene, limonene, myrcene, asarone, carvone, citral, eugenol, linalool, thujone, 1,8-cineole, camphor, or pinocamphone have been identified as **convulsive agents** (among others) (Bahr *et al.*, 2019). They are present in such commonly found essential oils as:

- Sage
- Rosemary

- Hyssop
- Camphor
- Pennyroyal
- Eucalyptus
- Cedar
- Thuja
- Fennel
- Lavender

Essential oils interact at the level of neurotransmitter release and metabolism, they influence neuronal excitability and modulate voltage-gated sodium, potassium, and calcium channels. Because of their size and lipophilic nature, they readily cross the blood–brain barrier. They have well-documented abilities as anxiolytics, antiseizure, neuroprotective, and sedative effects. Many of these isolated compounds show activity at multiple sites, with multiple neurotransmitters and their receptors. They are all to be considered *promiscuous* and *dirty* "drugs" until proven otherwise. For example, the "healing plant", *Acorus calamanus,* is used to treat mental illness, epilepsy, gastrointestinal upset, fever, arthritis, etc. Asarone, which is found in the roots of Acorus decreases the effects of chlorpromazine, which has known activity at dopamine, serotonin, histamine, adrenergic, and cholinergic receptors. Also, be mindful-mother nature intended for us to *experience* fragrance not be dosed by it.

Rosemary Rosemary is considered a natural reliever of stress and anxiety. It is advocated for humans to be used for improved cognition and as a memory enhancer (McCaffrey *et al*., 2009). It may also be used to treat muscle pain, inflammation, and indigestion. Rosemary is a common additive to dog and cat food as a flavor enhancer and natural preservative. Given its ubiquity in pet foods, pet owners who do their research have made the link between rosemary and its possible epileptogenic potential. This promotes the concern that animals who already have a lowered seizure threshold, those who are naturally walking closer to the "seizure cliff," may exhibit an increase in epileptic seizures or the sudden onset of epileptic seizures if pushed closer to the cliff with an outside influence. There are no scientific studies linking rosemary to an increased chance of epileptic seizures. The epileptogenic components of rosemary are suspected to be cineole and camphor (Burkhard *et al*., 1999). It is recommended rosemary oil not be ingested orally by humans nor used in any form other than food seasoning for children. Because rosemary is a mild diuretic, it may lower bromide concentration (via enhanced elimination) in dogs taking potassium bromide to control seizures. It is also recognized to delay blood clotting ability, interfere with ACE inhibitors (typically taken for heart disease and hypertension), and interfere with the control of diabetes (Bakirel *et al*., 2008; Naemura *et al*., 2008). Conflicting information surrounds rosemary as either potentially causing seizures or occasionally being used to treat epileptic seizures (Tilford *et al*., 2009; Bahr *et al*., 2019). Extracts of rosemary (linalool and rosmarinic acid) have been shown to bind to inactivated T-type calcium channels, which could explain their occasionally reported anxiolytic and neuroprotective effects (El Alaoui *et al*., 2017). Studies looking at linalool (in snail neurons) specifically show that it suppresses spontaneous neural activity at low levels but induces epileptiform activity at higher levels (Vatanparast *et al*., 2017). However, in a PTZ, nicotine and electroshock experimental model of epilepsy (sounds horrible BTW), mice pretreated with inhalation of lavender oil (contains linalool—among many other things) had a 100% survivability rate and all seizures were suppressed while all control animals experienced seizures and had a 100% mortality rate (Yamada *et al*., 1994).

Essential Oils Distilled oils from plants may provide concentrated and toxic amounts of otherwise innocuous commonly used culinary spices. These include the aforementioned rosemary and many others (Table 9.3). Undoubtedly, there are potentially thousands of compounds which alone, in combination with, or in a concentrated form have the potential to induce seizures. These essential oil preparations may be purchased over-the-counter and applied in various means to the skin and in food or inhaled as a component of aromatherapy.

Numerous essential oil products are available over-the-counter to prevent ectoparasite (i.e., flea and tick) infestations. These easy-to-obtain "natural" (i.e., *safe*) products, even when applied to the manufacturer's directions, have directly resulted in reactive seizures and in some cases, death of the cat or dog (Genovese *et al*., 2012). These products may be formulations for flea control as shampoos, flea sprays, and spot-on topical flea treatment. They are exempted from oversight by the Environmental Protection Agency and Food and Drug Administration. Many contain *peppermint oil*, *cinnamon oil*, *lemongrass oil*, *thyme oil*, *rosemary oil*, and many other concentrated substances. Pennyroyal, a relative of the mint family, is a common compound found in these over-the-counter, unregulated "natural" products (Sudekum *et al*., 1992). It is impossible to know what one element or combination of elements may contribute to seizures. It is also impossible to know if the compounds directly cause seizures or if seizures are secondary to hypothermia, organ failure, or other metabolic diseases. A literature review focusing on essential oils known to either have anticonvulsant or proconvulsant activity in humans and animals makes for informative (although a little scary) reading (Bahr *et al*., 2019).

Herbal Stimulants The greatest access to herbal compounds, which may cause epileptic seizures, will be from accidental ingestion by pets. These may include ephedra, cocoa, coffee, cola, guarana, maté, and tea (Table 9.4). These herbal stimulants are thought to potentially exacerbate seizures in humans. Many of the compounds such as cocoa, coffee, and tea contain compounds (e.g., caffeine, theophylline, and theobromine) that are known to result in reactive seizures, primarily in dogs, if taken in adequate amounts. Maté and guarana are traditional coffee or tea-like drinks made from the berries or leaves of respective sources. Guarana (an herbal source of caffeine) is also used as a supplement in energy drinks. Caffeine, theobromine, and theophylline are probably the most common stimulants dogs may ingest, typically by eating chocolate, although having coffee, tea,

Table 9.3 Herbal essential oils which may induce seizures.

Common name	Scientific name	Epileptogenic compound
Eucalyptus	*Eucalyptus globulus*	Cineole
Fennel	*Foeniculum vulgare*	Fenchone
Hyssop	*Hyssopus officinalis*	Pinocamphone
Pennyroyal	*Mentha pulegium* or *Hedeoma pulegioides*	Pulegone
Rosemary	*Rosmarinus officinalis*	Cineole, Camphor
Sage	*Salvia officinalis*	Thujone, Camphor, Cineole
Savin	*Juniperus Sabina*	Sabinylacetate, Camphor, Thujone
Tansy	*Tanacetum vulgare*	Thujone, Camphor
Thuja	*Thuya occidentalis*	Thujone, Fenchone, Camphor
Turpentine	*Pinus* species	Pinenes? (unproven)
Wormwood	*Artemisia absinthium*	Thujone

Sources: Burkhard, P.R., Burkhardt, K., Haenggeli, C.A., and Landis, T. 1999. Plant-Induced Seizures: Reappearance of an Old Problem. *Journal of Neurology*. 246(8):667–670. Bahr, T.A., Rodriguez, D., Beaumont, C., and Allred, K. 2019. The Effects of Various Essential Oils on Epilepsy and Acute Seizure: A Systematic Review. *Evidence-Based Complementary and Alternative Medicine: eCAM*. 2019:6216745.

Table 9.4 Herbal stimulants that may cause or promote seizures.

Common name	Scientific name	Epileptogenic compound
Cocoa (chocolate)	*Theobroma cacao*	Caffeine, Theobromine, Theophylline
Coffee	*Coffea arabica*	Caffeine, Theobromine, Theophylline
Cola, kola	*Cola acuminata*	Caffeine, Theobromine, Theophylline
Ephedra	*Ephedra* species	Ephedrine
	Cola nitida	
Ginko	*Ginko biloba*	Flavonoid glycodides, Terpene lactones
Ginseng	*Panax ginseng*	Ginsenosides
	Panax quinquefolium	
Guarana	*Paulinia cupana*	Caffeine, Theobromine, Theophylline
Maté	*Ilex paraguariensis*	Caffeine, Theobromine, Theophylline
St. John's Wort	*Hypericum perforatum*	Hyperforin
Tea	*Camellia sinensis*	Caffeine, Theobromine, Theophylline

Adapted from Spinella, 2001.

and cocoa are also possible sources. Caffeine-enriched pills and energy supplements may also be a potential source. When in supplement form, these compounds are often combined with ephedrine (ma huang) and/or pseudoephedrine, which may promote the effects of the compounds. The stimulatory effect of caffeine and its methylxanthine derivatives (i.e., theophylline and theobromine) is generated through the antagonism of *presynaptic adenosine receptors*. Adenosine is an inhibitory neurotransmitter. Caffeine blocks adenosine activity, which results in the release of several disinhibitory neurotransmitters, ultimately culminating in a net *excitatory* outcome (Fisone *et al*., 2004).

Cognitive and Memory Enhancers Many supplements and herbal medicines have gained popularity among humans for various illnesses as immune system support and cancer fighters (i.e., free radical scavengers), etc., so they are bound to find their way into the realm of veterinary medicine. Herbal cognitive and memory enhancers are of particular interest for the treatment of cognitive dysfunction and anxiety in elderly dogs. The most popular compounds used by humans to enhance learning and memory are *ginkgo* and *ginseng*. Certain components of ginkgo have been identified which have promnestic effects, as well as, antiseizure effects (e.g., bilobalide). Active research in cognitive improvement is being pursued in dogs (Araujo *et al*., 2008). However, the isolated elements, thought to result in cognitive enhancement experimentally, are not separated from the parent plant form commercially; therefore, the whole of the plant must be considered when it is used.

Many animal studies have been performed showing how *ginseng* can be promnestic (Jesky and Hailong, 2011; Oliynyk and Oh, 2013; Kim *et al*., 2013a). The active components of ginseng, the ginsenosides, activate the hypothalamic–pituitary–adrenal axis, resulting in an elevation of ACTH and subsequent corticosteroids, naturally produced by the body (Hiai *et al*., 1979). Corticosteroids have been shown to have epileptogenic capabilities, leading to the suspicion stress may be involved in the generation of seizures (Temkin and Davis, 1984; Betts, 1992; Maguire and Salpekar, 2013). Ginsenoside Rg1, a component of Asian ginseng (*Panax ginseng*), is a functional ligand of the glucocorticoid receptor (Lee *et al*., 1997). The association between ginseng and alterations in natural corticosteroid production has led to the recommendation (in some cases) ginseng be avoided if a person is epileptic. On the other hand, some evidence suggests ginseng may help alleviate or block some of the harmful metabolic consequences of stress (Kim *et al*., 2003).

St. John's Wort St. John's wort (*Hypericum perforatum*) is commonly used to treat depression in humans and is thought to have efficacy similar to conventional drug therapy (Brenner *et al*., 2000; Volz and Laux, 2000). However, difficulty in interpreting results and poor study design make these results questionable (Shelton *et al*., 2001). At the very least, the use of St. John's wort was found to have minimal side effects, although it is recommended not to use the remedy if a patient is taking other medications. St. John's wort has been found to upregulate cytochrome P450 through activation of the pregnane X receptor by the primary active constituent of St. John's wort, *hyperforin* (Moore *et al*., 2000). While it has been proposed St. John's wort would *not* interact with the metabolism of phenobarbital in humans, we must remember the liver of the dog and cat are quite different regarding the ability to metabolize drugs (Mannel, 2004). Of primary concern is that altered expression of cytochrome P40 may lead to enhanced metabolism of certain drugs, in particular phenobarbital, leading to lowered serum levels and a greater chance of breakthrough epileptic seizures.

Other potentially harmful herbs include the toothache plant (*Spilanthes acmella*); *Coriaria lactone*, extracted from plants of the mistletoe family; choline supplements (lecithin derived from soy or egg yolks); wormwood essential oils; and extracts of *Solanum pseudoquina*. Undoubtedly, there are hundreds of commercially available products and countless "homemade" products, which have the potential to be epileptogenic.

Potentially Helpful

Herbal Sedatives (Table 9.5)

Kava: Many herbal remedies have been tested in numerous animal studies for efficacy in alleviating epileptic seizures (Singh and Singh, 2002). The roots of the kava plant (*Piper methysticum*) have been used for centuries by the indigenous people of the South Pacific as a ceremonial drink. The plant, which is a member of the pepper family, is becoming more popular in Western cultures because of its "natural" calming properties. Although it is nonalcoholic, it is known to have sedative, anesthetic, and anxiolytic properties without disturbing mental clarity. In addition, it is thought to have analgesic, anticonvulsant, and neuroprotective properties (Gleitz *et al*., 1996a; Singh and Singh, 2002). Kavalactones, the principal constituent of the plant, have been shown to facilitate GABA transmission via enhanced ligand binding to the $GABA_A$ receptor through a nonbenzodiazepine receptor site (Davies *et al*., 1992). Additionally, kavalactones have been shown to inhibit voltage-gated sodium and calcium channels (Gleitz *et al*., 1996b). Kavalactones bind to the voltage-gated sodium channel when in its inactivated state, prolonging its inactivation and reducing the release of endogenous glutamate by inhibiting L-type calcium channels

Table 9.5 Herbal sedatives.

Common name	Scientific name	Active compound
Kava	*Piper methysticum*	Kavalactones
Valerian	*Valeriana officinalis*	Monoterpenes, Sesquiterpenes
Passionflower	*Passiflora coerulea*	Crysin
	Passiflora edulis	
Chamomile	*Matricaria recutia*	Apigenin?
	Chamaemelum nobile	
Huperzine	*Huperzia serrate*	Sesquiterpene

Sources: Spinella, M. 2001. Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects. *Epilepsy & Behavior: E&B*. 2(6):524–532. Schneider, B.M., Dodman, N.H., Faissler, D., and Ogata, N. 2009. Clinical Use of an Herbal-Derived Compound (Huperzine A) to Treat Putative Complex Partial Seizures in a Dog. *Epilepsy & Behavior: E&B*. 15(4):529–534.

(Gleitz *et al*., 1996b; Magura *et al*., 1997). While the science may seem sound, because kava may inhibit such important elements of neural conduction such as the potentiation of GABA or alterations in voltage-gated ion channel conductance, it should be approached with even greater caution if used in pets and only under the guidance of a veterinarian who is experienced in its use. While generally regarded as safe (GRAS), humans may experience allergic reactions to the remedy, and reports of severe rhabdomyolysis are in the literature (Bodkin *et al*., 2012).

Valerian Perhaps the most common and widely used veterinary herbal sedative is *valerian* (*Valeriana officinalis*). The perennial herb grows in all parts of the world although it is a native plant of Europe and northern Asia. Reports of valerian being used to treat medical conditions can be traced to *Dioscorides* (circa AD 55), and it was heavily used until the 20th century as a digestive aid, an expectorant, an anxiolytic (anti-hysterical), and a "nerve tonic" (Eadie, 2004). Valerian has been scientifically shown to be a mild sedative and sleep-promoting agent in addition to being an anxiolytic (Balderer and Borbély, 1985; You *et al*., 2012). In a study of firework-induced noise phobia, dogs receiving a compound containing valerian (along with tryptophan and passiflora) had reduced behavioral and stress reactions compared to placebo dogs (Ramos *et al*., 2024). Additionally, treated dogs had salivary cortisol levels close to those of a normal, "quiet morning." Although, we recognize the diurnal nature of cortisol secretion and the fact it is naturally higher in the morning (Kolevská *et al*., 2003; Castillo *et al*., 2009). The chemical composition of the plant varies greatly depending on the plant subspecies, the time of harvest (i.e., relative to the season), the age of the plant, and the type of extract made from the plant (World Health Organization, 1999; Hamedi *et al*., 2017). There are many chemical constituents consisting primarily of monoterpenes and sesquiterpenoids. Perhaps this is the reason, through the history of its use, variations of the effect have been reported from "significant and substantial" to "obnoxious and inefficacious" (Eadie, 2004). Experimentally, the chemical components of valerian have been shown to interact with $GABA_A$ receptors with high affinity and exert an anxiolytic effect on mice (Benke *et al*., 2009). Its anticonvulsive effects may also be mediated through interaction with adenosine receptors (Rezvani *et al*., 2010). Up to 1% of the root may be converted to isovalerate, which interestingly is structurally similar to valproic acid, a potent anticonvulsant used in humans (Pearl *et al*., 2011). The use of valproic acid in veterinary patients is limited, and studies looking at its long-term efficacy are scarce (see Chapter 7). Like kava, valerian is GRAS. Sometimes combined with alcohol in the extract form, there may be synergistic activity. Valerian should not be given to pets without the direction of a veterinarian experienced with its use. The dose, preparation, and length of time of treatment are all possible variables that could potentially affect its efficacy.

Passionflower Indigenous Americans historically have used *passionflower* tea for its sedative and anxiolytic effects (Spinella, 2001). It has been used in Europe since the 16th century, as a medicinal plant. The active compound of the passionflower (*Passiflora caerulea* and *Passiflora edulis*) is thought to be chrysin. *Passiflora incarnata* L. interacts with the $GABA_A$ receptor (Jawna-Zboińska *et al*., 2016). GABA and several other compounds have been isolated from the plant all of which may also play a role in inhibition of epileptic seizures. It is suspected the compounds also increase serotonin and dopamine levels in the brain. Chrysin acts as a partial agonist at benzodiazepine receptors (Medina *et al*., 1990). Animal studies have demonstrated its ability to inhibit experimentally induced seizures, improve spacial memory and its sedative and anxiolytic effects (Singh *et al*., 2012; Jawna-Zboińska *et al*., 2016). Passionflower is contained in many over-the-counter "calming treats" for dogs. It is not recommended to use the supplement if a pet is taking medication for the "nervous system." It is also contraindicated in pregnant animals as it is reported to stimulate the uterus. Most of the information regarding Passionflower is anecdotal.

Chamomile Commonly used as a sleep aid in the form of tea, *chamomile* (*Matricaria recutita* and *Chamaemelum nobile*) is a perennial flower shrub that grows in many parts of the world (e.g., Europe, Asia, and Africa) and has historically been an important component of traditional folk medicine in many cultures. It is known to be an anxiolytic, antispasmodic, anti-inflammatory, and mild sedative. The active constituent, apigenin, binds to the benzodiazepine receptor site; however, its effects are not blocked by a specific benzodiazepine competitive antagonist (RO 15-1788), leading to speculation its exact mechanism of action may involve interaction with other neurotransmitters or an altogether different component which has not yet been identified (Avallone *et al*., 2000). Extracts prepared from the plant are effective in inhibiting experimentally induced seizures in mice (Heidari *et al*., 2009). It is considered by the Food and Drug Administration to be GRAS.

Huperzine Considered more of a drug than an herbal remedy due to extensive purification and processing, *huperzine* is a sesquiterpene alkaloid, extracted from firmoss or clubmoss (Chinese clubmoss) (*Huperzia serrata*). It is an acetylcholinesterase inhibitor and NMDA receptor antagonist (blocks glutamate; recall an excitatory amino acid) (Tang and Han, 1999). Huperzine has been used as part of traditional Chinese medicine for centuries to improve cognition, enhance memory, reduce inflammation, and treat blood disorders. It has more recently gained attention in Western medicine as a possible treatment for Alzheimer's disease, as a neuroprotectant, and to alleviate epileptic seizures (Wang *et al*., 2011). Huperzine has been reported to reduce the frequency and intensity of focal seizures with cognition (e.g., fly-snapping, lick smacking, and stargazing) in one dog with presumed genetic epilepsy (Schneider *et al*., 2009). In this report, several components of the dog's behavior were suspicious for obsessive–compulsive disorder; however, EEG recordings demonstrated focal activity consisting of spikes, sharp waves, and spike-and-slow-wave complexes over the left occipital lobe, consistent with paroxysmal interictal discharges. The therapeutic effect was lost after the dog was treated with tramadol for joint pain. Breakthrough seizures were noted and the dog was switched to phenobarbital without a trial increase in the huperzine dose. Seizures secondary to tramadol administration are a reported side effect in humans (Shadnia *et al*., 2012). There is a greater risk of seizures as a component of serotonin syndrome (nausea, vomiting, mydriasis, hypersalivation, hyperthermia, and anxiety) when tramadol is combined with a selective serotonin reuptake inhibitor (SSRI, e.g., fluoxetine) or a serotonin agonist (e.g., trazodone) (Fitzgerald and Bronstein, 2013). There are no reports in the veterinary literature of this side effect despite tramadol's widespread use in dogs and cats as an analgesic. Huperzine has also been shown to be effective in suppressing seizure activity experimentally in other animal models (Lallement *et al*., 1997; Tonduli *et al*., 2001). In a case series looking at the efficacy of an extended-release preparation of huperzine used to treat idiopathic epilepsy in dogs, it was found to be well tolerated (two dog owners reported transient vomiting which resolved without treatment), although case numbers were two small to apply statistical analysis in regards to effect on seizure frequency (Grant and Long, 2025). Two owners reported dramatically improved quality of life due to increased energy levels and responsiveness, as well as, decreased restlessness. Huperzine appears to have a very wide safety margin with no significant clinical or clinicopathological effects in the dog, when used in normal recommended doses (Schneider *et al*., 2009). While it is available over-the-counter, appears safe and well tolerated in dogs, and may be efficacious in treating epileptic seizures in dogs, a veterinarian should oversee its use and prescribe huperzine.

Marijuana and Hemp (THC and CBD)

THC (Δ^9-tetrahydrocannabinol) The use of marijuana (*Cannabis sativa*) as a medicinal plant dates back to 4000 BCE, making it possibly one of the oldest documented herbal medications (Li, 1974). Both hemp and marijuana originate from *Cannabis sativa*. Cannabis has historically been used to

treat rheumatism, pain, and seizures (Jones *et al*., 2012). Through an online survey in the USA, the use of cannabidiol for the treatment of epileptic seizures in dogs and cats, was one of the top three conditions for which pet owners requested information from their veterinarian (Kogan *et al*., 2019). At the time, 30% of veterinarians responded they were not comfortable with having a conversation about marijuana use with their clients. A 2016 survey of pet owners in the USA found 58.8% of dog owners currently were using a hemp product for their dogs, with the most common usage being to treat seizures, cancer, anxiety, and arthritis (Kogan *et al*., 2016). In the same survey, 11.93% of respondents said they used a hemp product for their cats (anxiety, arthritis, and cancer). Of the owners who were giving it to their dogs to help with epileptic seizures, 19% responded it "helped a great deal."

The question of *marijuana's* ability to alleviate or *potentiate* seizures continues to be debated. Marijuana has been extensively studied with results demonstrating it is an anticonvulsant, as well as, wait for it . . .. an epileptogenic. But much of this nuance has to do with the combination of the two main active components—cannabidiol (CBD) and Δ^9–tetrahydrocannabinol (9THC) both of which are present in *Cannabis sativa*. However, hemp contains less than 0.3% 9THC and therefore does not have any psychoactive effects.

In cats treated experimentally with Δ^9–tetrahydrocannabinol (9THC), a protective effect was found with electrical stimulation of cortical structures resulting in decreased seizure activity (Wada *et al*., 1973). Similar results have been found in rats and primates. The antiepileptic effects of THC are much less significant when compared to its ability to suppress the kindling of amygdaloid seizures in cats (Wada *et al*., 1975).

A large amount of evidence from experimental research has shown THC and other components of the plant to be epileptogenic (Chiu *et al*., 1979; Turkanis and Karler, 1982). In humans, the recreational use of marijuana (and its withdrawal) has been associated with triggering seizures in susceptible patients (Gordon and Devinsky, 2001). The EEG and ECoG of rats, cats, and primates have been reported to show *increased* epileptiform activity in response to THC and its derivatives (Hockman *et al*., 1971). In an interesting study utilizing dogs who "smoked" marijuana cigarettes (via tracheotomy), epileptiform discharges were induced in dogs who "smoked" the marijuana and were exposed to penicillin injections, whereas controls did not display the changes on ECoG recordings (smoking alone or penicillin alone) (Labrecque *et al*., 1978). Generalized epileptic seizures were induced with penicillin injections in dogs exposed to chronic smoking (10 weeks at four cigarettes a day). The intoxication regimen was considered to be conservative (1–2.5 mg/kg of marijuana). In recent years, the use of medical marijuana has resulted in a significant increase in investigation into its use as an herbal remedy. As of 2025, 47 states in the USA allow legal possession of marijuana for medical or recreation uses; however, it is still a federal offense at the time of this writing, making it technically illegal to dispense or use marijuana (9THC) without a medical use exception. At the Federal level, marijuana is classified as a Schedule I drug, meaning it has no currently accepted medical use and has a high potential for abuse. There is currently no legal pathway for veterinarians to prescribe 9THC. However, it is possible to prescribe *CBD* (see below).

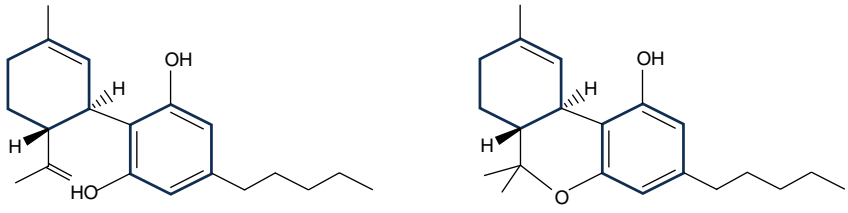
Of note, even small amounts of 9THC present in CBD extracts have been reported to worsen seizures in pediatric patients (Crippa *et al*., 2016). Once the children were switched to a purified form, the seizures went back into remission. This emphasizes the need to be very careful of the source being used for treatment. Sales of cannabis products for pets increased by 1000% between 2016 and 2017 (Amissah *et al*., 2022). A 4× increase in cases of canine marijuana intoxication between 2005 and 2010 has been reported since its medical use legalization in Colorado (Meola *et al*., 2012). The ASPCA reported a 765% increase in calls in 2019 compared to 2018 for reports of dogs ingesting marijuana products—primarily edibles (ASPCA, 2019).

The mechanism of action of 9THC is not completely understood but is hypothesized to be partially (definitely not exclusively) due to interaction with the G-protein-coupled cannabinoid receptors, CB_1 and CB_2. These receptors are densely expressed in the hippocampus, and activation

of the receptors has been proved to be antiepileptic in animal models (Wallace *et al*., 2001). However, after years of experimentation on animal and human subjects combined with clinical data, there is no evidence of 9THC influencing the development of epileptic seizures, and currently, its use is not recommended (Potschka *et al*., 2022).

CBD (Cannabidiol) Cannabidiol on the other hand . . . well, that's another story. CBD is extracted from the hemp plant (but also present in marijuana). Hemp and marijuana are the same plant but hemp is a mixture of male and female cannabis plants. Hemp flowers produce less than 0.3% 9THC. CBD has no psychoactive properties, despite having an identical chemical composition of 9THC, except for one bond between a carbon and oxygen atom (Figure 9.1). Highly purified cannabidiol is approved in the USA for the treatment of epileptic seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex, in patients 1 year and older. It is sold under the name *Epidiolex*® in the USA and *Epidyolex*® in the European Union, at a concentration of 100 mg/ml of CBD. With the FDA approval of a CBD product to treat human epilepsies, veterinarians now have a legal way to prescribe highly purified CBD (albeit through extra label use). The concentration of 100 mg/ml makes dosing convenient and the cost is reported to be comparable compared to veterinary products without the strict manufacturing oversite (Jukier *et al*., 2023). Cannabidiol has been shown to have anticonvulsant activity in both in vitro and in vivo experiments although results (and the doses necessary to achieve those results) vary considerably (Jones *et al*., 2010, McGrath *et al*., 2019; Rozental *et al*., 2023). Cannabidiol's antiepileptic effects are not associated with CB1 or CB2 receptors but are thought to primarily effect (Gray and Whalley, 2020, Lazarini-Lopes *et al*., 2020) (Figure 9.2):

- Antagonism of orphan G protein-coupled receptor 55 (GPR55) that is involved in modulating mobilization of neuronal calcium, causing an increase in synaptic activity. CBD reduces this activity
- Agonism of transient receptor potential vanniloid-1 (TRPV1), rapidly causes desensitization and subsequent receptor downregulation, resulting in decreased calcium influx into presynaptic neurons
- Increases extracellular adenosine, the brain's natural anticonvulsant, by decreasing adenosine uptake into macrophages and microglia cells through inhibition of the equilibrative nucleoside transporter (ENT_1) adenosine pump. By increasing the available amount of extracellular adenosine, seizure control is enhanced through decreased synaptic activity (reduces presynaptic calcium influx and postsynaptic hyperpolarization)



Cannabidiol (CBD)
$C_{21}H_{30}O_2$

Δ^9-Tetrahydrocannabinol (9THC)
$C_{21}H_{30}O_2$

FIGURE 9.1 Comparison of cannabidiol (CBD) and Δ^9–tetrahydrocannabinol (9THC). The two structures have the same molecular weight and chemical formula. However, a simple change in bond arrangement gives 9THC its psychoactive properties, which develops when the compound is dried or heated.

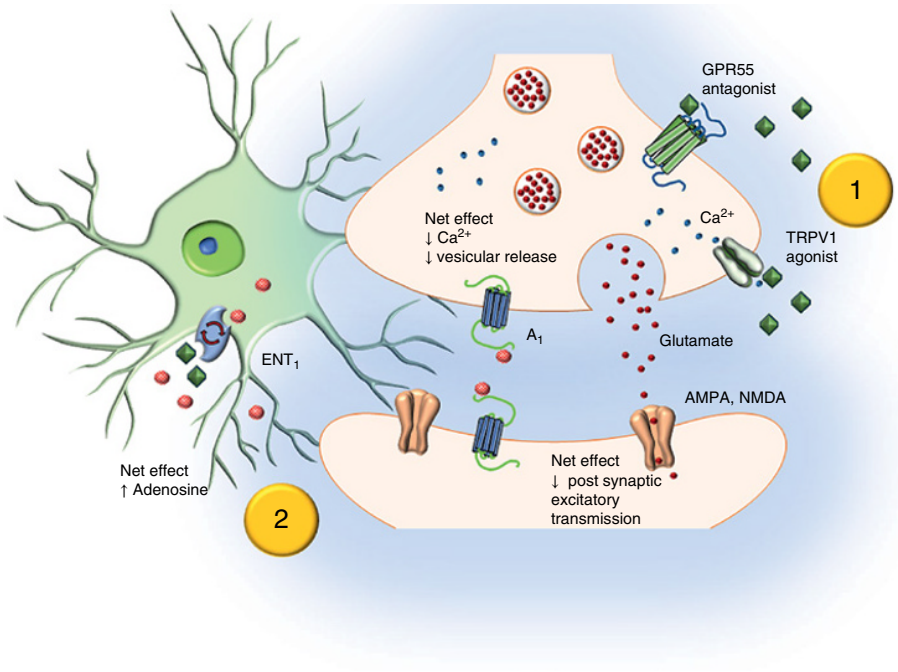


FIGURE 9.2 Some of the proposed mechanisms of action for the anticonvulsant effect of CBD. Two primary mechanisms are active. (1) The reduction of intracellular calcium that has a net effect of decreased postsynaptic excitatory neurotransmission by inhibiting vesical release of glutamate. This is done through antagonism of GPR55 which modulates the internal mobilization of calcium to cause vesicular release of glutamate and by agonism of the TRPV1 receptor (leading to rapid desensitization) which is responsible for influx of calcium into the presynaptic neuron. The net effect of both these actions is a reduction of intracellular calcium and excitatory neurotransmission. (2) Inhibition of adenosine transport. By increasing extracellular adenosine through inhibition of the equilibrative nucleoside transporter (ENT_1) on microglial cells. Extracellular adenosine will bind to the adenosine A_1 receptor, inhibit presynaptic calcium influx, and hyperpolarize the postsynaptic membrane via enhancement of inwardly rectifying potassium channels.

The exact mechanism of action of CBD is unknown, however, its cumulative actions act to inhibit presynaptic vesicle release of neurotransmitters, thereby reducing postsynaptic neuron activation (Lazarini-Lopes *et al.*, 2020). Much of this activity, as previously mentioned is through modulation of intracellular calcium and increased extracellular adenosine levels (Ross *et al.,* 2008).

Other nonpsychoactive components of the plant, such as cannabidivarin, have demonstrated antiseizure effects in a broad spectrum of experimentally induced seizure models (Hill *et al.*, 2012). Over 100 cannabinoids have been identified in the marijuana plant and they vary with their affinity for their target receptors (Marichal-Cancino *et al.*, 2017). The "entourage effect" proposes the combined effect of multiple compounds is responsible for the unique benefits. The pharmacological effects of CBD include (Potschka *et al.*, 2022):

- Anti-inflammatory
- Analgesic
- Anxiolytic
- Antiemetic
- Muscle relaxation

- Spasmolytic
- Sedative
- Tumor growth inhibitor
- Neuroprotectant
- Anticonvulsant

CBD has a low oral bioavailability which is improved if formulated into an oil base and given with food. Additionally, it has a high first-pass effect through liver metabolism (Samara *et al*., 1988). In dogs treated with daily doses of CBD (1, 2, 4, or 12 mg/kg/day), adverse effects were mild (Vaughn *et al*., 2021). As expected, the higher the dose the greater the side effect with gastrointestinal signs (primarily salivation) noted at the high dose. Additionally, as found in several other clinical trials, serum *alkaline phosphatase* activity was consistently increased. CBD and phenobarbital do not appear to have any interactions and it is recommended to not alter doses of either when used in conjunction with one another (Doran *et al*., 2021). Although, the Plumb's Veterinary Drug Handbook mentions that phenobarbital may lower the serum concentration of CBD in humans and to monitor for a reduction in efficacy if used in veterinary patients. CBD is tolerated well both in dogs and cats but a mixture of CBD and THC leads to more adverse effects, primarily related to gastrointestinal upset and lethargy. Cats seem to be more resistant to the effects of THC compared with dogs. The Corsata Alvarenga review article provides an excellent overview of its use and validation for cat and dog disease (Corsato Alvarenga *et al*. 2023).

In a randomized blinded controlled clinical trial at a dose of 2.5 mg/kg BID of CBD given with existing AEDs for 12 weeks, 33% of the treated group had a reduction in frequency compared to the placebo group (McGrath *et al*., 2019). However, there was no difference in the proportion of dogs considered to be responders between the two groups (measured as ≥50% decrease in seizure frequency). Side effects were considered mild but one dog dropped out of the study due to ataxia. There was a positive correlation between plasma CBD concentrations and a reduction in seizure frequency. In a double-blinded, placebo-controlled cross-over clinical trial, dogs were given a CBD/CBDA (cannabidiolic acid)-rich hemp extract at a dose of 2 mg/kg BID for 3 months (Garcia *et al*., 2022). Across both arms of the study, epilepsy seizure frequency decreased from a mean of 8 during the placebo portion of the study to 5 during the CBD/CBDA treatment arm. Six out of 14 of the dogs had a 50% decrease in seizure activity while being treated with extract, while 0/14 had ≥50% decrease in seizure frequency while on the placebo. Reported side effects included mild ataxia and somnolence which was not significantly different from the placebo group. A mild increase in serum ALP was noted but no changes to serum phenobarbital, zonisamide, or potassium bromide levels.

A double-blinded crossover study utilizing CBD oil at a dose of 4.5 mg/kg BID was utilized after the failure of response at a dose of 2.5 mg/kg BID in the first 13 dogs enrolled in the study (51 dogs completed the study) (Rozental *et al*., 2023). At the dose of 4.5 mg/kg BID, there was a 24.1% decrease in seizure days for the treatment group compared to 5.8% *increase* in seizure days for the placebo group. CBD-treated dogs consistently had elevated serum ALP and ALT. Two dogs had elevated serum bile acids at the end of the study. Out of all the side effects reported between the treated and placebo groups, only decreased appetite and vomiting were more frequently reported in the CBD-treated group.

Cats seem to tolerate CBD and THC better than dogs. In a study looking at increasing doses of CBD, THC or a CBD:THC blend, all cats were able to achieve the maximum dose of treatment (CBD = 30.5 mg/kg, THC = 41.5 mg/kg, 13.0:8.4 mg/kg CBD:THC) (Kulpa *et al*., 2021). All adverse events were mild and gastrointestinal adverse events were greater in the placebo group utilizing medium-chain triglyceride oil (as opposed to sunflower oil). When cats were given a single dose of

CBD (Epidiolex) at 5 mg/kg, there was an 11× increase in bioavailability when it was given with food (Jukier *et al*., 2023).

A pharmacokinetic study comparing dosing via oral (PO), intranasal (IN), and intrarectal (IR) routes has been reported (Polidoro *et al*., 2022). The study found no detectable CBD after the IR dose (100 mg) and reduced absorption when given IN (20 mg) compared to PO (100 mg), although when normalized for dose, the difference was not significant. The IN route demonstrated faster blood absorption, although, the CBC needed to be mixed with polyethylene glycol (PEG) and 0.9% saline (50:50) in order for it to be atomized. The study verified the oral route of administration provides the best route of treatment (ease of use, and no need for compounding), however, the IN route gives the fastest absorption and can be considered an alternate route of delivery when the PO route is not available. Rectal administration should not be used.

Considering a lack of definitive evidence one way or another as to its anticonvulsant benefits and the plethora of other options available to control epileptic seizures, until more studies on its effects in animals provide conclusive data, it cannot be recommended to use 9THC as an anticonvulsant in dogs and cats. However, if a reliable source of CBD is obtained (e.g., Epidiolex), it would be reasonable to try in cases of drug-resistant epilepsy, where more commonly used AEDs have failed. The extralabel prescription of Epidiolex would be a practical option. A recommended starting dose based on clinical trials would be 2.5 mg/kg BID for dogs, potentially increasing to 9 mg/kg/day. Although no dosing data is available for cats, they appear to tolerate the treatment (CBD) better than dogs.

Potentially Dangerous

In a bit of a gray area are herbs and botanicals, which have been shown either empirically or experimentally to produce sedation and anxiolytic effects and have anticonvulsive properties but at the same time potentially have harmful side effects and significant interactions with other medications or conversely actually regarded as potentially *proconvulsant* (Table 9.6). Some of these herbs are commonly found

Table 9.6 Potentially dangerous herbal sedatives (dangerous side effects or exacerbation of seizures).

Common name	Scientific name	Active compound
American Hellebore	*Veratrum viride*	Ester Alkaloids
Betony	*Stachhys offininalis*	Tannins?
Blue Cohosh	*Caulophyllum*	Methylcystine
	Thalictroides	
Mistletoe	*Viscum* sp.	Unknown
Mugwort	*Artemisia vulgaris*	Numerous bioactive compounds
Pipsissewa	*Chimaphila umbellate*	Unknown
Skullcap	*Scutellaria laterifolia*	Baicalin, Baicalein
	Scutellaria baicalensis	Oroxylin
		Wogonin
Marijuana	*Cannabis sativa*	Cannabidivarin
		Cannabidiol
		THC*

*Δ^9-tetrahydrocannabinol.

Sources: Pearl, P.L., Drillings, I.M., and Conry, J.A. 2011. Herbs in Epilepsy: Evidence for Efficacy, Toxicity, and Interactions. *Seminars in Pediatric Neurology*. 18(3):203–208. Tyagi, A. and Delanty, N. 2003. Herbal Remedies, Dietary Supplements, and Seizures. *Epilepsia*. 44(2):228–235.

in antiseizure preparations. Their use should be highly questioned and probably avoided until more research can provide specific effects, preparations, or isolation of the active constituents.

American Hellebore Generally considered to be extremely poisonous, *American hellebore* (*Veratrum viride*) should be avoided. While historically used by several indigenous American nations for medicinal purposes, it is not recommended for medicinal use. It is highly toxic, and the therapeutic index (the difference between a positive effect and a negative side effect) is extremely low, often resulting in death.

Betony One of the more ubiquitous herbal remedies, *betony* (*Stachys officinalis*) is a common ingredient in all-natural, over-the-counter, herbal-calming tonics for dogs and cats. In the Middle Ages, it was thought to have magical powers and used to treat basically everything. It was primarily used to ward off ghosts and protect people from evil spirits and bad dreams. Modern use of the herb in animals is as a "calming agent." Humans will use the herb to treat anxiety, asthma, bronchitis, diarrhea, headache, heartburn, palpitations, renal disease, parasitic infestations, seizures, gastrointestinal distress, toothaches, high blood pressure, neuralgia, gallstones, and wounds (Pearl *et al.*, 2011). There is no scientific evidence it has any beneficial effect. Wood Betony is heavily promoted as a natural dog-calming agent.

Blue Cohosh One of the active agents of *blue cohosh* (*Caulophyllum thalictroides*) is *N*-methyl cysteine, a compound similar to nicotine, although many alkaloids and saponins have been isolated from the roots of the plant (Rader and Pawar, 2013). Indigenous Americans first used blue cohosh as a medicinal herb. Following this discovery by European settlers, it was employed for various ailments including the treatment of epileptic seizures. It was and continues today to be used primarily by midwives to induce labor and abortion (Pearl *et al.*, 2011). It is still commonly used today in humans and veterinary patients. Extracts of the plant have demonstrated significant mitochondriotoxic activity resulting in the disruption of cellular respiration (Datta *et al.*, 2014). Blue cohosh can be found as a component ingredient in many over-the-counter herbal preparations designed to treat a variety of conditions.

Mistletoe While a common festive holiday decoration associated with awkward moments, *mistletoe* (*Viscum* sp.) historically was used to treat disorders of circulation and the respiratory system in humans. In addition, like many other nonspecific herbal remedies, it was used to treat a variety of conditions including, epilepsy, insomnia, headaches, restlessness, tachycardia, and sterility. It is also suspected to have anticancer properties and is used as an herbal remedy for cancer despite its known toxicity (Ernst, 2006). In European countries, 70–80% of human cancer patients will receive mistletoe extracts at some point in their treatment (Klingemann 2024). *In vitro* studies show an effect of the extract against canine high-grade astrocytoma cells (Wright *et al.*, 2022). Extracts of mistletoe have been shown to inhibit pentylenetetrazole (PTZ) and bicuculline-induced seizures in mice but not seizures created by *N*-methyl-DL-aspartic acid (Amabeoku *et al.*, 1998). In a more recent study, extracts of *Viscum album* were found to inhibit maximum electroshock (MES)-isoniazid (INH)- and PTZ-induced seizures in mice and rats (Gupta *et al.*, 2012). A child with refractory childhood absence epilepsy was successfully treated with European mistletoe (added to other AEDs) (von Schoen-Angerer *et al.*, 2015). The mechanism of action is suspected to be due to blocking of sodium channels, opening of chloride channels, or enhancing of the GABAergic system. The extract may also have antidopaminergic effects. Side effects of the plant in humans may be quite severe and include coma, sedation, and *seizures*. There are a few studies of its use in dogs in the treatment of cancer but no evidence supporting its therapeutic use in this manner, let alone for the treatment of seizures (Biegel *et al.*, 2022). Best to only bring it out once a year and tack it to the ceiling until we have more information on its medicinal use.

Mugwort (Ragweed) One of the most versatile herbs used since the time of Dioscorides, *mugwort* (*Artemisia vulgaris*), or ragweed as it is often referred to, has been traditionally used as an anticonvulsant, analgesic, anti-inflammatory, abortifacient, anthelminthic, antibacterial, antiflatulent, antifungal, antirheumatic, antiseptic, aphrodisiac, appetite stimulant, bile stimulant, CNS depressant, . . . and so on, basically covering just about any possible ailment one might have. Additionally, it was used to flavor beer, before the introduction of hops, as a repellant to moths, and to keep one safe on a long journey from evil spirits. Experimentally, this "jack-of-all-trades" herb has been shown to inhibit seizures induced by pentylenetetrazole, picrotoxin, INH, and penicillin but not MES-induced seizures. The difference in effect is hypothesized to be due to the extracts' ability to enhance GABAergic neurotransmission (Buznego and Pérez-Saad, 2004; Kediso *et al*., 2021). This data has been further supported by the demonstration of affinity for the $GABA_A$ benzodiazepine receptor site by extracts of *Artemisia herba-alba* (Salah and Katharina Jäger, 2005; Khan *et al*., 2016). Artemisia species contain various bioactive compounds such as flavonoids, isoprenoids, phenolic acids, coumarins, sterols, glycosides, polyacetylenes, and caffeoylquinic acids. These compounds result in the anti-inflammatory and neuroprotective qualities of the plant with a common theory of reducing mitochondrial oxidative stress, which is postulated to contribute to neural excitability, status epilepticus, and cognitive decline, through various mechanisms including (Sailike *et al*., 2022):

- Oxidative stress-associated neural apoptosis
- Mitochondrial DNA damage (via oxidative stress)
- Mitochondrial fission
- Mitochondrial Ca^{++} accumulation
- Neuroinflammation
- Excitotoxicity

The demonstrated antioxidant and anti-inflammatory activities of the plant are suspected to mitigate much of the above cellular damage secondary to oxidative stress (Abad *et al*., 2012). Artemisinin, derived from sweet mugwort and used to treat malaria has been linked to brainstem neurotoxicity (Genovese and Newman, 2008).

Pipsissewa Similar to mugwort, *pipsissewa* (*Chimaphila umbellata*), a traditional indigenous American herbal remedy, has been used as a flavoring agent and to treat a variety of medical conditions. It grows in the northern portions of North America, Europe, and Asia. No safe doses or therapeutic preparations have been documented. It is marketed as an anticonvulsant, a diuretic, a therapeutic agent for benign prostatic hypertrophy, and an antispasmodic (Oka *et al*., 2007). It has antifungal and antioxidant capabilities (Galván *et al*., 2008). It may be used in combination preparations as a sedative for pets and an anticonvulsant. Pipsissewa has been shown to have hypoglycemic action in animals (Pearl *et al*., 2011). It has primarily gastrointestinal side effects in humans (nausea, vomiting, diarrhea, and malabsorption syndrome). Because little research is available on the active constituents and possible side effects, it should be used cautiously in pets and only under the guidance of a trained and experienced veterinarian familiar with its use.

Skullcap Traditionally used to treat rabies, *skullcap* (*Scutellaria lateriflora* and *Scutellaria baicalensis*) is marketed as a sedative and anticonvulsant for pets. It is a common ingredient in many over-the-counter preparations used to "calm pets" often combined with other ingredients such as valerian and passionflower. There are no reported studies on the possible interactions of these various herbs and their use is primarily based on testimonial evidence and experience. Skullcap is also

referred to as having anticancer properties, being an antiviral, and having immunological and hematopoietic benefits (Kim *et al*., 2013b). The anticonvulsant and anxiolytic effects of skullcap come from a flavonoid known as *wogonin*, which has been shown to be a $GABA_A$ receptor agonist with activity similar to diazepam but without sedation or myorelaxant effects (Hui *et al*., 2002). When given experimentally to animals, in extracted and pure form, wogonin did not show any measurable side effects (Peng *et al*., 2009). Other potent-active constituents of skullcap include *baicalin*, *baicalein*, and *oroxylin*. Pharmacokinetic studies, based on the concern for the application of multiple components of the herb, have shown extensive interaction between the main constituents of the plant. This raises general questions as to how the plant is prepared and which components are having the desired clinical effect (i.e., anticonvulsant vs. anticancer vs. antiimmune, etc.) (Li *et al*., 2012). Additionally, because the major metabolism of these components involves glucuronidation and sulfonation and we know there are significant species differences in the ability to metabolize via these pathways, caution should be exercised when using these plants for medicinal purposes in pets. Extreme caution should be taken if used in conjunction with any other botanical or traditional drugs, which undergoes any hepatic metabolism. The major side effects reported in humans who take skullcap are hepatotoxicity, confusion, stupor, and *seizures*, among others (Pearl *et al*., 2011).

There are certainly hundreds of other compounds that are currently being investigated for the treatment of epileptic seizures and other disorders of the nervous system. To review them all would be beyond the scope of this book. Experts in the field should be consulted if there is an interest. Many undiscovered plant-based medications likely exist. When we consider a large number of currently used, purified, and scientifically proven drugs are derived from plants, the prospect for many others is quite plausible. We should not dismiss the potential of herbal medications to treat disease. After all, we are familiar with the effects of digitalis derived from the common foxglove plant (*Digitalis purpurea*), aspirin from the bark of the willow tree, vincristine from the periwinkle, taxol from the bark of the Pacific yew tree, and so on. No one should dismiss the potential for new and efficacious drugs to be developed from yet-undiscovered sources. However, for every successful development, there are tens of thousands of failures. As we all also know, some of the most potent poisons and neurotoxins are also derived from common, easily accessible plants, not to mention the possibility of interactions with other drugs, species-specific metabolism, and pharmacodynamics. The American Veterinary Medical Association states, "All aspects of veterinary medicine should be held to the same standards including complementary, alternative and integrative veterinary medicine, nontraditional or other novel approaches." Essentially, we need to critically evaluate the use of any proposed remedy equally against those that have "passed" the scientific method.

AROMATHERAPY

Valerian is known for having an unpleasant taste and odor, similar to "sweaty socks." This brings us to a potential segment that might be initially thought of as borderline ridiculous but perhaps also grounded in mainstream science. *Aromatherapy* has been used for centuries particularly by East Asian cultures to treat a variety of ailments. Essential oils are still used "medically" in the form of perfumes, compresses, massage oils, and inhalation and diffusion. It is well recognized, as previously mentioned, some essential oils can potentiate epileptic seizures, while others could be used to prevent the attacks (Jaseja, 2008). Aromatherapy has been shown to prevent epileptic seizures if applied prior to the attack (i.e., when an aura is first identified). Although not a controlled trial and admitted by the author to be taken at face value, the "study" may support ancient thoughts regarding aromatherapy and the treatment of epileptic seizures (Betts, 2003). The practice of "shoe smelling" is still performed today in rural parts of India. While the thought of seeing someone

whip off a stinky shoe and shove it in the face of a person having a seizure in a town square or along the side of the road seems outrageous, this ancient form of "first aid" may have some merit, especially considering it has survived for centuries. I'll attempt an explanation.

We are all likely familiar with the effect catnip (*Nepeta cataria*) has on certain felines. Catnip is a member of the mint family. A native European perennial, catnip was introduced to North America about the same time as the European settlers. Historically, the plant and its extracts were used to treat a variety of human ailments in the form of teas, juices, tinctures, infusions, and poultices and were sometimes smoked and chewed for its reported hallucinatory effects on humans (Grognet, 1990). It became less frequently used as modern pharmacology developed at the beginning of the 20th century. It is now more commonly associated with the effects it has on some cats. The primary chemical constituent of catnip responsible for creating the common behavior of sniffing, rubbing, chewing, biting, pawing, and grasping by cats is an unsaturated lactone, known as *nepetalactone* (McElvain *et al*., 1941). Nepetalactone binds to olfactory receptors within a few minutes and produces the noted effects in some but not all cats (Todd, 1962; Hart and Leedy, 1985). After approximately 5–15 min, the *euphoria* wears off, presumably from receptor fatigue. Within a few hours, the cat may seek out the plant again for another go. This behavior is presumed to be a *pleasurable response*. The effect shows the significance of the ability of volatile aromatic components to affect the olfactory lobe of higher mammals to generate an extremely consistent and reproducible behavioral response. The rhinencephalon is comprised of an olfactory portion (the paleopallium) and the limbic system (archipallium) comprising connections to both the telencephalon and the brainstem nuclei. The telencephalic connections are the only afferent sensory connections that do not pass through the thalamus to the cerebral cortex (de Lahunta and Glass, 2009). The special visceral afferent connections to the limbic system are responsible for the emotional response a mammal has to certain stimuli. A behavioral response to olfactory stimuli is a highly ancient and preserved function. We can all imagine the different responses we might have to a pleasurable scent such as baking bread and the behavioral response to the smell (e.g., salivation), as opposed to a malodorous smell such as rotting garbage and associated behavior response (e.g., nausea). The medial olfactory stria sends projections to the septal area and subcallosal area of the limbic system, while the lateral olfactory stria sends afferent projections to the amygdala and hippocampus (Figure 9.3).

As previously discussed, temporal lobe epilepsy is one of the most common epileptic syndromes in humans, and structures making up the mesial temporal lobe (the amygdala and hippocampus) are highly susceptible to injury (i.e., hypoxia, ischemia). These areas are also implicated in mesial temporal lobe epilepsy (MTLE) and removed surgically for the treatment of medically intractable epileptic seizures (see section *Surgery*, Chapter 10). The theoretical basis for excision of the epileptogenic site is based on the notion the *pacemaker cells* (i.e., damaged neurons) responsible for the tonic sub-seizure activity are located in these areas. A focal seizure may occur when neurons surrounding the pacemaker cells are sufficiently recruited to instigate a domino effect of spreading neuronal discharge. If the neuronal activity makes its way through thalamic relay nuclei, the cerebral cortex may become involved resulting in a generalized seizure. Since epileptic seizures often involve significant neural synchronization, commonly mediated through subcortical structures (e.g., brainstem, hippocampus, etc.), it is hypothesized disruption of synchronous discharges through strong olfactory stimulation may have effects similar to vagal nerve stimulation and conventional pharmacology to prevent or halt epileptogenic discharges which originate in these areas of the brain. It is well-documented that external stimuli (i.e., loud noises, noxious stimuli, etc.) can halt the progression of epileptic seizures (Rajna and Lona, 1989; Janszky *et al*., 2004). Rajna and Lona identified a significant inhibitory effect demonstrated through EEG recording associated with absence seizures in 16 of 19 people subjected to acoustic stimuli (Rajna and Lona, 1989). In humans, *olfactory hallucinations* combined with powerful emotional responses are reported as part of the aura that accompanies temporal lobe epilepsy (Chen *et al*., 2003). Testimonial evidence

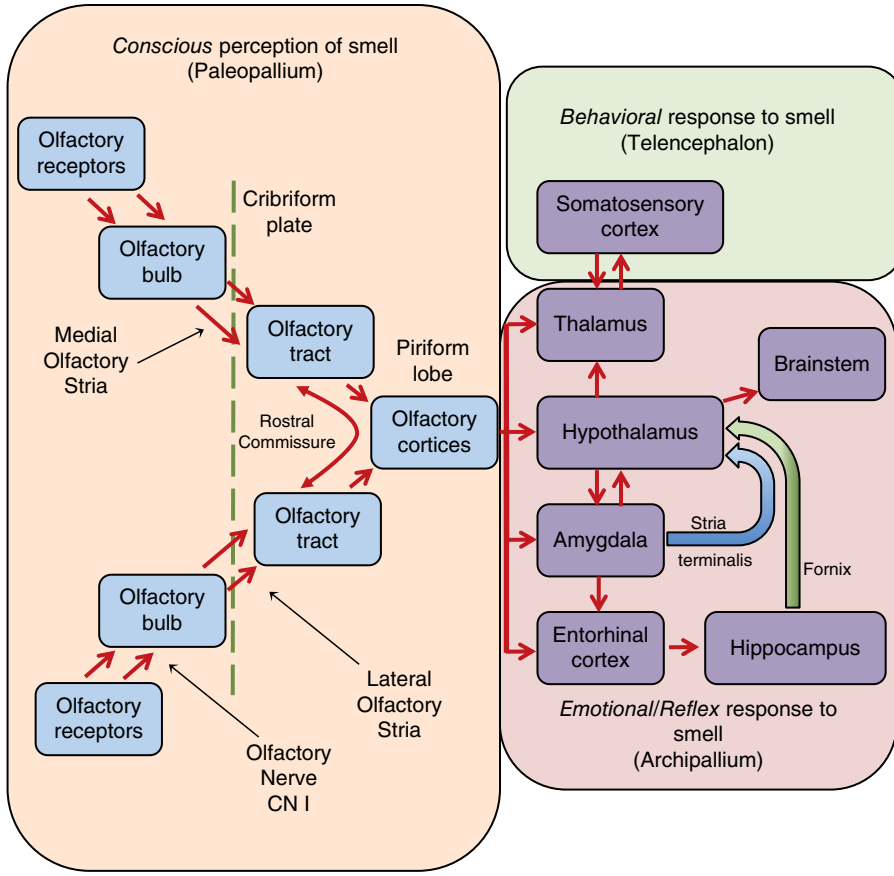


FIGURE 9.3 Olfactory system anatomic special visceral afferent connections. Axons of brush and mitral cells (olfactory receptors) project through the olfactory bulb, primarily ipsilateral directly to the piriform lobe and the olfactory cortex via the lateral olfactory stria (LOS) (bypassing the thalamus). Axons of the medial olfactory stria (MOS) project to the contralateral olfactory bulb. Commissural fibers also project between the two piriform lobes (paleopallium). This forms the *conscious* perception of smell. Axons from the MOS enter the septal area and axons of the LOS enter the amygdala and hippocampus to form the reflex and *behavioral-emotional* connections of the limbic system (archipallium). Reflex responses from the limbic system are associated with behavioral responses to smell.

of self-control using stimulatory countermeasures to stop a seizure in humans and *loose science* also supports the hard facts (Betts, 2003; Betts *et al*., 1995). So could the shoe-smell application be similar to a slap on the face, screaming in the ear, or compression of the eyeballs (i.e., vagal nerve stimulation)? Can olfactory stimuli have a similar result in the desynchronization of neuronal activity as auditory, visual, or proprioceptive stimuli? We can only imagine some empirical effect has been observed since antiquity to promote the application of this technique to present day. Mainstream scientific observations would support this methodology as potentially being effective, especially when considering the scientific body of evidence which has shown olfactory stimuli to have an inhibitory effect on the propagation of certain forms of epileptic seizures (Efron, 1956; Ebert and Löscher, 2000; Valentine *et al*., 2005). Desynchronization of neuronal firing can stop an epileptic attack. Widespread desynchronization and increased activity of the brainstem reticular activating system have been demonstrated in EEG recordings during the presentation of

olfactory-stimulating odors (Jaseja, 2008). Certainly, our scientific minds would much rather accept a directly measurable effect such as that generated from modern pharmacology rather than the methods surrounded by mystery and conjecture. Does it matter how it works, as long as it works and does not result in harm? If we occasionally think outside the box, we find bits of information and evidence that put the puzzle pieces together. Bottom line if a dog or cat is about to have a seizure or is observed having a seizure, first, give immediate therapy (e.g., rectal diazepam, intranasal lorazepam, or midazolam) and then shove your shoe in their face; it certainly can't hurt (as long as you don't get bit).

AYURVEDA

Ayurvedic medicine originated in the ancient Indian subcontinent around 6000 BCE. Literally translated from Sanskrit, Ayurveda means "science" (*veda)* of "life" (*ayur*). The first descriptions of human disease and its treatment date back to 2000–1000 BCE in the *Atharvaveda*, one of the original *Vedas* (sacred texts) of ancient India. As with many traditional or folk-based forms of medicine, disease was initially interpreted from a *magicoreligious* realm whereby demons were exorcised by magical spells and prayer. Around the 6th century BCE, Ayurveda became more associated with science than magic, with its description and definition in the popular Ayurvedic texts *Charaka Samhita* and *Sushruta Samhita* (Mishra *et al*., 2013). This deviation to a more "modern" scientific form of thinking was one of, if not, the first documented "*scientific*-esc" approaches to disease and medicine. It created a division between the former magicoreligious way of thinking and a new paradigm based on observation and ultimately the scientific method. While Ayurveda is a form of traditional medicine and considered alternative medicine, approximately 32% of human epileptic patients in India use it regularly, and 43% of the population uses it as monotherapy (Tandon *et al*., 2002). The principles of Ayurvedic medicine were equally applied to animals and humans. Ayurvedic practitioners treated both humans and their animals, as animals were considered valuable to the health and well-being of the humans who cared for them. Perhaps one of the earliest Ayurvedic practitioners to write about "veterinary medicine" was *Shalihotra* (ca. 350 BCE). His principal work, the *Shalihotra Samhita*, mainly focused on the anatomy, physiology, surgery, and diseases of horses and elephants (Singh and Chauhan, 2001). Ayurvedic medicine focuses on three fundamental systems of the body known as the *vāyu vāta* (air and space or "wind," responsible for motor and sensation), the *pitta* (fire and water or "bile," responsible for metabolism), and the *kapha* (water and earth or "phlegm," responsible for coordination and compactness of the body). Collectively, they make up the *doshas* (humors). The doshas regulate the physiologic and biochemical properties of the body. Any disturbance in the balance of the doshas results in disease with associated symptomology. Charaka first described epilepsy around 600 BCE in *Charaka Samhita* (Mishra *et al*., 2013). There are numerous causes described such as dietary transgression, poor hygiene, extreme mental weakness, fear, anxiety, and agitation (Ricotti and Delanty, 2006). The basis of treatment focused on diet and hygiene, as well as concocted remedies. If a diagnosis of epilepsy was made, remedies were prepared from mixtures of plants, minerals (e.g., sulfur), and animal products (e.g., milk, butter). The mixtures are often fermented, extracted, filtered, purified, and then heated. The most commonly used Ayurvedic remedy to treat epilepsy is *Mentat*, a polyherbal mixture of about 30 elements including pearl powder, which is thought to affect GABAergic neurotransmission (Kumar and Kulkarni, 2006). Other common remedies include herbs such as *Achyranthes aspera*, *Holarrhena antidysenterica*, and *Acorus calamus*. The roots of vacha (*Acorus calamus*) have been shown to suppress seizures in a MES model of epilepsy in rats (Bhat *et al*., 2012). *Ashwagandharishta* and *Atasi taila* (flaxseed oil) are also common, traditional Ayurvedic treatments for epilepsy, which have been shown to have protective effects against experimentally induced (MES) seizures in rats (Tanna *et al*., 2012). The effects of flaxseed oil are thought to be due to its high concentration of omega-3 fatty acids, which have been shown in small clinical studies

to alleviate epileptic seizures in humans (Schlanger *et al.*, 2002). Ashwagandha is reported to have a "calming" effect on hyperactive dogs and is considered safe to use in pets (Sodhi, 2012).

Although many of the preparations are considered to be very safe, possible contamination with heavy metals may lead to adverse side effects (Khandpur *et al.*, 2008). Arsenic is a common ingredient in Ayurvedic remedies and has been used for centuries for medicinal purposes. Toxic levels of arsenic were found in 42.8% of sampled over-the-counter Ayurvedic remedies in the USA. Additionally, toxic amounts of mercury and lead were also discovered (Saper *et al.*, 2004). In another investigation, lead was found in 65%, mercury in 38%, and arsenic in 32% of the 252 samples tested (Mikulski *et al.*, 2017). Of those samples that were contaminated, nearly 50% of the mercury samples, 36% of the lead samples, and 39% of the arsenic samples had concentrations in the pills up to several thousand times the recommended daily allowance for impurities. From 2000 to 2003, 12 cases of lead poisoning were reported in the USA associated with Ayurvedic medications (Araujo *et al.*, 2004). A study looking at Ayurveda practitioners from a small town in India found 40% of the participants had elevated blood lead levels ≥10 μg/dl and 9.6% had levels ≥50 μg/dl (Breeher *et al.*, 2015). A blood lead level ≥5 μg/dl is considered elevated.

Ultimate pro tip—if you are considering using any supplement, make sure it comes from a reputable source and seek out an expert in its use, preferably a veterinarian.

HOMEOPATHY

Samuel Hahnemann first documented the practice of homeopathy in 1807. To some degree, the essence of the practice may go as far back as Hippocrates (400 BCE). It is a form of alternative medicine, which is rooted in esotericism. Homeopathy does not claim to cure the disease itself but rather to stimulate the patient's body to fight the disease. Other forms of alternative medicine, such as transcendental meditation, color therapy, Bach flower therapy, or spiritual communication, also lack tangible or measurable mechanisms of action. Any misunderstanding or confusion comes from the key concept the proposed effect cannot be measured or proven by acceptable, current scientific (*physical*) methods. Hahnemann advocated and used homeopathic medicine for the treatment of disease in animals as well. The use of homeopathy in veterinary medicine is mistakenly thought to pose little or no risk to the patient from the direct application of the proposed remedy. However, like any (even conventional) treatments, risk is present. Homeopathic remedies, similar to any conventional drug, have the potential to be prepared or applied in a deleterious manner or contain potentially harmful ingredients. Reports of humans suffering from acute pancreatic necrosis, thrombocytopenia, anaphylaxis, coma, paralysis, and death suspected to be due to toxicities from arsenic, bromates, chromium, thallium, and kerosene, to name a few, are in the literature (Chakraborti *et al.*, 2003; Posadzki *et al.*, 2012). Numerous adverse reactions (including death) stem from substitution or delay of conventional therapy for homeopathy (Chakraborti *et al.*, 2003). By all standards of scientific measurement and understanding of stoichiometric principles of chemistry and the laws of physics, homeopathic remedies do not contain any purposeful disease-altering substance. The risk lies in the arena of *not* using or *delaying* the use of traditionally accepted and scientifically proven modes of preventing or treating disease. The basis of the homeopathic methodology is the notion "like cures like" and that a substance that would cause symptoms of disease in healthy people would also cure the disease in sick people. For example, to treat the symptoms of a poison, one would take a minuscule dilution of the poison as therapy. The "law of minimum dose" advocated by many (i.e., not all) homeopathic practitioners states the more dilute the medication, the more potent it is. The remedies used are dilutions of the mother tincture (known as "dynamization" or "potentization"). Dilutions are typically made as factors of 100. In this case, a drop of mother tincture diluted with 99 drops of vehicle (i.e., distilled water, ethanol, etc.) would equal a 1C dilution (in the traditional "centesimal" or "C scale" used by Hahnemann). Take a drop of the 1C dilution and add that to 99 drops of vehicle would give you a 2C dilution. The dilutions are repeated until the desired concentration is achieved. Common dilutions would be

12–30C. A common analogy used to grasp the degree of dilution would be to take 1/3 of a drop of the original substance and mix it with all of the water on the planet Earth. This would equal a 13C dilution. Between the dilutions, the substance is shaken vigorously by striking it against a solid but elastic object in a process called "succession." Not all dilutions are as extreme and they vary depending on the disease, patient, and clinical signs.

The preparation of the medication may also vary between ointment, tincture, or sugar pill. Remedies are created from natural substances such as minerals (i.e., arsenic or sodium chloride), animal, plant, and synthetic substances. *Nosodes* are produced from diseased (i.e., pathological) biological products such as tissue, blood, secretions, urine, or feces. *Sarcodes* are produced from healthy substances. *Imponderables* are created from electromagnetic energy, which has been trapped by a substance such as ethanol (e.g., certain forms of radiation such as sunlight or X-rays). Certainly, we cannot list all of the intricacies associated with the practice of homeopathic medicine, and this small section alone will likely conjure significant debate from those who advocate its use and those who discourage its practice. Mainstream medicine and homeopathic practitioners have hotly debated their differences since its formal inception at the turn of the 19th century (yes, that is over 200 years). Any experiment that has low plausibility, such as the notion of high dilutions resulting in basically water or ethanol to cure disease, must be subjected to critical thinking. The same rule applies to any new "miracle drug." If these standards are not applied to all treatment modalities, any current, prevailing medical paradigm, whether it be drilling holes in the skull to let the evil spirits out or frontal lobotomy to "treat" schizophrenia, would likely continue to be practiced without critical control and oversight. When the topic of critical thinking and the application of accepted measurements based on scientific method are discussed, the lack of scientific evidence is often replaced by reports of millions of satisfied human patients treated successfully for conventional disease with homeopathic remedies, resulting in "astonishing recoveries," over the *measured* course of two centuries (Chirumbolo, 2013).

In the last 20 years, more conventional methods of measuring outcome and means of demonstrating efficacy have begun to utilize mainstream scientific research regarding veterinary homeopathy (Clausen *et al*., 2013). Peer-reviewed, randomized, placebo-controlled clinical trials involving homeopathic treatments are becoming more common. However, while a veterinary *materia medica* may contain hundreds of remedies, only a few drug "provings" (i.e., the process by which the profile of the homeopathic therapy is determined) exist for animals (Clausen *et al*., 2013). Human homeopathic products are regulated by the Food and Drug Administration. No such oversight exists with veterinary homeopathic remedies. The scientific explanations which may account for how homeopathy may cure disease include:

- The placebo effect: Expectations may alter disease, and despite the notion animals cannot discriminate between a drug and placebo (the classical concept of placebo), significant evidence exists showing animals can be very biased toward a placebo, including conditioned responses (i.e., Pavlovian response), recognition of people, and recall of learned cycles (Wirth *et al*., 2011).
- The therapeutic effect of the intensive consultation creating a positive effect on the patient's well-being: This has been demonstrated in animals. The blood pressure and heart rate of many animal species, including dogs and horses, can be influenced by who is present when the measurements are taken (Lynch and McCarthy, 1969; Lynch *et al*., 1974). Dogs can respond differently to the emotional states of people (Feddersen-Petersen, 1994, *Abstract*).
- Unassisted natural healing.
- The effects of cotreatment modalities: Homeopathic treatments are often combined with other forms of therapy, which may create the beneficial effect. Homeopaths often recommend discontinuing other potentially unpleasant medications (e.g., drugs with negative side effects, alcohol, tobacco, etc.).

- Volume averaging or regression toward the mean: Many disease processes are cyclical, and any improvement in symptomology may be coincidental with the application of any remedy and enough time.

There is one case series published utilizing homeopathic treatment for epileptic seizures in dogs (Varshney, 2007). Dogs who were presumptively diagnosed with genetic (i.e., idiopathic) epilepsy were treated with *belladonna* at a 200C dilution. For some perspective of what a 200C dilution would be equivalent to, let's look at known physics. A similar example has been calculated related to a popular homeopathic treatment for the flu (*oscillococcinum*). There are approximately 10^{80} atoms in the observable universe. If you were to dilute 1 molecule of belladonna in the *observable universe*, it would equal a 40C dilution. To make a 200C dilution, it would take 10^{320} more observable *universes* to have a solution with one molecule in it. With dilutions up to 12C and above, the initial substance has been diluted beyond Avogadro's number (recall $\sim 6.022 \times 10^{23}$) to the point where the dilution should not contain a single molecule of the substance. The underlying basis of why the dilutions would work is explained as follows: during the process of dilution and succussion, bioenergy is transferred from the parent substance to the solvent (Ricotti and Delanty, 2006). In this study, owners of pets having seizures chose to treat with homeopathy over conventional drug therapy. Dogs were treated with 3–4 drops of *belladonna* 200C every 8 h for up to 8 months and every 15 min during a seizure until the seizure stopped. Prior to treatment, all dogs experienced between 1 and 5 generalized tonic–clonic seizures a week. From 2 months after the initiation of therapy to the end of the study (8 months), none of the dogs being treated with the remedy had any seizures. When the therapy was discontinued by two of the owners, on their own volition, the seizures returned but were again halted once therapy was again instituted. The plausibility of the carrier vehicle containing the "memory" of *belladonna*, resulting in a 100% treatment success of all patients given the therapy, is difficult to imagine when thought of critically. At the very least, the treatment (basically water or alcohol) lacks any mechanism, that can be defined by known and recognized natural science, and there is no way to verify the published results.

A large number of chronic diseases such as epilepsy, skin disease, or degenerative joint disease, to name a few, are more *managed* rather than cured. When allopathic means fail to treat or manage the condition, pet owners are likely to turn to unconventional means to help their animals. Pet owners who choose homeopathic medicine over traditional *evidence-based medicine* take the risk of delaying the treatment of potentially serious disease. Epileptic seizures are no different in that delay of treatment often leads to medically intractable seizures, euthanasia, or natural death. Homeopathy is not based on current scientific principles, as we understand them today. Veterinarians have a narrow line to walk when it comes to the recognition of homeopathy. We can passively ignore it. We can actively reject it. Or, we can take an active role in participation and dialogue, if not only to help our clients understand it. This would allow a group of medically trained individuals with an understanding of anatomy, pharmacology, disease, diagnosis, and treatment to supervise our patients. If we ignore or reject it, we potentially leave a vacuum that will be filled by the demands of the untrained public, seeking only to help their pets as best as they can with the limited understanding they have of medicine. This would likely result in the alienation of our clients and provide a platform for untrained therapists with no medical background to fill the void. The practice of veterinary medicine should not be guided by market demands and public interest of what is "in vogue" at any one time. It should be grounded on basic fundamental science and critical review. We may reject the notion water can retain the memory of a substance and that principle can help the patient cure their disease, but other less tangible aspects of homeopathic medicine warrants investigation. As mentioned previously, the placebo effect, an understanding of the natural progression of disease, attention to the patient (and client), and an increased *awareness* of aspects surrounding disease, such as lifestyle, diet, and stress, may contribute to the success of a homeopathic treatment. It is difficult to compare homeopathic to allopathic medicine. Allopathic

medicine treats the symptoms of the disease. Homeopathic medicine is based on the principle of treating the individual leading to various different treatments for two individuals with the same disease. The most common homeopathic remedies used to treat epilepsy are silicea, cuprum, causticum, hyoscyamus, *Aethusa cynapium*, *Agaricus muscarius*, *Artemisia absinthium*, *Cicuta virosa*, and stramonium (Ricotti and Delanty, 2006). The main purpose of this description of homeopathy (albeit *very* limited) is not to wholeheartedly dismiss it but to provide a general overview from which interest might be generated to motivate one's own research ("paging Dr. Google").

OTHER MODALITIES

There are certain complementary and alternative medicine modalities that despite any professed or demonstrated effect in humans simply cannot work on animals. These modalities require purposeful manipulation of thoughts and physical form. There is little in the scientific literature other than case reports or case series, without randomized or placebo-controlled trials to support their use in treating human epilepsy. Examples include *transcendental meditation*, *yoga*, and *biofeedback*.

Chiropractic treatment of humans is reported to be successful when treating epileptic seizures that may be due to upper cervical disease such as atlantoaxial subluxation and spinal segmental dysfunction (Hubbard *et al*., 2010). There are no reports in the literature of its use in companion animals for this purpose even though it is frequently used to treat spine disorders, particularly intervertebral disk disease in dogs.

Reiki is a form of energy healing developed by Dr. Mikao Usui, a Japanese physician in the early 20th century. The basic principles of Reiki is the transfer of "spiritually guided life force energy" from the practitioner to the patient through laying of the therapist's hands either gently on the patient or elevated slightly above the patient. Various hand positions are used to treat different ailments. The life force energy will seek out the problem and heal the patient (Kumar and Kurup, 2003). The treatments are thought to act through quantal perceptive mechanisms (i.e., the subatomic relationship between energy and matter). In the study published by Kumar and Kurup, 15 patients were evaluated for epileptic seizure control using transcendental meditation and Reiki healing techniques. Although criticized for poor study design (i.e., single arm, no randomization, and no control), the authors reported improved seizure control. In a study looking at the ability of Reiki in improving sleep quality and overall quality of life in humans with epilepsy, those in the treatment arm scored better in the sleep assessment and quality of life self-assessments (Arıkan and Turan, 2024). The first treatment was performed in person and all subsequent treatments (total of 10 sessions over 4 weeks), were performed remotely. While the study did contain a control arm, the controls were not "shammed" into thinking they were also receiving Reiki treatment.

A NOTE ON SAFETY

Herbal remedies, botanical extracts, and mixtures of substances are readily available at health food stores and pet stores, claiming to be beneficial. Chances are there are benefits to these medications; however, nothing should be given to a pet, no matter how seemingly safe or innocuous it might be without seeking the advice of a veterinarian and especially a veterinarian trained and experienced in the area of interest. Just because it is on the shelf does not mean it is safe. Side effects and toxicities from herbal remedies and folk medicine preparations may be due to several factors including:

- Misidentification of the plant species
- Unknown toxicity
- Known but ignored toxicity
- Species-specific differences in metabolism

- Variability of chemical constituents of the plant
- Confusion with nomenclature
- Addition of dangerous ingredients (i.e., heavy metals)
- Presence of unknown contaminants
- Lack of disposition studies
- Variability of potency depending on harvest, growth conditions, preparation, purification, and storage of the product
- Mislabeling
- Errors in the manufacturing process

Some of the products contain known poisons such as water hemlock (*Cicuta douglasii*), arsenic, lead, and mercury, to name a few. Any remedy should be obtained from a reputable source under the guidance of a veterinarian who has familiarity with the product and its manufacturer. There is no government oversight of herbal medications evaluating them for safety and/or efficacy. A lack of label restrictions or safety warnings (which if present may be vague) may be perceived as "safe." "Natural" remedies also carry a general perception of being "safe." The public perception that to be dangerous it needs to be synthesized in a chemical plant is naïve and misguided. The literature contains thousands of examples of humans who have been inadvertently poisoned by natural remedies. Companion animals are no different with the exception that they are involuntarily dosed with the remedies. Adding to the complexity of the problem, pets cannot tell us when they feel sick or are experiencing a negative side effect; they have to *show* us. Even when they do show us, we often just give more of the medications mistaking the side effects of the medication for clinical signs of disease. Often, it is too late, as in the case of fulminant liver failure, hemorrhagic gastroenteritis, acute renal failure, or status epilepticus. From 1997 to 1999, the National Animal Poison Control Center received 47 complaints of accidental ingestion and subsequent toxicity associated with human herbal supplements containing guarana (natural source of caffeine) and ma huang (natural source of ephedrine) (Ooms *et al*., 2001). Eight dogs either died or were euthanized as a direct result of the toxicity. "Natural" does not equal "safe."

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Advanced Invasive Therapy for Seizures

CHAPTER 10

KEY TAKEAWAYS

Advanced therapies for epilepsy parallel those used for human medicine.

Surgical treatment of epilepsy in veterinary patients, while in its early stages, promises to be as effective as it is for humans.

Pre-surgical identification of the epileptogenic zone is necessary for the ideal postsurgical outcome.

QUICK JUMP

Technique for Ocular Compression Figure 10.1

Types of Surgery for Epilepsy Figure 10.9

Definition of the Epileptogenic zone page 451

Pre-Surgical Diagnostics for Epilepsy Surgery page 441, 452

Epilepsy Surgery Protocols page 452

Introduction 432
Hypothermia 432
Deep Brain Stimulation 433
Vagal Nerve Stimulation 434
Implanted Device 435
Cutaneous Stimulation 437
Ocular Compression 437
Transcranial Magnetic Stimulation 438
Surgery 438
Similarities Between Species 438
Justification for Surgery 440
Presurgical Evaluation 441
Surgery in Dogs and Cats 443
Diagnostics 447
Surgical Protocols 452
Resection Surgery 455
Disconnection Surgery 456

Myelominutia: Shapiro Syndrome is a condition of paroxysmal, spontaneous, transient hypothermia and hyperhidrosis in humans.

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INTRODUCTION

Because epilepsy is one of the most common neurological conditions affecting humans, research regarding treatment both from conventional means and unconventional means will continue to be at the forefront of the medical community. Like humans, approximately 30% of veterinary patients with epilepsy are pharmacoresistant. Likely new discoveries will lead to less reliance on pharmacology, drugs with fewer side effects, and eventually "cures" for epilepsy rather than treatment alone. We may pass judgment on some of the following examples as impractical or implausible for veterinary patients; however, we must also remember all *conventional* therapies were at one time *unconventional*. Animal models have been used for centuries in the development of new therapeutic modalities for humans. The successes demonstrated through decades of effective human application may warrant investigation into the use of these same therapeutic modalities for the practical treatment of companion animal seizures.

HYPOTHERMIA

Hypothermia is considered a conventional treatment for conditions such as cardiac arrest and is often used as an adjunctive therapy to treat increased intracranial pressure (Motamedi *et al*., 2013). Cooling of core temperature and more direct cerebral cooling have been shown in animal models (*in vivo* and *in vitro*) of epilepsy to have neuroprotective effects, reduce or abolish epileptiform discharges, and reduce seizure activity (Liu *et al*., 1993; Maeda *et al*., 1999; Badawy *et al*., 2012). The International League Against Epilepsy (ILAE) recommends hypothermia when treating human neonates with hypoxic-ischemic encephalopathy (Pressler *et al*., 2023). Multiple mechanisms of action are thought to contribute to the positive effects of reduced epileptic seizure activity induced by hypothermia. These include (but likely there are many more):

- Alterations in the sodium/potassium ATPase pump (increased resistance with decreased ion conductance)
- Temperature dependence of adenosine regulation of glutaminergic synaptic transmission
- Temperature dependency of glutamate and glutamate receptor kinetics (glutamate binding affinity and speed of diffusion)
- Effect on ion channel gating properties
- Interference of neuronal network synchrony

Hypothermia may gain more popularity in the treatment of status epilepticus and with pharmacoresistant forms of epilepsy. The latter would most likely involve the use of an implanted microcooling device. Research in this area is limited to animal experiments (Fujii *et al*., 2012; He *et al*., 2013). In a prototype study of an implanted cooling tip to the hippocampus (cooled to 21 °C/69.8 °F) of nonhuman primates, there was a reported 80% reduction in penicillin-induced seizures, compared to control (Torres *et al*., 2024). Of course, practical use of targeted cooling in the brain would rely on the identification of an epileptogenic focus, and potential adverse side effects such as hypotension, respiratory depression, reduced cardiac function, and local tissue damage are possible. It is also possible, once cooling is stopped, seizures return as the brain warms back up (Pavel *et al*., 2024).

Whole body cooling of dogs to a temperature of 36.7–37.7 °C (98–99.9 °F) in combination with a ketamine-dexmedetomidine CRI was successfully used to treat three dogs with superrefractory status epilepticus (Gioeni *et al*., 2020). In human children, the target range for cooling (measured by rectal thermometer) is 33–34 °C (91.4–93.2 °F) and if direct cooling of the skull is performed (via specialized skull cap), the target temperature is increased by 1 °C (Sakr *et al*., 2024). Possible complications include cardiovascular and respiratory complications, electrolyte imbalances, coagulopathies, increased incidence of sepsis, delayed gastric emptying, and altered pharmacokinetics of medications.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an exciting field, which has grown tremendously in the last 40 years. DBS is FDA approved for the treatment of drug-resistant epilepsy (focal) in humans, using the anterior thalamic nuclei (Fisher *et al*., 2010). Brain stimulation using electricity was first documented in 1870 when Fritsch and Hitzig used it to generate contralateral movements in the limb muscles of dogs (Chapter 1). Stimulation of the brain can be performed directly by using electricity with deep electrodes and surface electrodes. The stimulus may be persistent, intermittent, or responsive to detection (i.e., triggered by epileptiform activity). DBS may also be used to modulate the endogenous, rhythmic electrical activity of the brain, of which different disease pathologies (epilepsy, movement disorders, psychiatric disorders, etc.) may have their own *cyclic properties*. Adaptive algorithms may be utilized to stimulate the brain with feedforward input based on the nature of the detected rhythm prior to the beginning of an ictal event, status epilepticus, or cluster seizures, truly treating the seizure before it occurs on an *as needed* basis. DBS is used to treat numerous disorders ranging from Parkinson's disease, Huntington's disease, neuropsychiatric disorders, chronic migraine headaches, chronic pain, movement disorders (e.g., tremors), and epilepsy. Investigators have even proposed it may be used for improved cognition and physical performance enhancement, which admittedly may have potential for misuse or nefarious reasons. The suspected mechanisms of action for DBS are diverse but include (Nowakowska *et al*., 2022):

- Ability to modulate cellular firing characteristics, creating stability, making cells less likely to transition into an epileptic state
- Preferential recruitment of brain inhibitory cells
- Suppression (and promotion) of brain circuit synchronicity
- Alteration of the electrical and chemical cellular environment
- Modulation of production and release of neurotransmitters
- Activation of glial cells, proliferation of neuroprogenitor cells, and astrocyte signaling

Similar to humans, a distinct subpopulation of pharmacoresistant patients exists in the veterinary world (roughly 30%) (Volk *et al*., 2008; Thomas, 2010; Sultana *et al*., 2021). Human patients with refractory epilepsy are often considered candidates for resective surgery or electrical stimulation. Electrical stimulation may be performed either through the brain directly (thalamus, cerebellum, hippocampus) or through the vagus nerve (see section "Vagal Nerve Stimulation"). While brain surgery has numerous limitations for the treatment of epilepsy in animals, of primary importance is the ability to be able to identify and locate the epileptogenic focus using advanced electrodiagnostic techniques. As previously discussed, this requires the use of sophisticated functional imaging and EEG analysis of the brain, which is a major limiting factor in veterinary medicine (Chapter 5). Electrical stimulation of the brain may be a successful work around this difficult problem, as the technique may be applied to the brain *without* specific knowledge of the epileptogenic location. DBS can de-synchronize epileptic networks in the brain, as well as, reduce interictal epileptiform spikes (Yu *et al*., 2018). An excellent review summarizing clinical and experimental data via animal studies is available (Fisher, 2013). It is generally accepted DBS is efficacious in reducing the frequency of epileptic seizures in humans (Chambers and Bowen, 2013). Chronic EEG recording has shown the risk of seizures varies with circadian and multidien cycles and seizure phase locking corresponds to the interictal epileptiform spike cycles associated with circadian and multidien cycles (Gregg *et al*., 2020, 2021). By varying the frequency of DBS (low frequency vs. high frequency), researchers were able to modulate the circadian spike rate cycle amplitude. Chronic use of DBS has been shown to disrupt these risk cycles, reduce seizure burden, and modify seizure phase locking and cluster episodes. DBS has the theoretical possibility of not

only preventing or interrupting epileptic seizures but also of *curing* epilepsy through the prevention of epileptic seizures. Currently, surgery is the only other method that has a similar potential. DBS carries many advantages over surgery including being less invasive (no need to resect brain tissue), adjustable, reversible, and perhaps even most important to animal application in a clinical sense; knowing the precise epileptic focus is *not necessary*. Thousands of experiments on animals have shown the technique is relatively safe and effective. Target areas for stimulation primarily include the cerebellum, caudate, subthalamic nucleus, hippocampus, thalamus, and specifically identified epileptogenic foci. Other sites, less actively under investigation for stimulation, include the locus coeruleus, substantia nigra, mammillary body, amygdala, neocortex, and corpus callosum. While most animal studies show efficacy in seizure control, others have shown worsening of seizures (Lado, 2006). This reinforces the well-accepted notion that specific stimulation parameters (e.g., time, frequency, strength), sites of implant placement, and patient selection are all variables that may affect treatment efficacy. Electrical stimulation of neural tissue may create *hyperexcitable networks* which has been reported in rats (Brandt *et al*., 2003). However, long-term results in humans treated with DBS with refractory epilepsy do not show a kindling effect (Fisher *et al*., 2010).

A pilot feasibility study using a unique system whereby EEG information is recorded and stimulation is provided with the same electrodes has been performed in dogs (Long *et al*., 2014). Using a 3D computer-controlled, frameless stereotactic system improves electrode placement. Studies in both humans and animals show low morbidity associated with the placement of deep brain electrodes (Koblik *et al*., 1999; Woodworth *et al*., 2006; Long *et al*., 2014). Although, in another study, two of seven dogs died as a result of DBS implantation (one from infection and another from the procedure itself) (Gregg *et al*., 2021). When used to treat movement disorders (e.g., Parkinson tremor), beneficial results are often immediate. In contrast, epileptic seizure control using DBS is improved the longer the electrodes are in place (Fisher *et al*., 2010; Salanova *et al*., 2015). A similar result was found using electrical stimulation of the vagus nerve in dogs (Muñana *et al*., 2002). In a proof-of-concept case study, a drug-resistant, canine diagnosed with idiopathic epilepsy was implanted with a novel chronotherapy-enabled device (Picostim-DyNeuMo) (Zamora *et al*., 2021). Using an adaptive algorithm, and tuning the device to the patient (its way, way more technically complex . . .) seizure severity was reduced, as well as, coherent cluster seizures and episodes of status epilepticus. Furthermore, the owner of the dog reported less anxiety about seizures and improved personal quality-of-life. While still in its early stages, DBS has the potential to significantly improve seizure control in drug resistant patients.

VAGAL NERVE STIMULATION

The vagus nerve is the longest cranial nerve. It arises in the nucleus ambiguous (medulla) and exits the skull through the jugular foramen/tympano-occipital fissure with efferent projections to the neck, thorax, and abdomen. Approximately 80% of the projections to the brain are from the viscera with afferent projections terminating in the nucleus of the solitary tract. Neurons then project from the nucleus of the solitary tract to the locus coeruleus and the raphe nucleus. These nuclei are involved in the production of noradrenaline and serotonin, which then stimulate interneurons to release γ-aminobutyric acid which has the effect of increasing seizure threshold. Modulation of cerebral blood flow through vagal activation has functionally shown to reduce activation of the limbic structures (hippocampus) and increase activity in the locus coeruleus, septum, and thalamus. Cerebral and vagal activation patterns, whether through implanted or noninvasive vagal stimulation, resemble each other (Frangos *et al*., 2015). Vagal nerve stimulation (VNS) can be achieved through mechanical compression of the eyeball (Speciale and Stahlbrodt, 1999) and electrical stimulation using an implantable or cutaneous surface-applied device (Muñana *et al*., 2002; Robinson *et al*., 2020; Hirashima *et al*., 2021). Generally, the left vagus nerve is stimulated in the neck of dogs, although in humans, the auricular branch of the vagus nerve has also

been shown to create similar activation patterns in the brain (Frangos *et al*., 2015). Both the right and left vagus nerves may be stimulated, although the left is more commonly performed as this has fewer side effects on the heart. Efferent fibers of the *right* vagus nerve innervate the sinoatrial node of the heart and regulate *heart rate*, while efferent fibers of the left vagus nerve innervate the atrioventricular node of the heart and regulate *cardiac contractility* (Saper *et al*., 1990; Schachter and Saper, 1998).

Vagal nerve stimulation has been shown to be effective in humans with a variety of seizure types (Wheless *et al.* 2018).

IMPLANTED DEVICE

VNS through an electronic device is widely used in human medicine to treat intractable epilepsy. In general, a 50% reduction in seizure frequency (i.e., success) is achieved in approximately 25% of human patients who have a vagal nerve stimulator implanted, although higher levels of efficacy are reported (Chambers and Bowen, 2013; Engel, 2013). Very few people become seizure-free; however, it often allows a reduction in medication dose. Efficacy tends to improve the longer the implant is in place, and it is suggested at least 1 year should pass before evaluating its efficacy. Relative to a novel antiseizure drug trial, beneficial results are similar among human patients (Engel, 2013). The efficacy is also similar to those having DBS, without the invasiveness of a brain implant, depending on the published report (Chambers and Bowen, 2013). For some, all attempts to control epileptic seizures have failed, and they may not be surgical candidates. It is natural to assume a person with intractable seizures would turn to any means necessary to gain better control of their epilepsy. Experimental research on animals, especially dogs, led to the development of current human medical devices based on the success of those experiments (Zabara, 1992). The implanted device consists of a sealed pulse generator with an average battery life of 6–11 years depending on programmed parameters. The generator is implanted in a subcutaneous pocket with an electrode, which is tunneled into the neck. At the end of the electrode, coiled flexible leads are wrapped around the left vagus nerve. The left vagus is chosen because of *less* influence over cardiac function. The device is programmed through an external "wand," which allows variation in stimulation parameters. An external magnet can be used to directly turn on the device in the event the patient is experiencing a seizure, in order to provide a more direct and immediate stimulus (Morris, 2003). The device is currently FDA approved for the treatment of epilepsy in humans, although much of the underlying research showing success is based on experiments conducted on dogs (Zabara, 1992).

The neurophysiological rationale behind the use of VNS to reduce seizure frequency stems from normal vagal anatomy and innervation reported in the 1930s (Foley and DuBois, 1937; Rutecki, 1990). The vagus nerve (cranial nerve X) transmits afferent information from approximately 80–90% of the viscera. These afferents terminate in the brainstem (myelencephalon) at the nucleus of the solitary tract. From here, afferent projections ascend to innervate many cortical and subcortical areas of the brain, including the cerebellum, cerebral cortex, areas of the brainstem, thalamus, and hippocampus (Figure 2.22). Inhibition of cortical motor activity by vagal stimulation has been demonstrated, as well as suppression of EEG spiking activity in experimental seizure models (Schweitzer and Wright, 1937; Zanchetti *et al*., 1952; Chase *et al*., 1967). Additionally, GABA is present in brain areas of vagal nerve innervation (D'Amelio *et al*., 1987). Experimental stimulation of the cervical vagus in dogs, whereby either epileptic seizures or tremors were induced, led to the rationale for the development of the implantable stimulating device (Zabara, 1992). In these studies, stimulation typically had a prolonged effect (many minutes) of reducing seizures and tremors. An after-effect was also present once stimulation ceased. Stimulating parameters necessary to *reduce tremors* were lower than those needed to *reduce seizures*. The effect is mediated through the stimulation of small, unmyelinated C fibers of the vagus nerve (Woodbury and Woodbury, 1990).

From the experimental data provided by Zabara, optimal parameters for VNS were elucidated including a frequency of 20–30 Hz, a strength of 10–20 V, and a duration of approximately 0.2 ms (Zabara, 1992). Depending on the stimulating paradigm used, cortical electrical activity may become synchronized or desynchronized. Higher frequencies (<30 Hz) tend to result in desynchronization, whereas lower frequencies tend to result in synchronization of cortical activity.

In 2002, Muñana *et al*. published results of the use of VNS through an implanted device in nine dogs. The results showed a decrease in seizure frequency of four of the nine dogs (44%), no change in two patients (22%), and an increase in seizure activity of three patients (33%). There was no statistical difference found between seizure frequencies of those treated during the control period and the treatment period. However, in the last 4 weeks of the treatment period, a statistical difference was found between those dogs with reduced frequency and those with no change or increased frequency (Muñana *et al*., 2002). There are several possible reasons for the reduced efficacy in dogs. These include:

- Short evaluation period. It was noticed efficacy improved toward the end of the study. Long-term suppression has been previously identified with the implantable device (Hammond *et al*., 1990; Penry and Dean, 1990; Wilder *et al*., 1991). Larger human trials have also shown improved efficacy with time (Morris and Mueller, 1999; DeGiorgio *et al*., 2000).
- Low current. The current used experimentally was reduced compared to that of humans and in other studies of dogs. In humans, coughing is an acceptable and tolerated side effect of VNS due to increased current. In the Muñana study, the current was reduced to the point where coughing did not occur in order to keep the study blinded.
- Inclusion of the sympathetic trunk. The anatomy of humans allows for relatively easy distinction of the vagus nerve and the sympathetic trunk as they are adjacent to one another but completely separate. In dogs, the two nerves are joined together in the neck and not easily separated. For this reason, the electrodes were wrapped around both the vagus and the sympathetic trunk. Stimulation of the sympathetic fibers may have influenced the efficacy.

Experimental implantation of a human device was conducted in beagle dogs using a modified surgical approach (Martlé *et al*., 2016). The dogs were followed for 3 years at which time the implant was removed. All dogs tolerated the procedure well with only minor complications such as seroma, oculosympathetic paresis (Horner's syndrome), twisting of lead wires, and trauma-induced breakage of the leads. Intraoperative and postoperative (48 hours) testing of the device did not cause any ECG changes. From this study, it was concluded that modifications such as a post-operative compression bandage, restricted activity, and potentially placement in a more stable location may lower the chance of complications.

A 5-year-old, male, Shetland sheepdog with drug-resistant epilepsy and hepatic cirrhosis (presumed to be a consequence of multiple antiepileptic medications) was successfully treated with vagal nerve stimulation (Hirashima *et al*., 2021). This particular patient had been treated with zonisamide, potassium bromide, phenobarbital, levetiracetam, and gabapentin. Despite numerous medications, he continued to have focal seizures, which often generalized. The patient experienced clusters of focal to generalized, tonic–clonic seizures 5–14 times a month. EEG evaluation failed to identify an epileptogenic zone and a hepatic disorder (presumed to be a consequence of antiepileptic drug therapy) made further pharmacological treatment risky (Hasegawa, 2016). Therefore, a vagal nerve stimulator was implanted around the left vagosympathetic trunk (DemipulseTM Model 103; LivaNova USA, Inc., Houston, TX, USA). The antiseizure drug protocol was unchanged for 3 months prior to implantation and 1 year after implantation while the stimulation of the vagal nerve was evaluated. A magnet was used to temporarily activate the stimulator when a focal seizure was detected, in an attempt to prevent secondary generalization, which has been shown to be beneficial in humans (Morris, 2003). In this patient, seizure frequency was reduced by 87% and cluster seizures by 89% in the 1-year treatment and evaluation period. The owner reported

after VNS implantation, the dog's personality and quality-of-life were significantly improved (as well as the owner's). For this patient, VNS was a success. It is important to remember statistics from a population do not apply to the individual in isolation. For this one patient (and his guardian), VNS made all of the difference and potentially prevented this dog from being humanely euthanized or succumbing to chronic hepatitis. Even if there is only a 1% chance of success, we never know which patient will be that one, if we do not at least try.

Because of the invasiveness of the treatment, the expense associated with implantation, the difficulty in obtaining the device, and the unpredictability of its effectiveness, cutaneous stimulation may be a more viable alternative.

CUTANEOUS STIMULATION

Transcutaneous or noninvasive vagal nerve stimulation (nVNS) via a handheld device shows promise as a therapy for patients with drug-resistant epilepsy. In human studies, treatment success as high as 64.4% have been reported (mean seizure reduction from baseline at 6 months) (Liu *et al*., 2018). Similar to results with an implanted device, *chronic* therapy appears to result in a greater benefit with the application of a cutaneous device. Studies at this time are limited and consist of small groups of dogs, no sham or control arm of the investigations, and are biased to owner-reported results (Robinson *et al*., 2020). At home, treatment consists of the application of the current generating device to a shaved area on the left side of the dog's neck, over the vago-sympathetic trunk, 3 times a day for 90–102 s/treatment. While most dogs appear to tolerate the treatment fine, a small number experienced negative effects including lethargy, behavior changes, hoarse bark, and forelimb tremors, and in one case an *increase* in seizure activity. One of the primary benefits of nVNS is the ability to withdraw the treatment in the case of the development of an adverse effect or lack of effect, similar to a medication and without the need for surgery. Most adverse effects reported in canines with implanted devices, are due to the surgical procedure and consisted of Horner's syndrome, seroma formation and migration of the implanted device (Muñana *et al*. 2002).

OCULAR COMPRESSION

VNS through ocular compression in dogs has been reported as a potentially effective and noninvasive way to suppress epileptic seizure activity (Speciale and Stahlbrodt, 1999). In this report, pulsatile compressions of the eyeballs were applied for 10–60 s at 5 min intervals. The results were not consistently successful; however, the report suggested improved seizure control both in the hospital setting and a home environment. A similar mechanism to electrical stimulation of the vagus nerve is hypothesized. Ocular compression has been used for decades to diagnose excessive vagal activity, leading to syncope in human children via the *oculocardiac* reflex. The afferent arc of the response is mediated through cranial nerve V. The efferent arc is the vagus nerve. In humans, the thumbs are placed over the eyeballs, and enough pressure is exerted to achieve a 2–3 mm blanching of the nails (Stephenson, 1980). If an ECG is monitored, a variable slowing of the heart rate is visible. The degree of pressure necessary to create a positive ocular compressive response as measured by *EEG* was found to be as little as 30 mmHg (Haneef *et al*., 2008). To test the degree of pressure necessary to achieve 30 mmHg with your thumbs, inflate a blood pressure cuff and press down with a thumb while simultaneously observing the pressure reading on the sphygmomanometer (Figure 10.1). The author has treated a canine patient whose owners employed ocular compression to help treat focal epileptic seizures. The owners observed that the dog would seek them out for the compression just prior to an impending focal seizure. The dog tolerated the treatment very well and his owners felt it was a useful therapy for him.

The benefits of VNS include minimal adverse effects, no additive or cumulative adverse effects, and no development of tolerance, as is commonly observed with drug therapy. Additionally, in the case of an *implanted device*, reliance on owner compliance is not necessary. Finally, the

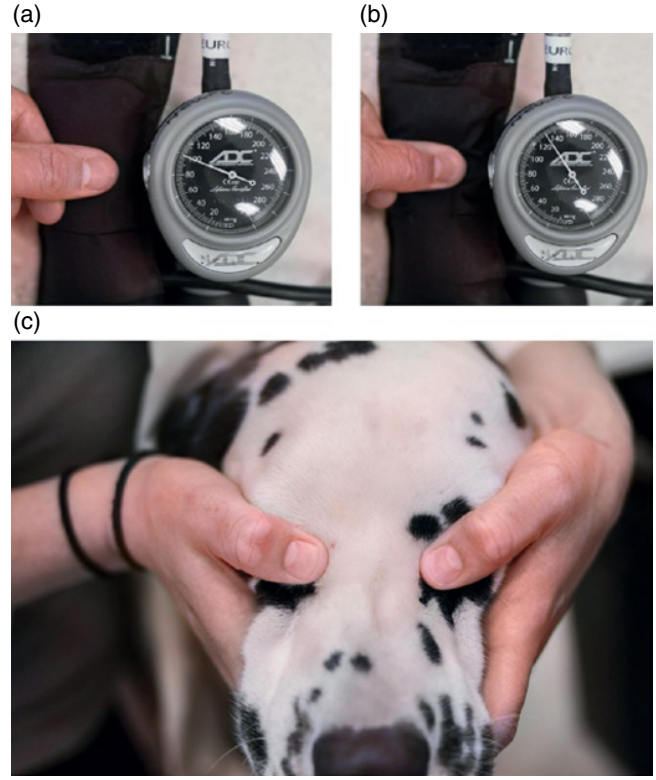


FIGURE 10.1 Ocular compression for vagal stimulation. (a) An inflated blood pressure cuff and attached sphygmomanometer may be used to gauge the appropriate amount of pressure to apply to the closed eyeballs. (b) Pressure is applied to the cuff in order to generate 30 mmHg of pressure or approximately, 2–3 mm blanching of the tips of the fingernails. (c) The thumbs of the clinician are gently placed over the closed eyes of the patient and pressure is applied for approximately 10–60 s at 5 min intervals. Only enough pressure to blanch 2–3 mm of the fingernails should be applied (~30 mmHg). The patient should tolerate the pressure.

method does not interfere with any other treatment options. The disadvantages of the implanted device include the high cost, necessity for surgery, difficulty in obtaining the device, and no guarantee the implant will influence epileptic seizure frequency.

TRANSCRANIAL MAGNETIC STIMULATION

Repetitive transcranial magnetic stimulation (rTMS) shows promise as a noninvasive treatment for canine and feline epilepsy. The basic premise is using magnetic fields to either increase (high frequency >1 Hz) or decrease (low frequency <1 Hz) neural activity in the brain. The therapy is designed to target identified epileptogenic zones but may also work on diffuse epileptic networks in the cerebral cortex. The effects are limited to superficial areas of the brain as the strength of the magnetic field is reduced the further the tissue is from the stimulator (thus having less effect on deep structures of the brain). While human studies show disparate and inconsistent results; in a single-blinded, randomized, sham-controlled clinical trial, in 12 dogs with drug-resistant epilepsy, there was a significant reduction in seizure frequency and monthly seizure day frequency in treated dogs compared to sham-treated dogs (Charalambous *et al.*, 2020). Moreover, when the sham-treated dogs were exposed to treatment, there was significant improvement.

SURGERY

SIMILARITIES BETWEEN SPECIES

Many similarities exist between the pathophysiology, diagnosis, and treatment of epilepsy in humans and animals. The fact most human treatments are derivations of animal experiments further strengthens the parallels in human and veterinary allopathic medicine. Within both groups

of patients, the primary treatment option is pharmacotherapy; however, pharmacoresistance is encountered in approximately 25–30% of both human and dog populations (Lane and Bunch, 1990; Berg, 2004). Cats tend to be more successfully treated with estimates around 20% considered to be pharmacoresistant (Schwartz-Porsche and Kaiser, 1989). Furthermore, some secondary causes of epilepsy may be removed surgically (i.e., neoplasia, infection, trauma, malformation, etc.). Other similarities exist between species, such as types of seizures, response to medications, and electroclinical analysis. While it is important to remember pathophysiology of a similar disease process may differ between species, we must also investigate the similarities, as treatment options for one cohort may be viable for another. The goal of treatment is to eliminate seizures entirely, although *treatment success* is often defined as a 50% reduction in the frequency of seizures. Pharmacoresistance is defined as the failure of two appropriate antiseizure drug trials in achieving long-term seizure freedom for a sufficient amount of time (Kwan *et al*., 2010). A sufficient amount of time for each individual human patient is defined operationally as three times the longest interseizure interval or 1 year, whichever is longest (Engel and Wiebe, 2012). "Appropriate antiseizure drug trial" means a maximal tolerated dose was achieved (to side effect or the high zone of a reference range) or a maximum practical dose was attempted (i.e., more of what is not working at double the starting dose is probably not going to work with further dose increases). When conventional therapy fails, the clinician should look to unconventional means to treat epileptic seizures. Surgery for the treatment of epilepsy offers a possible *cure* for the condition. Despite over 100 years of surgical treatment for epilepsy in humans and thousands of scholarly articles demonstrating its success, brain surgery for the direct treatment of epilepsy in humans is still considered underutilized (Engel, 2013). Because of the similarities among species, one would expect veterinary patients to have similar benefits as humans. Other similarities to consider despite the known incidence of pharmacoresistance include:

- A similarity between the percentages of the population affected (dogs and humans).
- Relative similarity between the costs associated with the treatment of medically intractable seizures. Considering in humans, 80% of the cost of the treatment associated with epilepsy is for patients who are considered medically intractable epileptics (Begley *et al*., 2000).
- Temporal lobe epilepsy (TLE) is the most common cause of pharmacoresistance in humans (Jallon *et al*., 2001). Could the most common form of pharmacoresistant epilepsy be TLE in dogs or cats?
- TLE is the most successfully controlled epileptic syndrome with surgery, with 60–80% of surgery patients becoming free of disabling seizures (Wiebe *et al*., 2001; Engel *et al*., 2003).
- Surgery for the treatment of TLE may also prevent early death associated with epileptic seizures in humans (Sperling *et al*., 1996).
- Hippocampal sclerosis, a form of TLE, is the most common cause of limbic seizures in humans and is regarded as a common cause of limbic (i.e., "psychomotor") seizures in cats (Fatzer *et al*., 2000; Brini *et al*., 2004; Marioni-Henry *et al*., 2012; Gelberg, 2013; Pakozdy *et al*., 2014).

Many factors limit the frequency of surgery to treat epilepsy in humans. These factors would only compound other variables, which exist in the veterinary world. Surgery for the treatment of epilepsy should be considered in veterinary patients, especially when euthanasia becomes the only other viable option (a variable that does not exist in human medicine). In a sense, human physicians, surgeons, and investigators are continuously motivated to find new, alternative treatment methods simply because there are no other *options* (i.e., euthanasia). A similar approach can be explored with veterinary patients, building on the success of our human physician counterparts. After all, as mentioned earlier, nearly all treatments used in humans were initiated,

explored, and perfected on animal models. These successes—initially invented for the treatment of human disease, experimented and perfected on animal models, and then applied to human disease—may be able to come full circle back to the species from which the initial experiments served to validate the treatment (i.e., dogs and cats).

JUSTIFICATION FOR SURGERY

We often consider surgery for any neurological condition as a *last resort* and surgery for the treatment of epilepsy in those patients who are refractory, may prevent unnecessary euthanasia. Even in human medicine, surgical treatment for epilepsy is considered underutilized with only 2% of the potential candidates having this form of treatment in a year, despite significant evidence of success in curing people of epilepsy, the development of advanced diagnostics, demonstrated cost-effectiveness, lower morbidity rates, and lower incidences of sudden death associated with epilepsy (Engel and Wiebe, 2012). Some of the postulated reasons for the large gap between those who would qualify for the treatment and those who actually receive it include; poor understanding of safety, fear of surgery, and cost for both potential patients and their physicians, who may not provide the patient with adequate information. To counter these concerns, thousands of papers have demonstrated the safety and efficacy; studies have shown surgery has less morbidity associated with it compared to pharmacotherapy and the costs associated with surgery are significantly less than a lifetime of pharmacoresistant drug therapy (Cockerell *et al*., 1994). Even the American Academy of Neurology (AAN) has concluded surgery is the treatment of choice for medically intractable epilepsy in humans (Engel *et al*., 2003). The conclusion of the AAN was based on a detailed literature review and a randomized clinical trial out of the University of Western Ontario, showing surgery to be more effective compared to continued pharmacotherapy in those patients with pharmacoresistant TLE (Wiebe *et al*., 2001). Despite this, the average time from the onset of epilepsy to referral to a surgery center for humans was 22 years (Berg *et al*., 2003).

In veterinary medicine, we may reach a point where we cannot attain a good balance between the quality-of-life and seizure control for the patient. We have a built-in "out," which is euthanasia. This does not exist in human medicine, so clinicians and researchers are motivated to evolve new treatment options and refine or perfect old ones. We are fortunate that we do not have to watch our failures languish in long-term convalescent care facilities. This last statement is not meant to be in the pejorative, but rather, to emphasize the different philosophical approaches that create the foundation upon which our decision-making and treatment options are built. Pushing the boundaries of neurosurgery will help us to achieve our goal of superior care. In the last few decades, there has been a shift in veterinary medicine, where we are starting to dip our toes into the world of advanced surgical treatment options. But we have always done this. From the first descriptions of brain surgery in dogs and cats—every step we take is a new frontier. This is primarily driven by:

- Consumer demand—pet owners are not willing to euthanize their animal family members.
- Accessibility to technology—cost of advanced technology is lower and availability is greater.
- Expertise—veterinarians and veterinary researchers are refining the procedures and publishing their results.

We could place clinician interest on the list but I think it has always been present in a small population of veterinarians and researchers. The nexus of the above conditions is being met at this time. Ten years ago, with the first edition of this book, I predicted it would be decades before we reached this point. I was wrong. The amount of literature not only on surgical techniques and case reports but also of sophisticated diagnostic techniques being applied to veterinary patients is inspiring. Our application of neurosurgery to treat epilepsy is growing and evolving. Specialists are

becoming even more *specialized* in their specialty. The amount of detail associated with appropriate case selection, presurgical diagnostics, and surgical technique cannot be given adequate page space in this book. Fortunately, clinicians and researchers are doing an amazing job at cranking out the papers.

PRESURGICAL EVALUATION

Surgical treatment for epilepsy originally relied on semiological features to determine the epileptogenic site from the late 1800s to the early 1900s. With the development of pneumoencephalography and cerebral angiography, diagnosticians were able to better identify lesions. The EEG provided the biggest leap in technology and to this day is heavily utilized to determine an epileptogenic site in humans. The first brain surgery using EEG data alone was performed on a human in 1951 (Bailey and Gibbs, 1951). Following EEG came the development of interictal scalp EEG, the use of intracranial depth electrodes, video telemetry, and advanced neuroimaging. A general (incorrect) assumption made in veterinary medicine is brain surgery, even in humans, was not performed prior to advanced imaging modalities such as MRI. PET scans and MRI were the first diagnostic modalities to confirm hippocampal sclerosis. Hippocampal sclerosis is the most common cause of mesial temporal lobe epilepsy (MTLE) (Velez-Ruiz and Klein, 2012). The utilization of SPECT imaging in dogs has been evaluated and may be useful when combined with EEG data (Chapter 5) (Peremans *et al*., 2001; Lass *et al*., 2006; Martlé *et al*., 2009). While SPECT imaging possesses the ability to identify the epileptogenic focus, it has poor spatial and temporal resolution. The limitations of temporal resolution may be overcome through various EEG recordings, while issues associated with spatial resolution (e.g., where *exactly* is the lesion) may be overcome by overlying SPECT data combined with high-field MRI. Interictal and ictal EEG recordings are increasingly being used as confirmatory tools prior to brain surgery. Ultimately, a combination of various advanced diagnostic modalities will provide the surgeon with as much information as possible.

In order to apply surgical methods for the treatment of epilepsy in veterinary patients, new paradigms are being developed (Hasegawa, 2016; Hasegawa *et al*., 2022a, 2022b). Several gaps must be overcome in order to make surgery for the treatment of epilepsy even a consideration. These include:

- Refinement and acceptance of a standardized categorization of the epilepsies, which affect animals based on *functional* syndromic classification. We already use this system in a crude, mechanistic form (i.e., idiopathic/genetic, metabolic, reactive/provoked, and structural syndromes). Those patients who are recognized to have a *distinctive constellation of* features or symptoms associated with their epilepsy would then be classified in a more refined and sophisticated *operational* syndromic classification. The recognition of a syndromic classification, such as orofacial and focal seizures associated with hippocampal sclerosis in cats, would allow veterinarians to *predict* which patients are likely to be pharmacoresistant based on similarities between human and veterinary patients. They would be considered surgical candidates at an earlier time.
- Access to advanced diagnostic modalities. Granted over 130 years ago, the pioneers of modern brain surgery were limited in their neurodiagnostics, they still pioneered early brain surgery using what was available at the time (which they thought of as state-of-the-art). These bold surgeons primarily relied on seizure semiology to deduce and successfully resect epileptogenic lesions (Macewen, 1881; Horsley and Schäfer, 1886). With the advent of clinically useful electrodiagnostics, epileptic surgery slowly progressed in its specificity and selective sparing of eloquent functioning tissue (Penfield, 1936). Veterinary diagnostics are in nearly lockstep with human diagnostics as far as availability. We still have the cost gap to cover which is being bridged by the pet insurance industry (for now).

As we consider syndromic classification in animals, new models of previous syndromes will change. For example, it is well recognized that humans who suffer from TLE tend to have focal seizures (previously complex, partial seizures) with or without dyscognition, beginning at a young age (Wiebe *et al*., 2001). As previously mentioned, feline patients with focal facial seizures (i.e. "psychomotor" seizures, see Videos 16-18) are increasingly being diagnosed with pathology of the hippocampus. While some forms may be acquired pathology, secondary to their epileptic seizures, others are immune mediated (Pakozdy *et al*., 2014). Generalized seizures were previously thought to be the most common seizure type dogs experienced, and this notion alone may have prevented a parallel from being drawn between humans and animals. However, as our recognition and early detection of epileptic seizures improves, the semiology associated with various types of seizures becomes more *defined*, allowing for an even more *refined* (i.e., the ability to distinguish characteristics) recognition. Epidemiological studies have now shown focal seizures (with dyscognition) to be more common in dogs than previously thought (Berendt and Gram, 1999). Pet owners do not tend to recognize the focal aspects of the seizure (aura) but have little trouble identifying a generalized seizure. More animals are affected by focal seizures, which then secondarily generalize. The generalized seizures are easily recognized by owners (likely with the exception of *absence* generalized seizures); however, the preceding focal seizure (aura) may be missed. Considering this information, we can refine the operational syndromic classification of animals, which is likely to parallel that of humans (given enough identifiable and recognized variables). We can then establish more sophisticated guidelines for treatment based on an operational syndromic classification (i.e., that specific disease entity associated with the characteristics of the clinical signs and diagnostic tests – see Chapter 3).

Being able to make a syndromic classification in humans as having TLE combined with EEG recordings of the brain led to some of the early case series of surgery (Penfield and Flanigin, 1950). Standard presurgical evaluation now consists of multiple forms of EEG recordings, advanced imaging of the brain (MRI), advanced functional brain imaging (PET, SPECT scanning, etc.), and neurocognitive studies. An important consideration when removing brain tissue is determining what the functional capacity of the resected tissue is and whether or not the remaining brain tissue will be able to compensate for the loss (assuming there is functional capacity as opposed to aberrant signaling alone). This, of course, will be less of a barrier for veterinary patients not only when considering our patients have significantly less developed eloquent areas of the brain but also in regard to the ability to actually perform the necessary tests to determine what the functional capacity may be. Neurocognitive studies are an important part of presurgical screening in human patients (Wagner *et al*., 2012). Functional MRI (fMRI) and EEG may be used to help localize cortical function; however, more discriminatory evaluations using the *intracarotid amobarbital procedure* (i.e., Wada test) help evaluate memory and learning capacity in humans (Hauf *et al*., 2012; Wagner *et al*., 2012). During the Wada test, one side of the brain is anesthetized with sodium amobarbital (via a carotid injection), while a neuropsychologist and/or epileptologist evaluates the other side for the ability to retain memory, speech, and language. The Wada test adds information to fMRI and MRI volumetric studies of the hippocampus to help the surgeon plan the resection, as well as evaluate the patient's predicted ability to retain language and memory function (Cohen-Gadol *et al*., 2004). A simple derivation of the Wada test in a dog may be the recognition of the owner, a treat, or the ability to perform learned "tricks" and respond to commands. We should not discount the ability to develop some form of standardized neurocognitive testing for veterinary patients, although the barriers of sedation and anesthesia would certainly be difficult to overcome. It can be done as demonstrated by highly trained canines which allow fMRI scans to be performed without anesthesia (Figure 10.2) (Berns *et al*., 2012). Applying this to a feline patient . . . well, *that* is another challenge altogether. For veterinary patients, we will primarily rely on case reports of postoperative functionality based on what area of the brain was resected. This is essentially what we do at this time regarding brain tumor removal. We have a generally good idea of what we can get away with as far as resection goes. A significant amount of controversy exists, as one can imagine, among human surgeons and between surgical centers, as to what constitutes adequate

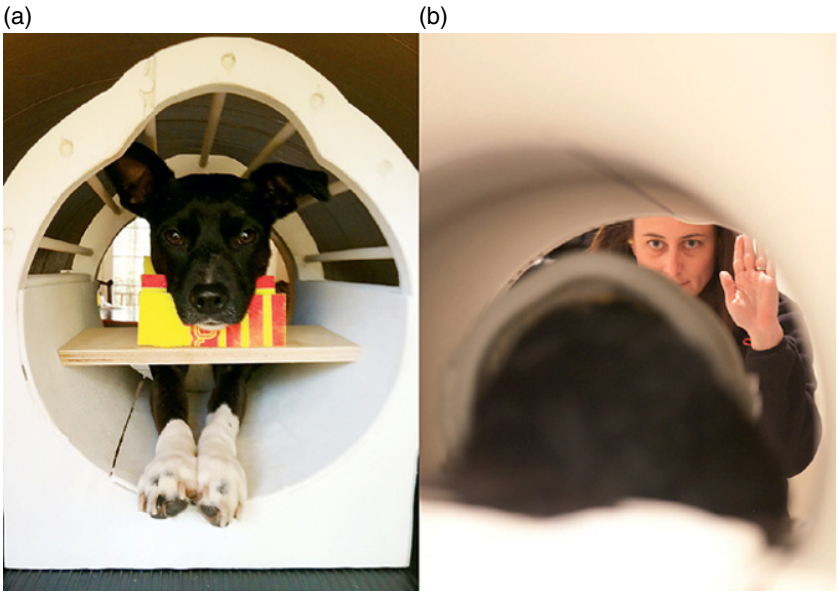


FIGURE 10.2 Training an awake dog to lie still in an MRI scanner. Modified figure from original publication. (a) Patient placed in a training apparatus mimicking the actual MRI coil. No restraints were used. The training procedure gradually shaped the desired behavior of placing the head in the rest and not moving through positive reinforcement only. Dogs were free to exit the apparatus at any time. (b) Patient inside the head coil of the MRI. The handler is giving the hand signal, which signifies an upcoming "reward." A simple instrumental conditioning task was used, in which the required behavior was to place the head on the chin rest and not move. Permission to use figure granted through PLoS ONE Open Access under the terms of the Creative Commons Attribution License and by the author. Berns *et al.* (2012)/PLOS/ CC BY 4.0. To see this amazing training in progress, visit: http://www.youtube.com/watch?v=F6C_3urmsJ0 &feature=relmfu.

presurgical screening in order to preserve critical cortical function, as well as provide the greatest chance for surgical success with minimal morbidity and mortality. Historically, veterinarians have relied on more *empirical* evaluations of the outcome based largely on trial-and-error observation.

SURGERY IN DOGS AND CATS

Removal of compressive lesions in the brain is the most common form of intracranial surgery for dogs and cats. These surgical techniques are aimed at removing a lesion, thought to be the cause of secondary epilepsy or other neurological deficits (Figure 10.3). As these surgeries become more commonly performed, veterinary neurosurgeons will continue to advance toward brain surgery for the treatment of drug-resistant epilepsy (DRE). Case reports and case series regarding surgery for epilepsy in veterinary patients are becoming more frequent. A specific case report on the success of removing an *epileptogenic focus* was reported as early as 1971 (Parker and Cunningham, 1971). In the last decade, we are seeing more information regarding not just lesionectomy but also hippocampectomy, cortical resection, corpus callosotomy, and multiple subpial transection for the treatment of epilepsy. Surgery for epilepsy, whether in a human or a veterinary patient, carries an appropriate amount of social unacceptability. We must consider results acceptable for a human to have reduced seizure frequency may not be acceptable for veterinary patients (i.e, a lifetime of living in a chronic care facility but with fewer seizures). Of course, the clinical results for a human following epileptic surgery span a spectrum from complete care convalescence to normal life. The same spectrum of existence for a companion animal is (and always will be) significantly narrower.

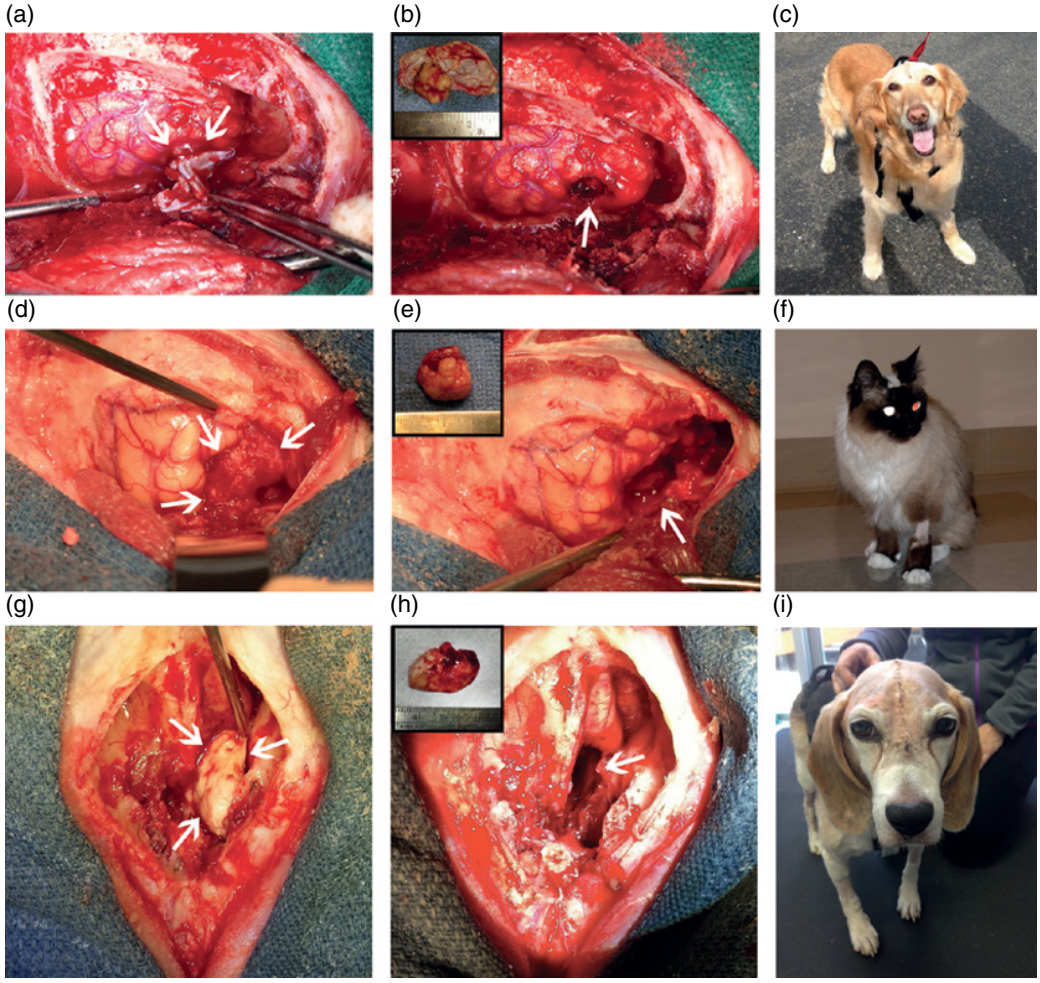


FIGURE 10.3 Various intraoperative brain surgery images. (a) Lateral tentorial craniectomy to remove a superficial meningioma in a dog (MRI is Figure 5.12). The arrows point to a firm, nodular mass, connected to the overlying meninges by a narrow stalk. (b) The arrows point to the defect left in the brain following the removal of the tumor (inset, resected meningioma). (c) the patient at discharge. (d) Combined lateral and rostral tentorial craniectomy. Feline forebrain meningioma. The arrows point to the firm, miliary appearing mass. (e) Margins of the craniectomy defect are extended to the frontal bone and sinus in order to ease removal. Arrow points to defect after removal (inset, resected meningioma). (f) The patient 48 hours after surgery. (g) Modified transfrontal craniectomy, with left-sided cribriform plate removal. Arrows point to a firm forebrain glioma in a dog. (h) Defect left from removal of the glioma (inset). (i) The patient two weeks after surgery.

To explain it in another way, the clinical outcome for a veterinary patient must be the reduction of the clinical signs you hoped to alleviate along with a good quality-of-life. The only way to overcome this stigma is through demonstration of success (i.e., lack of long-term suffering and defined benefit to the treatment). Veterinary patients tend to fare well with common brain surgeries to remove tumors, correct malformations, repair trauma, or treat hydrocephalus, as long as patient selection is the utmost focus. Most patients will leave the hospital in an improved state compared to prior to brain surgery (Figure 10.4). Long-term success is variable with slow-growing meningiomas tending to survive for years (Figure 10.5).



FIGURE 10.4 Postoperative brain surgery patients. Welcome to the Bad Haircuts Club. Overcoming the notion of "suffering" following brain surgery is not only present in veterinary medicine but human medicine as well. With proper patient selection for brain surgery, the outcome can be very good to excellent with survival times of many years being attained. Many patients are effectively "cured" of their brain neoplasia and often seizures will cease following removal of the mass. Other conditions such as head trauma, congenital malformation, and infection can also lead to the generation of epileptic seizures. Neurosurgery will always have a place for the treatment of epilepsy and, as in the case of human medicine, is becoming more refined.

With improved techniques and practical experience, we may consider resection of epileptogenic tissue as a plausible alternative to long-term treatment of drug-resistant epileptic patients (as is the similar case for humans). For humans, the vast majority of medical costs, cognitive decline, and lower quality-of-life scores are within the group of DRE. Yet, 77% of children and adolescents undergoing various surgical treatment procedures for DRE were seizure-free 1 year post-op, compared to only 7% who were managed with medications (Dwivedi

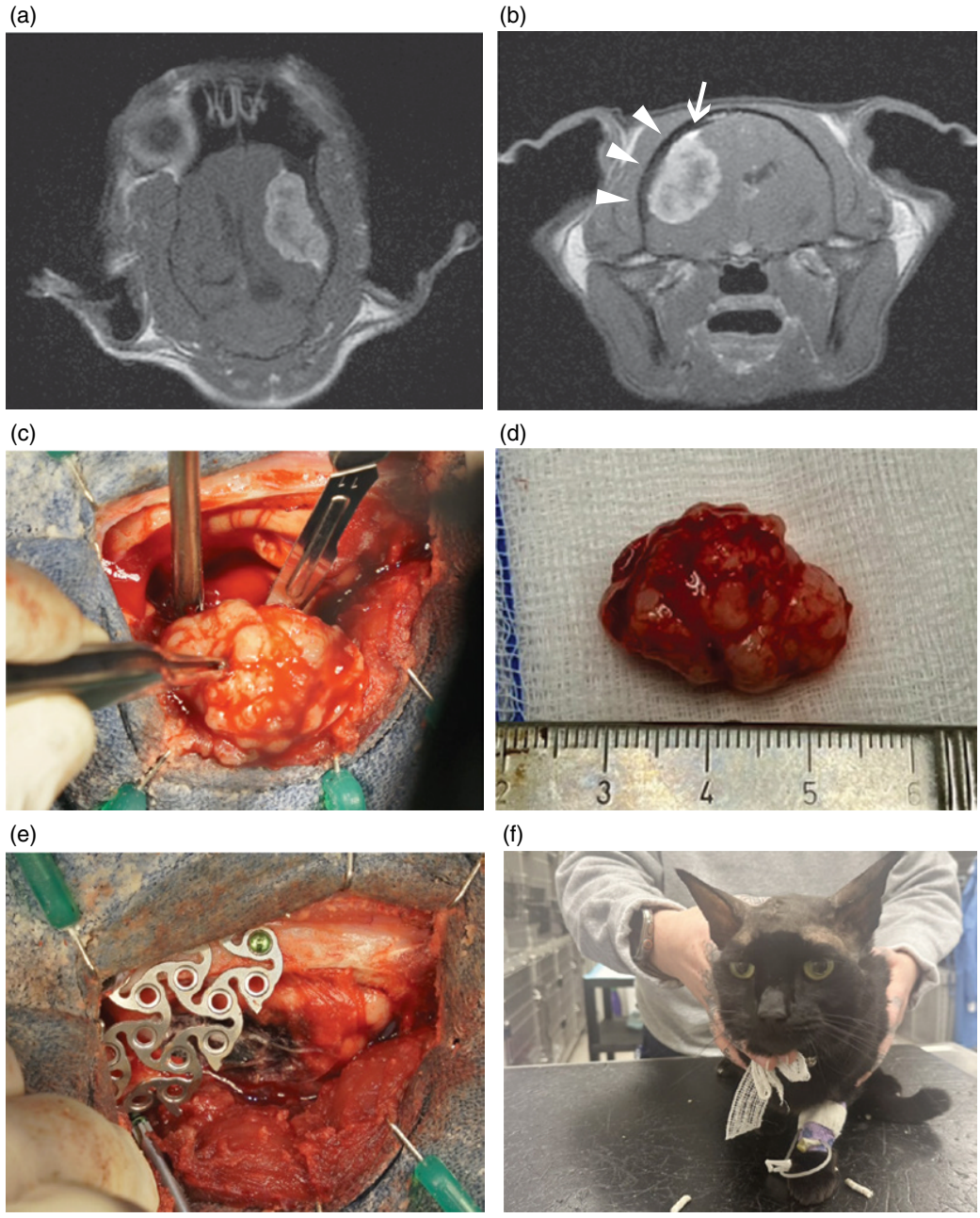


FIGURE 10.5 Removal of a typical feline meningioma. (a) T1-weighted, post-contrast, dorsal MRI of a feline brain tumor with characteristics common for a meningioma (arrow). (b) T1-weighted, post-contrast, transverse image at the level of the midbrain. Note the hyperostosis (arrowheads), typical for slow-growing tumors and the dural tail sign (arrow), common for meningiomas. The mass also has central changes consisting of hemorrhage or necrosis. (c) Appearance of the mass following durectomy. The solid mass, which does not invade deep brain parenchyma, is removed with a combination of blunt and sharp dissection (the left side of the image is rostral). (d) Appearance of the deep surface of the mass following visually complete excision. (e) The tumor was located at the junction of the transfrontal and lateral approaches, therefore, a combined, left hemi-transfrontal and lateral craniectomy was performed to aid in removal. The temporal line was disrupted (left intact in Figure 10.6), necessitating cranioplasty to restore structure to the skull. (f) The 6-year-old, female, spayed cat 2 days following surgery with a normal neurological exam. The histopathological diagnosis was a low-grade, fibrous meningioma.

et al., 2017). For veterinary patients, we are again faced with a viable alternative to unconventional treatment options. That alternative is euthanasia. Our overwhelming goal and underlying foundation of practice as veterinarians is to eliminate the suffering of our patients. Where a human may "exist," a companion animal must *thrive*. This is a high mark we are constantly reaching for. Radical and unconventional treatment options must always be considered against the potential to make the patient worse. Certainly, a fair amount of perioperative morbidity may be accepted as long as the long-term benefits to the patient outweigh the short-term costs (i.e., "suffering"). Technically, the consequences of radical neocortical resection appear to be transient in an experimental setting with minimal short-term disability noted following the removal of large portions of the cerebral cortex in both dogs and cats (Sorjonen *et al*., 1991). Division of the corpus callosum has also been empirically demonstrated to be a viable surgical technique in dogs and cats (Bagley *et al*., 1995; Asada *et al*., 2021; Hasegawa *et al*., 2021a). The technical aspects of *general* brain surgery in dogs and cats have largely been overcome, and techniques between species (i.e., dog, cat, and human) are similar. Surgical avenues have been continually improved with combined approaches to the brain, hypophysectomy and cranioplasty representing more advanced techniques for the treatment of structural brain disease (Figures 10.5–10.7). However, the pinnacle (at this time) is surgery to treat epilepsy, with one of the main *limiting steps* being specific lesion localization. The determination of a syndromic classification, through advanced diagnostic testing, may also aid in localization of the epileptogenic focus. However, there will always exist a "gap" between what is a societally acceptable outcome between a human or veterinary patient. A human may spend the remainder of their life, following brain surgery in a convalescent care center, whereas a similar existence for a dog or cat is unacceptable. As we consider surgery directed specifically at primary causes of epilepsy, our understanding of the pathophysiology and use of diagnostics to identify the abnormal tissue will continue to evolve.

DIAGNOSTICS

EEG/ECoG

A greater surgical success is associated with an accurate and precise localization of the epileptogenic zone. As its name suggests, the *implied* epileptogenic zone is the discrete region of the brain, from which the epileptic seizure (particularly focal seizures) originates. The true epileptogenic zone is the minimum amount of cortex that must be removed or disconnected to prevent epileptic seizures, which can only be determined through postoperative evaluation showing cessation of epileptic seizures (Hasegawa, 2016). This is often attempted intraoperatively. The area to be resected or disconnected is identified in *real time*. The procedure is performed and the surgeon evaluates the effectiveness of the procedure. The epileptogenic zone is a theoretical concept because it is impossible to consider areas of the cortex that may become active following resection or disconnection (a potential, postoperative epileptogenic zone) (Rosenow and Lüders, 2001). A combination of diagnostics (neurological exam, video EEG, ECoG, etc.) is used to determine the epileptogenic zone, which is composed of five individual zones (see below). The initial evaluation is performed by using extensive scalp EEG. Scalp EEG alone may not identify subcortical epileptogenic zones. In these cases, electrocorticography (ECoG) or intracranial EEG may be used along with deep epidural or subdural electrical recording taken as part of presurgical evaluation or during surgery (Figure 10.8). Limitations to the use of these modalities in veterinary medicine include limited access to the equipment, limited training, understanding and practical use of the equipment by veterinary neurologists, excessive cost associated with the tests, and even less controllable variables such as recording protocols (use of anesthesia or sedatives which may suppress or alter electrical activity) and artifacts created by variations in skull shape and the often thick muscles of mastication of veterinary patients. Deep EEG recordings may overcome some of these limitations. Precise

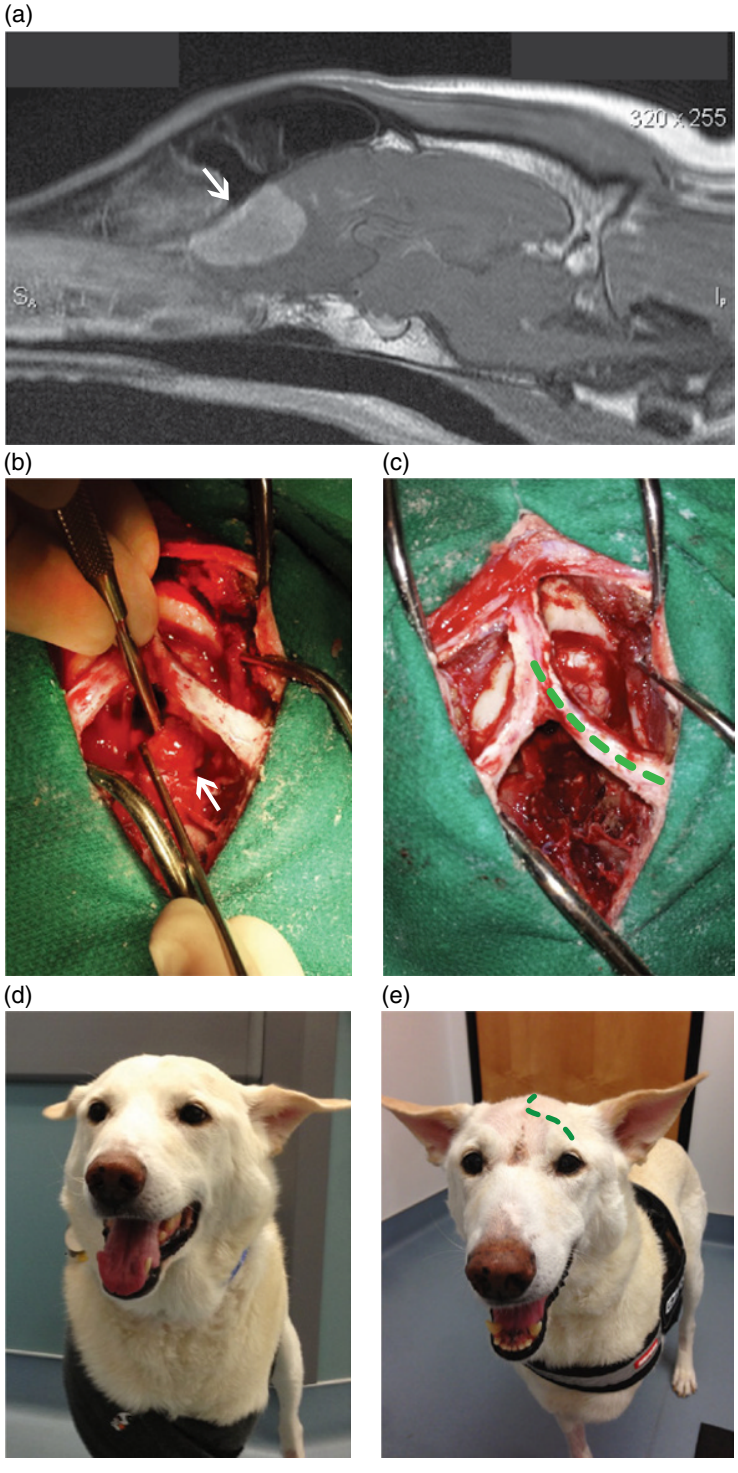


FIGURE 10.6 Combined rostral and lateral tentorial craniectomy. (a) T1-weighted, post-contrast, sagittal MRI of a left-forebrain mass (arow) in a 7-year-old, male, neutered, German Shepherd who presented for epileptic seizures with a normal interictal neurological exam. (b) A combined modified transfrontal and lateral craniectomy was performed to remove the mass (arrow) which extended beyond the limits of either independent surgical approach. (c) By preserving the temporal line (green dashed line extending from sagittal crest to the zygomatic process of the frontal bone) the surgeon gains greater access for meningeal margins and cranioplasty is not necessary. (d) The dog before surgery. (e) The dog after surgery showing maintenance of the skull shape without cranioplasty (green dashed line is temporal line). A meningioma was confirmed on histopathological examination of the mass.

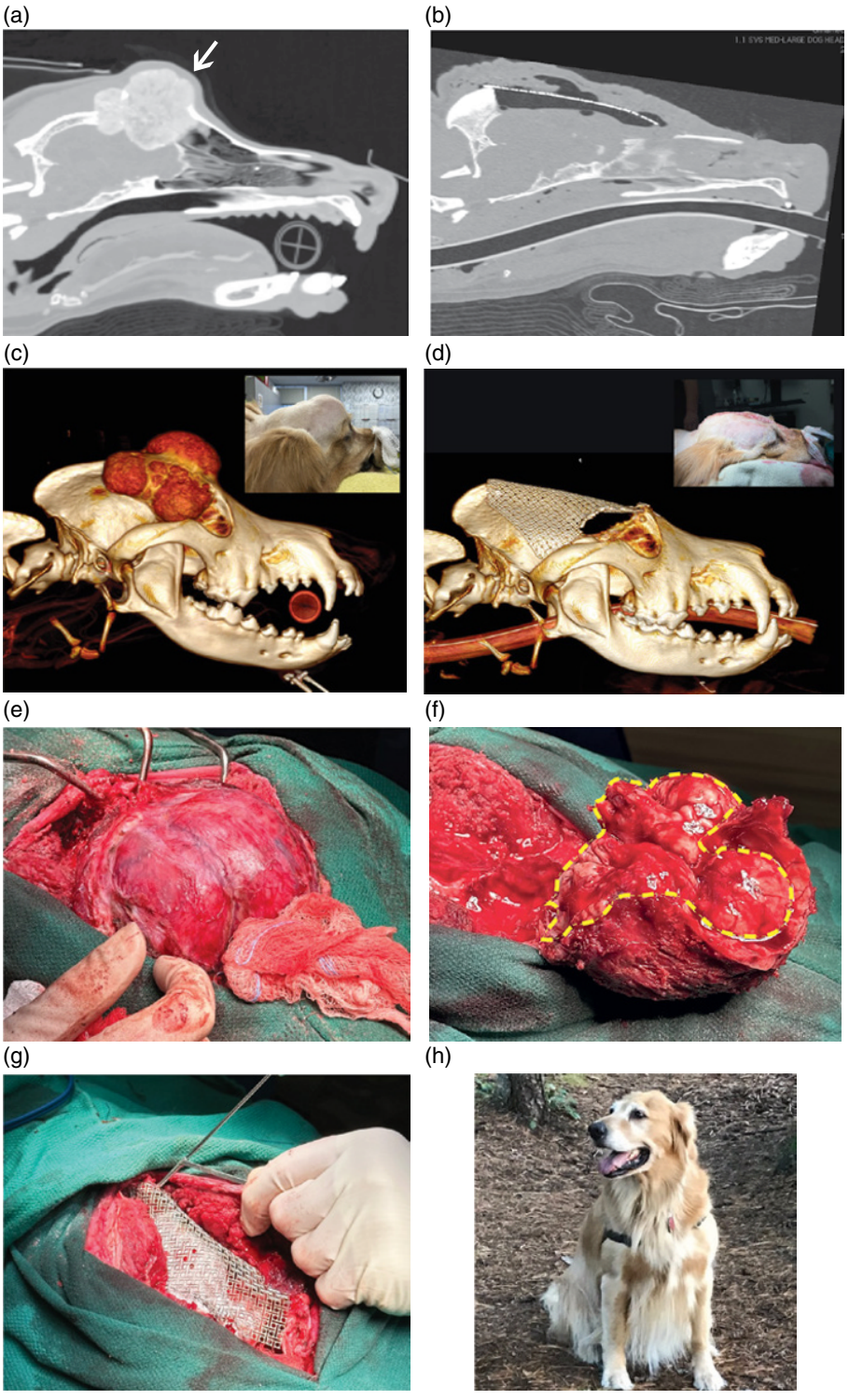


FIGURE 10.7 Cranioplasty. (a) Sagittal, post-contrast CT of a histologically confirmed multilobular tumor of bone in a Golden Retriever. The mass extended over the entire frontal bone and into the medial orbits of the patient (arrow). (b) Postoperative CT scan. A radical dorsal and frontal craniectomy and cranioplasty was performed. (c) CT reconstruction of the skull prior to surgery (inset: appearance of the dog prior to surgery). (d) Postoperative CT reconstruction (inset: appearance of dog at recovery). (e) Appearance of mass at surgery (rostral is to the right). (f) The mass was removed en block with at least 1 cm margins were possible (mass outlined in dashed yellow line). (g) A titanium mesh implant (Neuromesh™—Orthomed, UK) was shaped an affixed to the skull in order to protect the brain, provide attachment points for soft tissues, and reconstruct the aesthetic appearance of the dog. (h) The dog ~1 year after surgery.

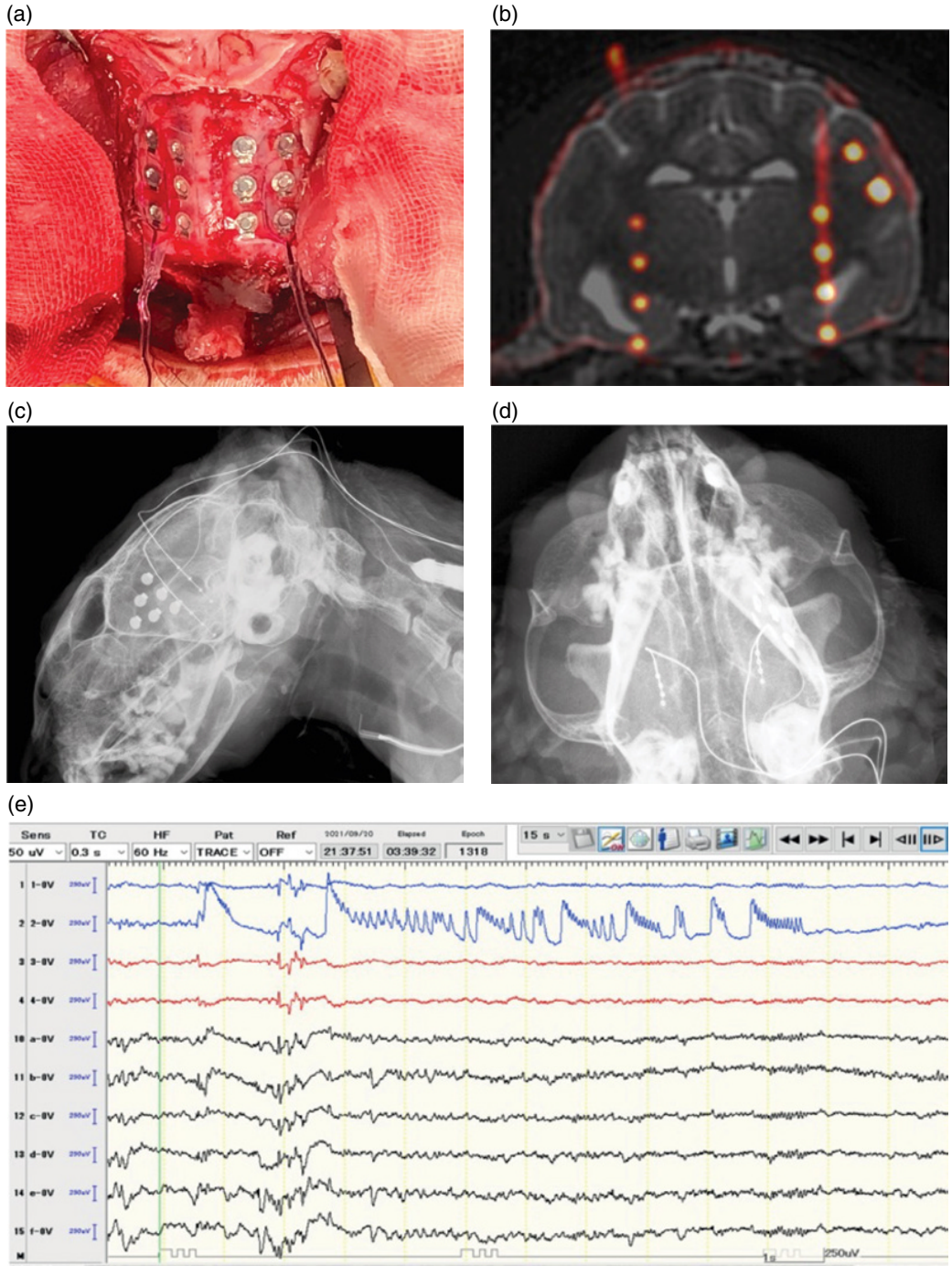


FIGURE 10.8 Presurgical ECoG. (a) Bilateral surface electrode placement in a cat prior to corpus callosotomy (looking down at the top of the brain). (b) Fusion image of preoperative T2W and post-electrodes-implantation CT showing deep electrode placement. (c) Lateral radiograph of same cat as (b) showing bilateral depth electrodes directed into ventral hippocampi and amygdala and a triangle-shaped six-channel ECoG electrode on the left fronto-temporal lobe. (d) Ventral-dorsal radiograph of same cat in (b) and (c). (e) Recordings from same cat in (b–d). First four channels are from the deep electrodes. First blue channel is the left, parahippocampal gyrus/amygdala and the second blue is the left hippocampal head. First red channel is the right parahippocampal gyrus/amygdala and the second red is the right hippocampal head. The remaining six channels (10–15, black) are the ECoG. A left hippocampal seizure is recorded from the deep electrodes but the ECoG did not capture the seizure activity. With thanks to Dr. Daisuke Hasegawa, Laboratory of Veterinary Clinical Neurology, Nippon Veterinary and Life Science University, Tokyo, Japan.

lesion localization may also be aided through the use of a broad montage followed by a more specific montage once an area of interest is identified. Ideally, the epileptic seizure will be recorded at the precise time it occurs. This is unlikely to happen in veterinary hospitals, as prolonged EEG studies may not be practical for the veterinary patient (i.e., similar to human epilepsy centers). We may, however, gain adequate information through the identification of interictal spike discharges. While these electrical events are not always present, if they are identified, they tend to have a strong correlation with the epileptogenic location (Bagley *et al*., 1996). *Ambulatory* (awake) *EEG* offers a start to overcome some of these boundaries. Eliminating anesthesia and being able to record the brain for hours or days at a time, increases the chance we will identify epileptogenic foci.

If only it were as simple as an EEG recording of the brain to identify the region to be resected or disconnected (but . . . then again, even that is not so simple). The epileptogenic zone is composed of five different regions (Rosenow and Lüders, 2001):

1. *Symptomatic* zone: the area of the cortex, which when activated produces the ictal symptoms. This is defined through seizure semiology, aided by video recording of the seizure (ideally onset to completion).
2. *Irritative* zone: the area of cortical tissue from where interictal spikes originate. Elucidated through EEG, ECoG, magneto-encephalography, and functional MRI (fMRI).
3. *Seizure-onset* zone: the area of the cortex that is responsible for the clinical onset of epileptic seizures (where the clinical signs are generated). Discovered through video EEC, ECoG, and single photon emission computed tomography (SPECT). This may or may not be in the epileptogenic zone.
4. *Epileptogenic lesion* (structural abnormality): the structural abnormality suspected to cause the epileptic seizure. Evaluated by MRI and ideally correlated with video EEG, semiology and/or fMRI if necessary.
5. *Functional deficit* zone: area of the cortex that is functionally *abnormal* in the interictal period. Measured by neurological exam, SPECT, interictal PET scans, and fMRI.

If all of the above zones are located in the same area (such as a brain tumor, where the mass lesion affects surrounding tissue), the definition of the epileptogenic zone would be relatively straight forward and therefore resection or disconnection would have a high probability of being curative. This may also be the case in cats with orofacial automatisms (focal limbic seizures), where removal of the ipsilateral hippocampus (and possibly amygdala) would theoretically carry a good prognosis as it does in humans with mesial temporal lobe epilepsy (hippocampal sclerosis/necrosis). Unfortunately, the zones do not always correspond to one location and lesionectomy alone may not be curative (Shihab *et al*., 2014). While lesionectomy may be curative (see Figures 5.4 and 5.12), we must also consider the removal of normal brain tissue to access a lesion (as in the Shihab case report) or even damage to surrounding cortex may create a new irritative zone.

Advanced imaging and diagnostic modalities may identify structural lesions of the brain responsible for epileptic seizures. The correlation of pathologically abnormal excised tissue is generally regarded as specific with 79% of the temporal neocortex, 65% of the amygdalae, and 93% of the hippocampi showing abnormal pathological changes. Following extensive follow-up (20–71 months), 67% of human patients undergoing temporal lobe resective surgery were seizure-free, and 94% had at least a 90% reduction in seizure frequency (Swartz *et al*., 1992). Freedom from seizures following anterior temporal lobectomy, in humans is reported to be from 60 to 80% (ILAE 1997; Mcintosh *et al*., 2004; Téllez-Zenteno *et al*., 2010).

Minimum diagnostic testing for dogs and cats undergoing consideration of surgery for drug-resistant epilepsy is (Hasegawa, 2016):

- Interictal neurological examination
- Video analysis of the epileptic seizure event (semiology from initial onset to conclusion)
- Scalp EEG (under sedation)
- MRI

Additional recommended diagnostic testing include:

- Video EEG (awake)—ambulatory EEG
- 3D volumetry (requires >1.5T MRI)
- Advanced MRI exam (DWI, PWI, magnetic resonance spectroscopy)

Diagnostic testing modalities comparable to those used for the determination of resection or disconnection in human epilepsy are becoming more commonplace in veterinary medicine. Long-term EEG monitoring and ambulatory (awake) video EEG are a few of the tools which hold great promise to further enhance our diagnostic abilities (Rogers *et al.*, 2024; Lyon *et al.*, 2024). Let's also not forget how impactful the presence of smartphones and the ability to video an event at home has improved our ability to describe epileptic seizures. Certainly, epileptic seizure detection devices coupled with advanced artificial intelligence will help bridge the gap between what we *want* to do and what we *can* do. However, there will always be diagnostic limitations because of the inherent inability to communicate with our patients (i.e., description of semiology or determination of eloquent areas of the brain). Regardless, the advances pioneering veterinary neurosurgeons are making today will become the standard of care tomorrow.

SURGICAL PROTOCOLS

The most commonly employed surgical options for humans include standard resections, tailored resections, disconnection surgeries, and ablative surgery (Figure 10.9) (Engel, 2013). These surgical possibilities are being optimized for veterinary patients. Surgery for the treatment of DRE can be categorized broadly into (Hasegawa *et al.*, 2022a):

- Resection surgery
  - Cortical resection
  - Lobectomy
  - Lesionectomy (including ablative surgery)
- Disconnection surgery
  - Corpus callosotomy
  - Multiple subpial transection
- Neurostimulation (neuromodulation such as deep brain stimulation and VNS)

Standard resections are most often used to treat TLE in humans. They are based on years of experience and knowledge associated with invasive EEG recordings, identification of abnormal anatomic substrate (e.g., hippocampal sclerosis or necrosis), and the association of a defined syndrome with pharmacological failure. In addition, the similarities and outcomes of surgery from patient to patient are predictable both with treatment success and knowledge that removal of

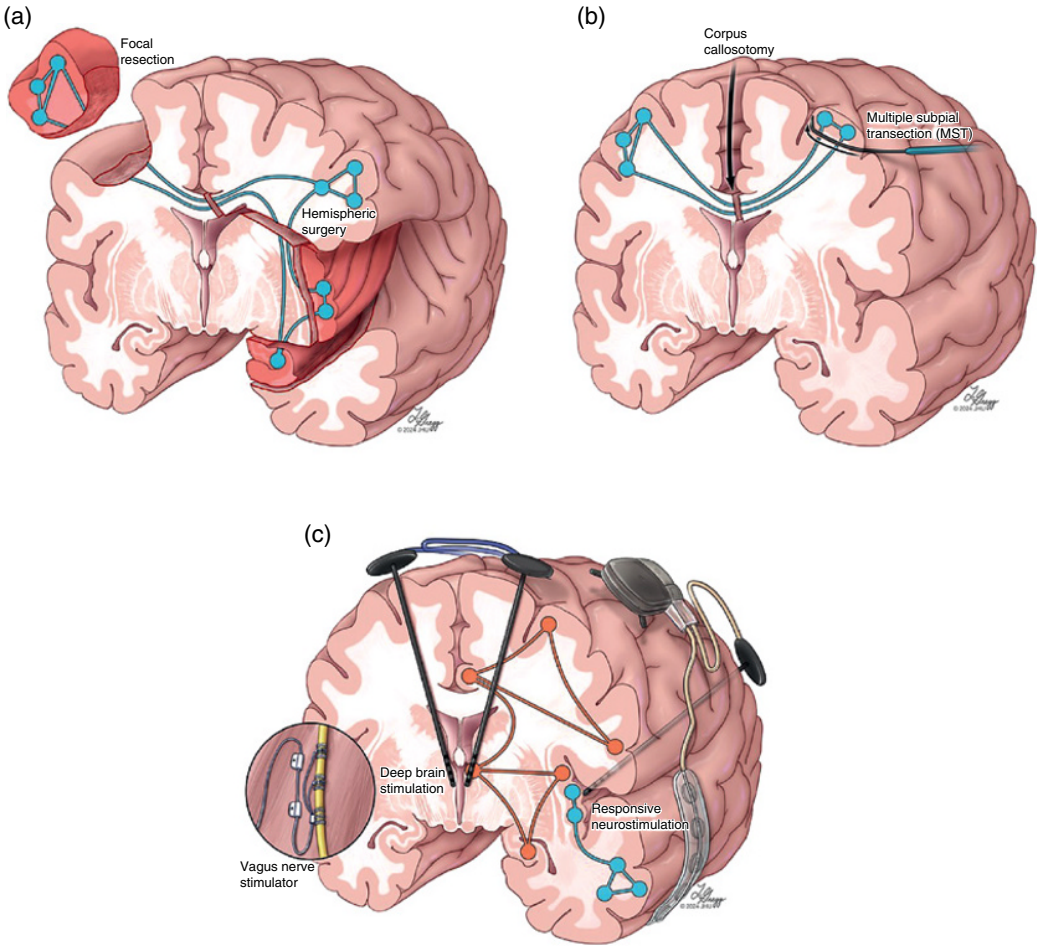


FIGURE 10.9 Representation of the various neurosurgical treatments for epilepsy. (a) Standard resective surgery. This may represent neoplasia, malformation, or epileptogenic zones. (b) Disconnective surgery to prevent the spread of epileptic activity from one area of the brain to another. (c) Neuromodulation, which may include vagal nerve stimulation, trigeminal nerve stimulation, deep brain stimulation, and responsive neurostimulation. Reproduced from Niazi et al. (2024)/Frontiers Media S.A./CC BY 4.0.

epileptogenic tissue can be performed without residual functional deficits. They are aimed at removing a specifically identified epileptic focus, used to treat focal seizures and generally considered to be curative with minimal postoperative deficits. Standard resections include removal of the anteromesial portion of the temporal lobe including the amygdala, the hippocampal pes, and most of the hippocampal tail. If the epileptogenic zone is limited to the hippocampus, a selective *amygdalohippocampectomy* may be performed. Even more radical surgical procedures including *hemispherectomy* and *hemispherotomy* may be performed for certain epileptic syndromes. Hemispherotomies have largely replaced hemispherectomies in humans due to less postoperative complications by leaving abnormal cerebral tissue *in situ* but removing its connections to the contralateral hemisphere. These types of surgeries have been performed in humans since the mid-20th century. They are only performed if it can be demonstrated the contralateral cerebral hemisphere can support normal function (relative to the patient at that time). A *tailored* resection may be performed if the epileptogenic zone can be specifically identified, usually through direct EEG recordings of brain tissue during surgery. These *lesionectomies* are made possible by the

identification of discrete epileptogenic areas through functional imaging such as fMRI, PET, and MEG. The specificity of identifying tissue to be excised can be enhanced with SPECT or apparent diffusion color map imaging and electrodiagnostic information, especially when superimposed over imaging modalities having greater anatomic resolution (Figure 10.10) (i.e., MRI).

With *disconnection* surgery, the surgery is performed to prevent the propagation of epileptic activity from one area of the brain to the other. These procedures are directed at treating generalized seizures, when a specific epileptogenic focus cannot be identified or when the identified focus resides in a critical area of the brain (an *eloquent* area such as speech, motor, or sensory areas) and surgery in that area would result in unacceptable postoperative deficits. Since disconnection surgery does not remove the specific epileptic substrate (i.e. not aiming for a *cure*) it is considered palliative. The most common *disconnection* surgery performed is the *corpus callosotomy*, whereby the corpus callosum, anterior commissure, hippocampal commissure, and fornix are disconnected. This method was previously used for seriously debilitating generalized seizures in humans, although it came with significant side effects. Modifications of the technique now typically only include an anterior two-thirds callosotomy, which is one of the most effective treatments for the prevention of tonic and atonic *drop attacks* in people (here we see the strong association between a syndromic classification and a treatment). However, callosotomy is usually only performed once VNS has failed, as it (VNS) can be as effective as callosotomy in preventing the attacks (Rosenfeld and Roberts, 2009). *Ablative surgery* using highly focused radiation therapy (gamma knife surgery) has been reported as effective as open resective surgery for the treatment of MTLE in people; however, healing from cerebral edema may take months, and the benefits of the procedure (reduction in epileptic seizures) may take over a year to occur (Barbaro *et al.*, 2009; Chang *et al.*, 2010). Prior to its use in humans, a significant reduction in seizure frequency was observed in experimental animal models. In contrast to humans, however, experimental animals did not suffer from severe radiation necrosis or neuronal cell loss (Liščák *et al.*, 2002). Considering the potential lack of side effects in experimental animals, we may infer this technique may be more useful in veterinary patients compared to human patients. It is important to consider, what may not work for a human may work for a companion animal—and vice versa.

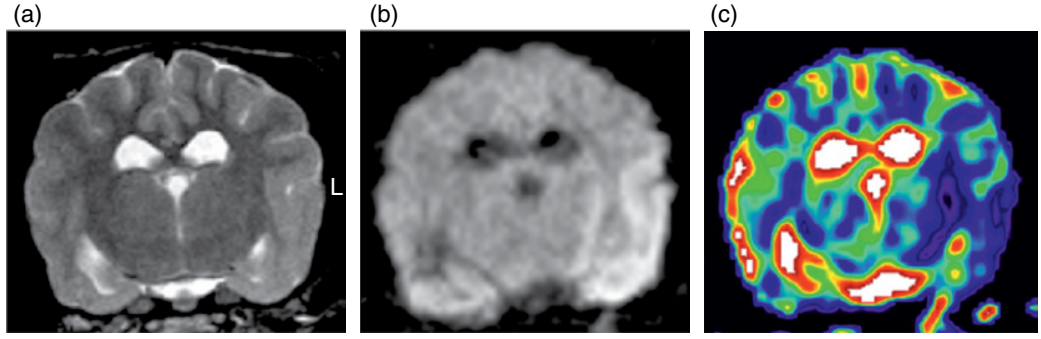


FIGURE 10.10 (a) Standard T2-weighted, transverse image through the midbrain of a 6-year-old, male, mixed breed dog, diagnosed with idiopathic epilepsy, immediately after a focal epileptic seizure which secondarily generalized. There is a focal but diffuse hyperintense signal change in the left temporal lobe but no obvious structural abnormalities of the brain. (b) Same area on diffusion-weighted imaging (DWI) showing more obvious hyperintense signal change in the mesial and lateral temporal lobe on the left. (c) Apparent diffusion coefficient color map showing low values (purple to black) in the same general region as (b). The hyperintense signal in (b) is representative of altered diffusion of water at a microscopic level in an area corresponding to the epileptogenic zone (cytotoxic edema generated at the time of the seizure). Source: Hasegawa D. (2016) / Elsevier / CC BY-NC-ND 4.0.

RESECTION SURGERY

Resective surgeries have been experimentally performed in dogs, and the morbidity/mortality has been recorded as transient and mild neurological deficits to death (Sorjonen *et al*., 1991; Asada *et al*., 2021). These experimental surgeries were carried out to evaluate the surgical landmarks, tissue manipulation techniques, and postsurgical outcome with the idea of being able to remove deep cortical brain tumors in dogs or for the purpose of specific removal of ventrolateral temporal lobe structures. In the Asada study, 3/8 normal beagle dogs died following or during surgery (euthanized). Two of the dogs were euthanized due to severe hemorrhage from the middle cerebral artery which lies in close proximity to the mesial temporal structures, which were being removed. Another dog went into cardiac arrest during closure and was euthanized after unsuccessful resuscitation. No cause could be found for the arrest on postmortem examination. From the study, it was concluded there is a fairly steep learning curve and the approach to the mesial temporal structures in dogs is limited by their anatomy (as opposed to humans whose temporal lobe is located dorsal to the zygomatic arch with very thin muscle coverage—compared to dogs). The last two dogs to be operated on did not suffer any operative or postoperative complications and no postoperative neurological deficits or behavioral abnormalities. The approach in cats may carry a more favorable prognosis given their reduced mass of overlying temporal muscle (Zilli *et al*., 2021). Cats may also be more likely to benefit from certain resective surgeries based on a syndromic diagnosis of TLE, due to limbic encephalitis (autoimmune encephalitis), hippocampal sclerosis/necrosis (through primary disease of the hippocampus or due to chronic epileptic seizures), and cats with *familial spontaneous epilepsy*. Similar to humans, with TLE, the symptomatic zone (and therefore *cure*) may be located within the structures to be removed (partial cortico-hippocampectomy). A strong association with drug-resistant epilepsy exists for many humans with TLE and surgical treatment has become a treatment of choice with success rates (i.e., seizure freedom defined as an inter-seizure interval greater than 3 times the longest pre-intervention interval or no seizures greater than 12 months—whichever is greater) reported to be between 69 and 90% when the seizures originate from the hippocampus (Salanova *et al*., 2002; Muzumdar *et al*., 2016). Changes in the cellular cytoarchitecture, whether due to primary disease or as a consequence of epileptic activity, may result in propagation of epileptic seizures and/or predispose patients to antiepileptic drug resistance.

Hasegawa reported on a case where focal cortical resection was successfully used to treat a cat with drug-resistant epilepsy (Hasegawa *et al*., 2021b). Of equal importance to the surgical technique and outcome were the diagnostic tests used to identify the epileptogenic zone. These consisted of:

- Scalp EEG
- MRI with volume rendering for hippocampal volumetry
- Isotropic diffusion-weighted imaging with colored apparent diffusion coefficient maps
- Long-term intracranial EEG monitoring with synchronous video-EEG

The suspected epileptogenic zone was identified as an atrophied portion of the right temporo-occipital cortex and right hippocampus. A two-step surgery was planned. Prior to surgery the cat was being treated with phenobarbital, diazepam, zonisamide, and gabapentin and the cat was having on average 2–3 epileptic seizures a month which has been progressively worsening (from a "control" level of 0.3–0.7/month). The initial surgery consisted of a focal cortical resection of the identified epileptogenic zone (the right-sided, atrophied portion of the temporo-occipital cortex). The cat was seizure-free following the first surgery for 2 months (now being treated with only phenobarbital and diazepam). After the seizures returned, a right hippocampectomy with

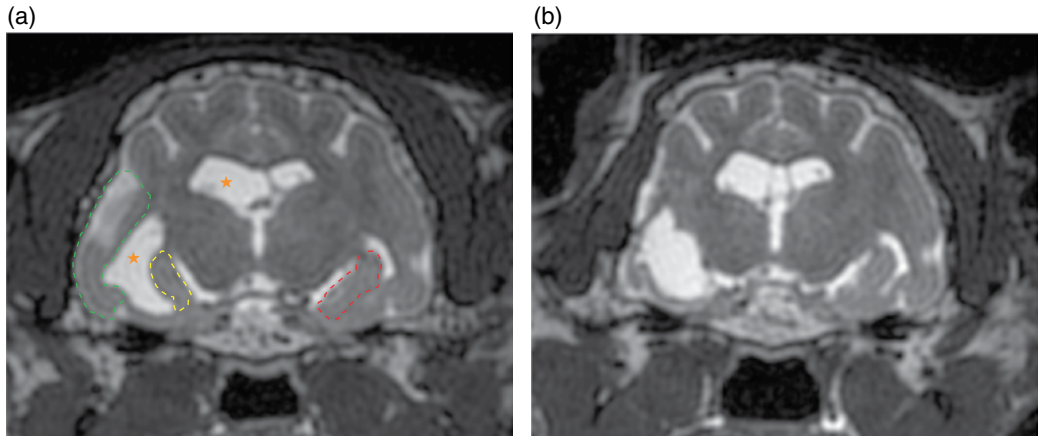


FIGURE 10.11 Pre- and postoperative images of hippocampectomy in a cat. (a) Preoperative T2-weighted, transverse MRI at the level of the medial geniculate nucleus of a 12-year-old, male, neutered, domestic shorthair cat with presumed congenital atrophy of the right temporo-occipital cortex and hippocampus. Green dashed line is the approximate temporal lobe on the right. Yellow dashed line is the approximate right hippocampus. Red dashed line is the approximate left hippocampus. Note there is dilation of the right lateral ventricle (stars). (b) Postoperative T2-weighted, transverse MRI at the approximate same level of (a). The right hippocampus and temporal lobe have been resected. Following surgery, the cat's seizure frequency was reduced from 2–3 to <0.3/month. With thanks to Dr. Daisuke Hasegawa, Department of Clinical Veterinary Medicine, Nippon Veterinary and Life Science University, Tokyo, Japan. For a more detailed explanation, intraoperative images and video, see Hasegawa *et al.* (2021b).

additional cortical resection was performed (Figure 10.11). Following the second surgery, the cat was seizure-free for 3 months. The seizure frequency following the second surgery was a >85% reduction compared to presurgical frequency.

Being able to offer this treatment for cats and dogs, who may suffer a similar epileptic syndrome is a potential alternative to euthanasia.

DISCONNECTION SURGERY

Corpus callosotomy (CC) has been performed experimentally in many species. It is the most common form of disconnection surgery for humans with drug-resistant epilepsy (DRE), although considered to be a palliative procedure. It may be used for generalized seizures (tonic–clonic, atonic, myoclonic, and absence), inhibition of secondary generalization of focal seizures, and where a specific focus cannot be identified or multiple foci or bilateral foci are present. There is a paucity of data regarding the use of the technique in dogs or cats. The described technique appears safe with limited long-term complications in *normal* dogs (Bagley *et al.*, 1995). In a small group of dogs where CC was performed for the treatment of drug-resistant epilepsy, the mortality rate was 33% (6/6 survived surgery) (Hasegawa *et al.*, 2022a). Two dogs in the group died or were euthanized for surgically unrelated causes. The efficacy of corpus callosotomy to prevent the propagation of generalized seizures has been demonstrated in three Cavalier King Charles Spaniels with DRE (Asada *et al.*, 2021). In this case series, all dogs were suffering from significant daily focal, focal to generalized tonic–clonic seizures (15–37/day), and in one dog, daily instances of SE lasting up to 40 m. One dog died 10 h after surgery but the other two dogs had their seizures significantly reduced. One of the dogs had its seizure frequency reduced by 88% at 12 months post-op and the remaining seizures were focal, mild, and lasted only a few seconds each. The remaining dog that

survived (the one with daily SE and up to 37 seizures a day was 100% seizure-free at 12 months after surgery. Both dogs and their owners experienced significant quality-of-life improvements. In all three cases, surgery was considered a "last resort." A corpus callosotomy was chosen due to the difficulty in finding an epileptogenic focus. A cat with DRE was successfully treated with a partial corpus callosotomy (Hasegawa *et al*., 2021a). In this case report, intraoperative ECoG was used prior to transection to help determine if a corpus callosotomy would be helpful (presence of bilaterally, synchronized spike-containing burst suppression). The goal of the surgery was a complete CC, however, due to complications, the genu of the corpus callosum was preserved (Figure 10.12). While the cat did experience some persistent postoperative (acceptable to quality-of-life) neurological deficits (occasional periods of somnolence, bilateral absent menace, ataxia with decreased postural responses) for up to 1 year after surgery, seizure frequency was markedly reduced (76% reduction) and generalized, tonic–clonic seizures stopped altogether. In humans undergoing the CC procedure, it is generally regarded that a complete CC gives the best seizure control but also results in greater complications. Compared to VNS, CC provides better seizure control in humans (although with greater complications) (Nei *et al*., 2006). In the limited veterinary reports (Bagley *et al*., 1995; Asada *et al*., 2021; Hasegawa *et al*., 2021a), it appears difficult to attain a complete corpus callosotomy, with the genu of the corpus callosum remaining intact, despite efforts to completely severe the connection.

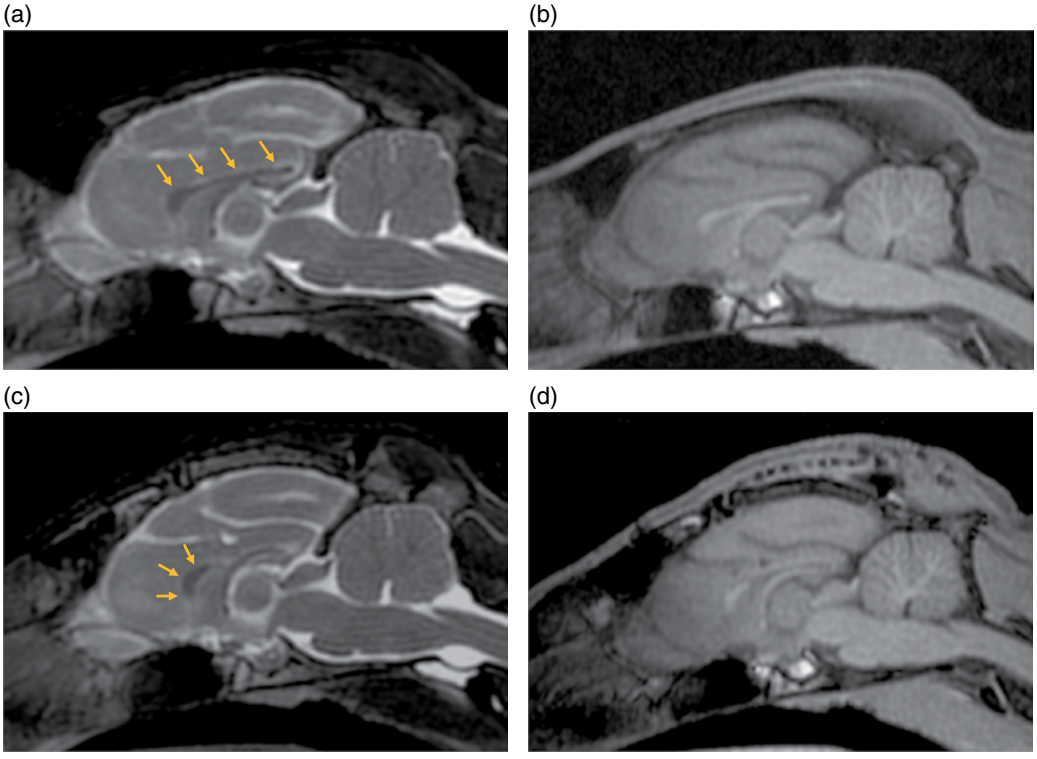


FIGURE 10.12 Partial corpus callosotomy in a cat. T2-weighted (a) and T1-weighted (b) mid-sagittal images through the brain of an 8-month-old, male, domestic shorthair cat showing the presurgical corpus callosum (arrows). 12 months, postoperative T2-weighted (c) and T1-weighted (d) mid-sagittal images in the same plane as (a) and (b) showing the remnant (genu) of the corpus callosum (arrows). With thanks to Dr. Daisuke Hasegawa, Laboratory of Veterinary Clinical Neurology Nippon Veterinary and Life Science University, Tokyo, Japan.

Multiple subpial transection (MST) refers to *transection* of cortical gray matter within an epileptogenic zone that resides within an eloquent area(s) of the brain. Resection of these areas would likely result in significant neurological deficits (areas such as language, motor, and sensory cortices) (Morrell *et al.*, 1989). MST is a disconnection surgery and is therefore considered to be palliative. The basic principle relies on the notion the spread of epileptic activity from one area of the brain to the other is via horizontal fibers in the cortex. The columnar organizational theory of the brain implies vertical fibers are necessary for functionality. By severing horizontal fibers, the functionality of the cortex is preserved while disrupting the horizontal spread of epileptic activity and preserving the blood supply to those areas. Areas of the cortex greater than 5 mm are capable of supporting paroxysmal discharges, therefore transection of horizontal fibers occurs every 5 mm in the defined epileptogenic zone (Figures 10.9b and 10.13) (Kaufmann *et al.*, 1996; Krishnaiah *et al.*, 2018). In humans, complications are generally mild and transient, while seizure control is considered better than neurostimulation (Hasegawa *et al.*, 2022a; Ma *et al.*, 2024). MST surgery was performed in two dogs with a diagnosis of idiopathic epilepsy, following ECoG of the fronto-parietal lobe which resulted in near complete cessation of interictal epileptic discharges (Hasegawa *et al.*, 2022a). With a follow-up of 7 years after surgery, no neurological abnormalities or seizures were recorded. Clearly, mapping out the epileptic zone is critical to the success of the procedure. Discovering eloquent zones of a dog or cat's cerebral cortex would be challenging since most mapping in humans is done during *awake* brain surgery where the patient's responses to questions, visual, auditory, and cognitive tests can be recorded. However, for our patients, as demonstrated in the above example, being able to map out the epileptogenic zone within the cortex may be enough to provide excellent treatment.

Multiple hippocampal transection (MHT) is a technique that may offer similar benefits to resective surgery with fewer postoperative complications (Abramov *et al.*, 2022). Removal of mesial temporal lobe structures (hippocampus, amygdala, selective temporal lobectomy) usually is followed by a very good prognosis in humans afflicted with TLE, which is the most common form of epilepsy for people. However, the surgical techniques are not without possible complications including postoperative learning, and behavioral or language deficits. Expected postoperative deficits in cats and dogs undergoing resective surgery are highly dependent on the surgical area,

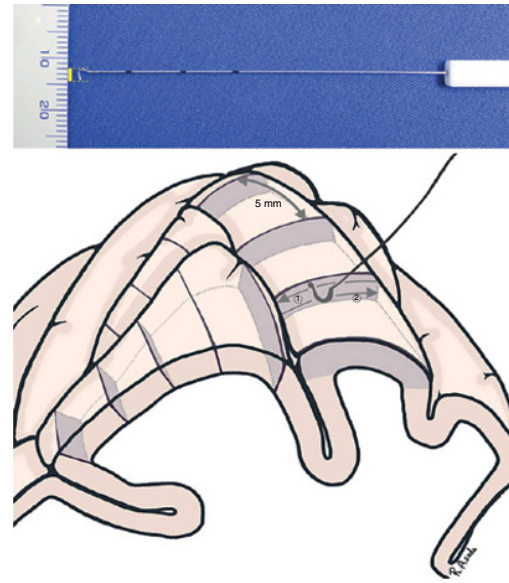


FIGURE 10.13 Diagram of the multiple subpial transection surgical technique. A specific transector (top), and schematic diagram (bottom) of multiple subpial transection (MST). The height of the transector tip (indicated with yellow bar and dot lines; 2.5 mm in this one) is matched with the thickness of the gray matter on MRI. The schematic diagram illustrates the movement of the transector. Hasegawa *et al.*, (2022) / Elsevier / CC BY 4.0 (top). Reproduced from Hasegawa *et al.* (2022a)/Frontiers Media S.A./CC BY 4.0.

however, if we focus on the most common portion of the brain to be resected (temporal lobe, hippocampus, and amygdala) postoperative deficits may include unilateral partial hearing loss (caudal ectosylvian gyrus), loss of learned behaviors, conditional reflex responses, and deficits in motivation, spatial memory, and orienting response (Zilli *et al*., 2021). Iatrogenic damage to adjacent structures may also lead to homonymous hemianopia (loss of visual field on the same side – e.g., right nasal and left temporal fields) due to inadvertent damage to the ipsilateral optic radiations, hemorrhage and cognitive decline. Microsurgical techniques combined with minimally invasive surgery will greatly reduce the possibility of both intentional deficits (those we know will happen) and unintentional or iatrogenic deficits.

Developed in 2006, the technique is used to sever longitudinal connections (in the anterior–posterior direction of the length of the hippocampus—or rostral—caudal in a veterinary patient), which are thought to mediate the propagation of seizures. At the same time, circular fibers, which course perpendicular to the long axis of the hippocampus, are preserved. These input/output fibers to the hippocampus are necessary for memory function and their preservation lessens the chance of postoperative complications. With a goal of preserving, postoperative verbal memory, the original report showed that 14/17 patients (82%) were seizure-free, 1 year post-op, while the remaining patients had rare seizures (2/3) and the last patient was significantly improved (Shimizu *et al*., 2006). The improved seizure control also came with preservation of function following surgery in 7/8 individuals who underwent neuropsychometric testing before and after surgery. The remaining individual was initially worse following surgery but regained function by 6 months post-operation. Up to 75% of patients treated with this method were reported to be seizure-free without the typical damage to eloquent areas of the brain associated with resection (Patil and Andrews, 2013). Our ability to measure postoperative deficits in veterinary patients may be limited to assessing behavior, cognition, proprioceptive, and cranial nerve deficits, however, any chance to have a similar outcome without postoperative complications should be pursued.

Surgery to treat epileptic seizures through the resection of epileptogenic tissue may be thought of as a great leap forward in veterinary medicine. In the first edition of this book, I predicted it may be a threshold we would not cross for several decades. Happily, we have crossed that threshold thanks to some very curious and talented veterinary neurosurgeons. Veterinarians are continually pushing the envelope in areas of primary investigation. The development of surgical techniques and long-term demonstrated success in the removal of canine and feline brain tumors and malformations will help bridge the knowing–doing gap. Recognizing hippocampal sclerosis is often associated with MTLE in humans and having access to high-field MRI, veterinarians are starting to integrate what is known in human medicine with applications to veterinary medicine (Milne *et al*., 2013). The use of advanced imaging to diagnose hippocampal sclerosis in dogs and cats combined with advanced EEG recordings and experienced veterinary brain surgeons will ultimately allow us to bridge the gap (Davis *et al*., 2011; Long *et al*., 2013; Pakozdy *et al*., 2014). Diagnostic and treatment algorithms have been proposed for both feline and canine epilepsy surgery (Hasegawa *et al*., 2022a, 2022b). While there are numerous limitations to the practical use of surgery in the treatment of epilepsy in companion animals, the identification of the epileptogenic zone might be the most difficult to overcome. A survey in 2023 of veterinary neurologists reported that fewer than 50% used EEG in clinical or research settings (Luca *et al*., 2023). Predictably, the use of subcutaneous, ECoG, and deep recording of brain electrical activity is even more infrequent. However, as advanced diagnostics become more accessible, new diagnostics are employed, common human diagnostics are modified for use in veterinary medicine, and new treatment modalities are investigated, surgery for epileptic seizures may become a reasonable treatment option. The cost associated with the procedures is likely one of the easiest variables to overcome, especially with the increasing popularity of insurance companies allowing pet owners to carry less of the financial burden. Perhaps an even greater hurdle to overcome is the willingness of veterinary neurosurgeons to try new techniques. Certainly, a significant amount of

research into the practicality and efficacy of this modality is needed. As clinicians, we must try to educate pet owners as to the necessity of a certain degree of surgical-associated morbidity in order to provide treatment. Above all, we must also remember the treatment, no matter how advanced, must not contribute to an even lesser quality-of-life for the patient.

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Glossary of Descriptive Terminology for Veterinary Ictal Semiology

APPENDIX 1

General Terms 468
Descriptive Terms of Epileptic Seizures 468
Motor 468
Nonmotor 470
Autonomic Events 471
Somatotopic Modifiers 471
Modifiers and Descriptors of Seizure Timing 472
Duration 472
Severity 472
Prodrome 473
Postictal Phenomenon 473

Modified from the ILAE Task Force on Classification and Terminology (Blume et al., 2001) with permission, John Wiley & Sons, Inc. Additional modifications based on International Veterinary Epilepsy Task Force consensus report on epilepsy definition, classification and terminology in companion animals (2015).

The International League Against Epilepsy published the Glossary of Descriptive Terminology for Ictal Semiology in 2001 to provide a standard terminology for healthcare workers in order to create a common language used between clinicians, researchers, and educators. Because of a wide number of parallels between epileptic seizures recognized in humans, dogs, and cats, the framework has been preserved, with the addition of certain veterinary-specific terms and the subtraction of human elements, which at this time are not recognized in veterinary medicine. It is the author's belief that as veterinarians, it is important to at least be aware of similar semiology in humans—as identification of that semiology may lead to better classification of epileptic syndromes among veterinary patients (e.g., orofacial automatisms associated with limbic encephalitis in humans and cats). In 2015, the International Veterinary Epilepsy Task Force (IVETF) published a consensus report on the definition, classification, and terminology of epilepsy. For an exact copy of the report, see: Berendt, M., Farquhar, R.G., Mandigers, P.J., Pakozdy, A., Bhatti, S.F., De Risio, L., Fischer, A., Long, S., Matiasek, K., Muñana, K., Patterson, E.E., Penderis, J., Platt, S., Podell, M., Potschka, H., Pumarola, M.B., Rusbridge, C., Stein, V.M., Tipold, A., and Volk, H.A. 2015. International Veterinary Epilepsy Task Force Consensus Report on Epilepsy Definition, Classification, and Terminology in Companion Animals. *BMC Veterinary Research*. 11:182.

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GENERAL TERMS

1. Semiology: The study of signs and symptoms.
2. Epileptic seizure: The manifestation(s) of excessive and/or hypersynchronous (epileptic) activity of brain neurons, which is usually self-limiting. This results in a transient manifestation, which may appear as convulsions or focal motor, autonomic, or behavioral signs.
3. Ictus: The epileptic seizure itself as determined clinically or electrophysiologically [i.e., electroencephalography (EEG)].
4. Epilepsy:
   a. Epileptic disorder: A chronic neurologic condition characterized by recurrent epileptic seizures from an intracranial origin. In practice, this means at least two unprovoked epileptic seizures >24 h apart.
   b. Epilepsies: Because there are many disorders causing epilepsy, they are referred to as those conditions involving chronic recurrent epileptic seizures considered to be epileptic disorders.
5. Focal epileptic seizure (aka partial): A seizure whose initial semiology indicates, or is consistent with, initial activation of only part of one cerebral hemisphere (i.e., the seizure has a *focal* origin within the brain). Ictal onset is consistent from one seizure to the next and often propagates to the contralateral hemisphere. The patient may maintain an outward appearance of awareness (formerly simple partial or focal seizure) or be unaware (formerly complex partial or focal seizure).
6. Generalized epileptic seizure: A seizure whose initial semiology indicates involvement of both cerebral hemispheres.
7. Convulsion (also "fit"): A lay term. Episodes of excessive, abnormal muscle contractions, usually bilateral, which may be sustained or interrupted. Not necessarily a seizure or an epileptic seizure. In many contexts, it is implied to be an epileptic seizure.

DESCRIPTIVE TERMS OF EPILEPTIC SEIZURES

MOTOR

The musculature of the patient is involved to create either an increase (positive) or decrease (negative) in muscle contraction, resulting in a motor event.

The following terms are adjectives used to modify "motor seizure" or "seizure" (e.g., "tonic motor seizure or dystonic seizure"):

- **Elementary motor:** A single type of contraction of a muscle or group of muscles that is usually stereotyped.
  - Tonic: A sustained increase in muscle contraction, which may last a few seconds to minutes.
    - Epileptic spasm (noun): A sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles, which is usually more sustained than a myoclonic movement but not so sustained as a tonic seizure (i.e., ~1 sec). Limited forms may occur: facial contraction or head bobbing (see Video 31).
    - Postural: A posture which may be bilaterally symmetric or asymmetric is present.
      a. Versive: A sustained, forced conjugate (i.e., joined) eye, head, and/or truncal rotation or lateral deviation from the midline (see Video 14).

b. Dystonic: Sustained contractions of both agonist and antagonist muscles, producing athetoid (i.e., slow, involuntary, writhing movements) or twisting movements, which, when prolonged, may produce abnormal postures.

- Myoclonic: Sudden, brief (<100 msec) involuntary single or multiple contraction(s) of muscle(s) or muscle groups of variable topography (axial, proximal limb, distal limb, and facial). Appears "shock-like." (see Videos 12, 13, 15–17, 36, 40, 43, and 45).
  - Negative myoclonic: Interruption of tonic muscular activity for <500 msec without evidence of preceding myoclonia.
  - Clonic: Myoclonus, which is regularly repetitive, involving the same muscle groups, at a frequency of ~2–3 cycles/sec and is prolonged (aka rhythmic myoclonus).

    a. Jacksonian march (noun): A traditional term used to describe a focal seizure, which spreads from a distal aspect of the body (i.e., a limb) toward the ipsilateral face. It is a representation of a seizure spreading (or "marching") from one area of the brain to another.

- Tonic–clonic: A sequence consisting of a tonic phase (sustained contraction) followed by a clonic phase (myoclonus or repetitive contraction/relaxation). Variants such as clonic–tonic–clonic may be seen.
  - Generalized tonic–clonic seizure (aka bilateral tonic–clonic seizure): Formerly known as a "grand mal" seizure. Bilateral symmetric tonic contraction and then bilateral clonic contractions of somatic muscles, usually associated with autonomic phenomena (e.g., urination/defecation, ptyalism) (see Videos 1–4).
- Atonic: Sudden loss or attenuation of muscle tone without a preceding myoclonic or tonic event lasting 1–2 sec, involving the head, trunk, jaw, or limb musculature (see Videos 5 and 36).
- Astatic (also known as "drop attack"): Loss of erect posture resulting from an atonic, myoclonic, or tonic mechanism (see Videos 6 and 41).
- Synchronous/asynchronous: Motor events which occur at the same time at the same rate in sets of body parts (synchronous) or not at the same time or rate (asynchronous).

- **Automatism**: Tends to be a coordinated, repetitive (i.e., stereotypical) motor activity usually occurring when cognition is impaired. They often resemble a voluntary movement such as the extension of a limb or the continuation of a preictal movement but abnormally and involuntarily.
  - Oroalimentary: Lip smacking (aka "chewing gum fits"), chewing, excessive licking, bruxism, or swallowing (see Videos 8 and 16–18).
  - Mimetic: Facial expression suggesting an emotional state, such as fear, panic, or aggression (see Videos 11 and 12).
  - Hyperkinetic: Involves mainly proximal limb or axial muscles producing irregular sequential ballistic movements, such as pedaling, pelvic thrusting, thrashing, whole-body sway, or rocking movement. Aimless, back-and-forth pacing, circling, or running (see Video 33).
  - Hypokinetic: A reduction in the amplitude and/or rate or cessation of ongoing motor activity.
  - Dyspraxic: Inability to perform learned movements or tasks spontaneously or on command despite seemingly intact relevant motor and sensory systems and adequate comprehension and cooperation (may appear "confused").

- Vocal: Single or repetitive vocal utterances, such as growling, mewing, meowing, barking, grunting, groaning, whining, or crying (see Video 39).
- Spontaneous: A stereotypical behavior involving only the patient virtually independent of surrounding environmental influences.
- Interactive: A behavior, which is not stereotypical, involves the patient and others and is influenced by the environment.

NONMOTOR

- **Aura**: Typically referred to as a "warning" of an impending seizure, although considered the beginning of the ictal event. If they occur alone, they are considered a sensory seizure. Because the term originates from human medicine and is defined as a forewarning of a motor seizure via subjective sensory phenomena, its use is not recommended in veterinary medicine by the IVETF. Rather, any signs preceding an epileptic seizure (the actual onset of the ictus), recognized by a pet owner, should be referred to as a "focal" seizure. However, once again, we refer to the semiology as a reference for the possibility of recognition of any associated similarities in veterinary patients. The author has attempted to apply what he "interprets" as associated semiology to the descriptive terms.
- **Sensory**: A behavior not caused by appropriate stimuli in the external world. Modifies "seizure" or "aura."
  - Elementary: A single, unformed phenomenon involving one primary sensory modality (e.g., somatosensory, visual, auditory, olfactory, gustatory, epigastric, or cephalic).
    - Somatosensory: Tingling, numbness, electric shock sensation, pain, sense of movement, or desire to move. The dog or cat may excessively lick a body part in a stereotypic manner, rub its face on the carpet, cry out for no apparent reason, stumble or fall without cause, or pace or run frantically (see Video 42).
    - Visual: Flashing or flickering lights, spots, simple patterns, scotomata, or amaurosis. The dog or cat may bite at objects not present (i.e., "fly-biting"), look at objects not present, growl or hiss at nothing, or appear to be "staring into space" (see Videos 7 and 9).
    - Auditory: The patient may cock its head as if "listening"; whip around to look at something not there; act scared, frantic, or panicked; hide; or become withdrawn (see Video 10).
    - Olfactory: Odor, usually disagreeable. The patient may sniff the air incessantly, cower, avoid certain areas, or make unusual facial expressions (e.g., "crinkle" the nose).
    - Gustatory: Taste sensations. Typically disagreeable, which may lead to lip smacking, chewing gum fits, excessive licking, excessive swallowing, etc. (see Video 8).
    - Epigastric: Abdominal discomfort including nausea, tightness, malaise, pain, and hunger; sensation may rise to throat. Some phenomena may reflect ictal autonomic dysfunction. Patient may vomit, regurgitate, eructate excessively, foam at the mouth, or exhibit excessive "gulping," etc. (see Video 37.
    - Cephalic: Sensation in the head such as headache. The patient may hold its head and neck in a "neutral" position, look out of the corners of its eyes (i.e., "guilty" look), or seem reluctant to lie down. May mimic neck pain (see Videos 25 and 26).
  - Experiential: Emotional or composite perceptual phenomena, including illusory or hallucinatory events; these may appear alone or in combination. These may be difficult to distinguish

in animals, as most accounts of the "feeling" are made through the verbal description by a human.

  - Affective (i.e., emotional): Components include fear, depression, joy, and aggression. The dog or cat may seem excessively friendly, aggressive toward individuals or other pets for no apparent reason, reclusive, anxious, or panicked (see Video 11 and 12).
  - Mnemonic: Components which reflect ictal dysmnesia (i.e., lack of learned retention or an impairment of memory), such as feelings of unfamiliarity (*jamais vu*) toward an individual or another pet. The dog or cat may seem scared, confused or aggressive toward an individual or other pet with no provocation (see Videos 11 and 12).

- **Dyscognitive**: Events in which a disturbance of cognition is the predominant or most apparent feature. In dogs and cats, this may appear as a patient who suddenly stops what they are doing and "stares into space." They typically do not respond to external cues in the environment, such as calling their name. Occasionally referred to as a "behavioral arrest."

Components of cognition include (but may be difficult to recognize in pets):

- **Perception**: Symbolic conception of sensory information. The appropriate reaction to environmental cues.
- **Attention**: Appropriate recognition of environmental cues or the environment in general.
- **Emotion**: Appropriate emotional significance of a perception or to an individual or another pet.
- **Memory**: Ability to recall learned tasks. In pets, this typically means "on cue." For instance, a dog who is asked "to sit."
- **Executive function**: The ability to analyze an environmental situation and react appropriately. Granted, our pets tend to lack this often; however, if the patterns of behavior are out of the "norm" for a particular patient, they may be labeled as such.

AUTONOMIC EVENTS

- **Autonomic seizure**: An objectively documented and distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, vasomotor [collapse (hypotension) or panic (hypertension)], sudomotor (control of sweat glands), and thermoregulatory functions.

SOMATOTOPIC MODIFIERS

- **Laterality**
  - Unilateral: Exclusive or virtually exclusive involvement of one side of the body as a motor, sensory, or autonomic behavior.
    - Hemi: Prefix to other descriptors (e.g., *hemi*-clonic).
  - Generalized (also known as "bilateral"): More than minimal involvement of each side of the body as a motor, sensory, or autonomic behavior. The motor component is further modified as:
    - Asymmetric: A clear distinction in the quantity and/or distribution of behavior on the two sides of the body.
    - Symmetric: Virtually bilateral representation in both sides of the body.

- **Body part**: Refers to the area involved (i.e., arm, leg, face, trunk, and others).
- **Centricity**: Modifier describing the proximity to the body axis.
  - Axial: Involves the trunk, including the neck.
  - Proximal limb: Signifies involvement from the shoulders to carpus and hip to tarsus.
  - Distal limb: Indicates involvement of the paw, metacarpals, metatarsals, and phalanges.

MODIFIERS AND DESCRIPTORS OF SEIZURE TIMING

- **Incidence:** Refers to the number of epileptic seizures within a time period or the number of seizure days per unit of time.
  - Regular and irregular: Consistent (inconsistent) or predictable (unpredictable, chaotic) intervals between such events.
  - Cluster: Incidence of seizures within a given period (usually one or a few days), which exceeds the average incidence over a longer period *for the particular patient*. Clinically, cluster seizures are defined as two or more epileptic seizures within a 24 h period.
  - Provocative factor (aka "stressor"): Transient and sporadic endogenous or exogenous element capable of augmenting seizure incidence in animals with chronic epilepsy and evoking seizures in susceptible individuals without epilepsy. May include, for example, fireworks, trips in the car, etc.
    - Reactive: Occurring in association with transient systemic perturbation such as a metabolic disturbance (e.g., portosystemic shunt) or toxin (e.g., metaldehyde). The seizure is reversible once the cause or disturbance is removed. Synonymous with *provoked* seizure.
    - Reflex: Objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by activity of the animal. Afferent stimuli can be elementary [i.e., unstructured (light flashes, startle, rubbing or petting, a sound)] or elaborate [i.e., structured (a song)]. Activity may be elementary [e.g., motor (a movement)] or elaborate [e.g., cognitive function (performing a learned task)]. See Videos 35 and 38.
- **State dependent**: Occurring exclusively or primarily in the various stages of drowsiness, sleep, or arousal (see Video 1).
- **Catamenial**: Seizures occurring principally or exclusively in any one phase of the female heat (i.e., estrous) cycle.

DURATION

The time between the beginning of the initial seizure manifestations, such as the aura, and the cessation of experienced or observed seizure activity. It does not include the postictal states.

- **Status epilepticus**: A seizure which shows no clinical signs of stopping after a duration encompassing the great majority of seizures of that type in most patients or *recurrent* seizures without interictal resumption of baseline central nervous system function.

SEVERITY

A multicomponent objective assessment of a seizure by observers of the patient. Components primarily of observer assessment include duration, extent of motor involvement, impairment of

cognitive interaction with the environment intraictally, and the maximal number of seizures per unit of time. Assessment may include the length of the postictal affected time period and body temperature. The *scale* of severity is relative to that particular patient and their previous epileptic seizures.

PRODROME

A preictal phenomenon. An objective clinical alteration (e.g., a stereotypical behavior) which indicates the onset of an epileptic seizure but does not form part of it. A prodrome may last hours to days, whereas a focal onset of seizure signs is usually brief, lasting seconds to minutes.

POSTICTAL PHENOMENON

A transient clinical abnormality of the central nervous system function which appears or becomes accentuated when clinical signs of the ictus have ended (e.g., anxiety, polyphagia, polydipsia, "clinginess," hiding behavior, etc.).

- **Lateralizing phenomenon:** Any unilateral postictal dysfunction relating to motor, somatosensory, and/or integrative functions (including visual, auditory, or somatosensory). For example, Todd's paralysis—temporary paralysis following an epileptic seizure.
- **Nonlateralizing:** Behavioral changes such as fear, aggression, polyphagia, anxiety, hiding, clinginess, etc.

The Neurological Exam and Clinical Exam Forms

APPENDIX 2

Mental Status 475
Posture 475
Conscious Proprioception 478
Cranial Nerves 478
Reflex Testing 484
Pain Sensation 487
Lesion Localization 487
Neurological Examination (Blank form) – download on the companion website 491
International Veterinary Epilepsy Task Force Epilepsy Questionnaire (https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0462-1#additional-information) 493
Linear Seizure Log (Blank) – download on the companion website 497
Emergency Treatment of Seizures Algorithm (www.theneurovets.com) 499

MENTAL STATUS

A patient's mental status is best characterized through observation and reaction to external stimuli. Normal mental status implies that the patient is awake and aware of their surroundings. A depressed patient is quiet but responds to stimuli in a normal manner. A demented patient will respond to environmental stimuli, but the response is abnormal. A stuporous patient is unresponsive to normal environmental stimuli but will react to extreme stimuli such as deep pain. A comatose animal is unresponsive to both environmental stimuli and applied noxious stimulation (i.e., deep pain) (Figure A2.1).

POSTURE

An animal with a head turn will usually turn toward the lesion. A *head turn* is characterized by the head remaining level and the nose deviating away from the midline (Figure A2.2b). This usually implies forebrain disease and may be accompanied by circling in the direction of the head turn. A head turn should be differentiated from *torticollis*. Torticollis may result from cervical lesions resulting in the abnormal curving or twisting of the neck (Figure A2.3).

A *head tilt* means one ear is held lower than the other (Figure A2.2a). A head tilt implies vestibular or cerebellar disease. The head tilt is usually toward the side of the lesion (i.e., the down ear on the lesion side). A head tilt is the result of decreased input from the vestibular apparatus to the vestibular nuclei in the brainstem or a lesion of the vestibular nuclei. The vestibular nuclei, by

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(a) (b)



FIGURE A2.1 (a and b) Assessing a dog's and cat's mental status in the exam room. Consider the animal's surroundings and how you would expect them to behave in a strange environment. This dog is stuck in the corner and head pressing. A sign of altered mental status, usually due to forebrain disease. Similarly, this is not typical behavior for a cat in an exam room, where they should either be trying to hide or exploring.

(a) (b)



FIGURE A2.2 (a) Dog with a head tilt. With the exception of paradoxical vestibular syndrome, the "down" ear is usually toward the side of the lesion. Localization is usually vestibular or cerebellar disease. (b) Dog with a head turn. Note deviation of the muzzle to the dog's left. Localization would be left prosencephalon (forebrain).



FIGURE A2.3 A dog with torticollis to the left due to intervertebral disk extrusion. The curve is usually toward the side of the problem.

default, want to extend the muscles of the forearm and neck. When one side loses input (due to a lesion), the other side now has more extension than the lesioned side, which pushes the animal toward the side of the lesion. An exception to the rule is *paradoxical vestibular syndrome*. In this case, the head tilt is away from the lesioned side. Paradoxical vestibular disease results from injury of the flocculonodular lobe of the cerebellum or the caudal cerebellar peduncle. In the case of paradoxical vestibular disease, a small portion of projecting Purkinje neurons from the cerebellum exit the cerebellum directly (bypassing the cerebellar nuclei) via the caudal cerebellar peduncle to synapse directly on the vestibular nuclei on the same side. These neurons exert an inhibitory effect on the vestibular nuclei. Loss of these neurons, via a lesion in the caudal cerebellar peduncle or flocculonodular lobe of the cerebellum, creates an imbalance in the vestibular system whereby the lesioned side has an *excess* of input causing the head to tilt toward the unaffected side. The lesion is typically on the same side as the proprioceptive deficit.

Decerebrate rigidity is characterized by opisthotonus (severe extension of the head and neck) and extension of all limbs. Animals in decerebrate rigidity are usually *not conscious*. This results from a severe brainstem lesion, which functionally separates the forebrain from the brainstem (Figure A2.4).

Decerebellate rigidity is characterized by opisthotonus, extension of the thoracic limbs, extension or flexion of the pelvic limbs (depending on the location of the lesion), and *maintenance of consciousness*. This posture occurs with severe cerebellar lesions (Figure A2.5).

The *Schiff–Sherrington* posture is characterized by extension of the thoracic limbs and paralysis of the pelvic limbs. It results from a severe lesion to the T3–L3 spinal cord segments, which causes a loss of innervation from fibers originating in the lumbar segments and ascending to the



FIGURE A2.4 A cat with decerebrate rigidity. Opisthotonus, extension of all limbs. The cat is comatose. Lesion localization is the mesencephalon.



FIGURE A2.5 A cat with decerebellate rigidity. Opisthotonus, extension of the front limbs and flexion of the pelvic limbs. The cat has normal mentation. Lesion localization is the ... wait for it ... cerebellum.

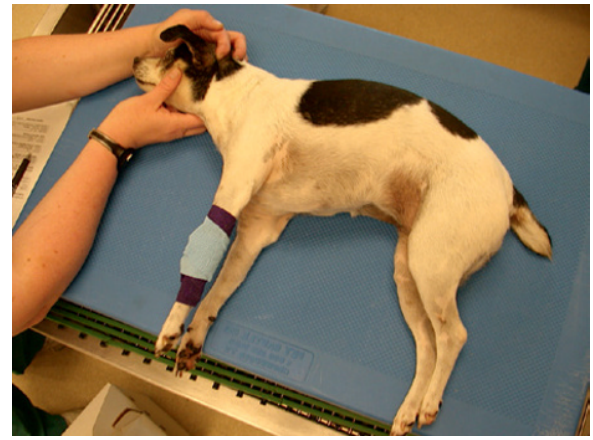


FIGURE A2.6 A dog with Schiff–Sherrington posture. There is extension of the forelimbs and paralysis of the pelvic limbs. The localization is T3–L3. This posture implies a severe lesion. The dog is mentally appropriate, and there is no opisthotonus. This dog suffered from a spinal fracture at T12–T13 (she got better).

cranial thoracic segments, which serve to inhibit the thoracic limb extensor muscles. Consciousness is maintained if a pure spinal lesion exists. Consciousness may be impaired if a forebrain or brainstem lesion exists concurrently (as this lesion is often seen with vehicular trauma) (Figure A2.6).

CONSCIOUS PROPRIOCEPTION

Conscious proprioception is the ability of the animal to recognize the location of certain body parts in space. There is much confusion as to whether or not conscious proprioception refers to a lack of spatial awareness, weakness, or both. This is one of the most sensitive indicators of neurological dysfunction. However, taken by itself, it is not usually localizing. If an animal has conscious proprioceptive deficits, then it has neurological dysfunction. The best test for this function is turning over the paw on its dorsal surface and waiting for the immediate response of the animal correcting the position. It is very important to support the animal's weight so orthopedic or muscle disease does not contribute to a decrease in the response. Hopping, wheelbarrow, hemistance, hemiwalk, placing, and extensor postural reactions are used in cases where the animal is uncooperative for knuckling (cats) or when the response is unclear and needs extra verification. If a proprioceptive deficit is found with knuckling, then there is no need to perform the other postural reaction tests (Figure A2.7).

CRANIAL NERVES

CRANIAL NERVE I: THE OLFACTORY NERVE

The olfactory nerve is unique in the central nervous system as it is the only nerve which continually regenerates (the sensory nerve endings). The function of the olfactory nerve is tested by covering the animal's eyes and bringing a small portion of food to its nostril. An appropriate response such as sniffing or licking the lips should be seen. It is important to use a substance that will not irritate the nasal mucosa, as this would be sensed by the trigeminal nerve endings (CN V). The pathway for olfaction is very diffuse within the brain. *Anosmia*, or a lack of smell, is rarely seen clinically (Figure A2.8).

CRANIAL NERVE II: THE OPTIC NERVE

The optic nerve is evaluated through the pupillary light reflex—direct and consensual—visual following, and the menace response. The menace response should be tested on each eye individually, with the opposite eye covered (Figure A2.9). Visual following can be performed by dropping a

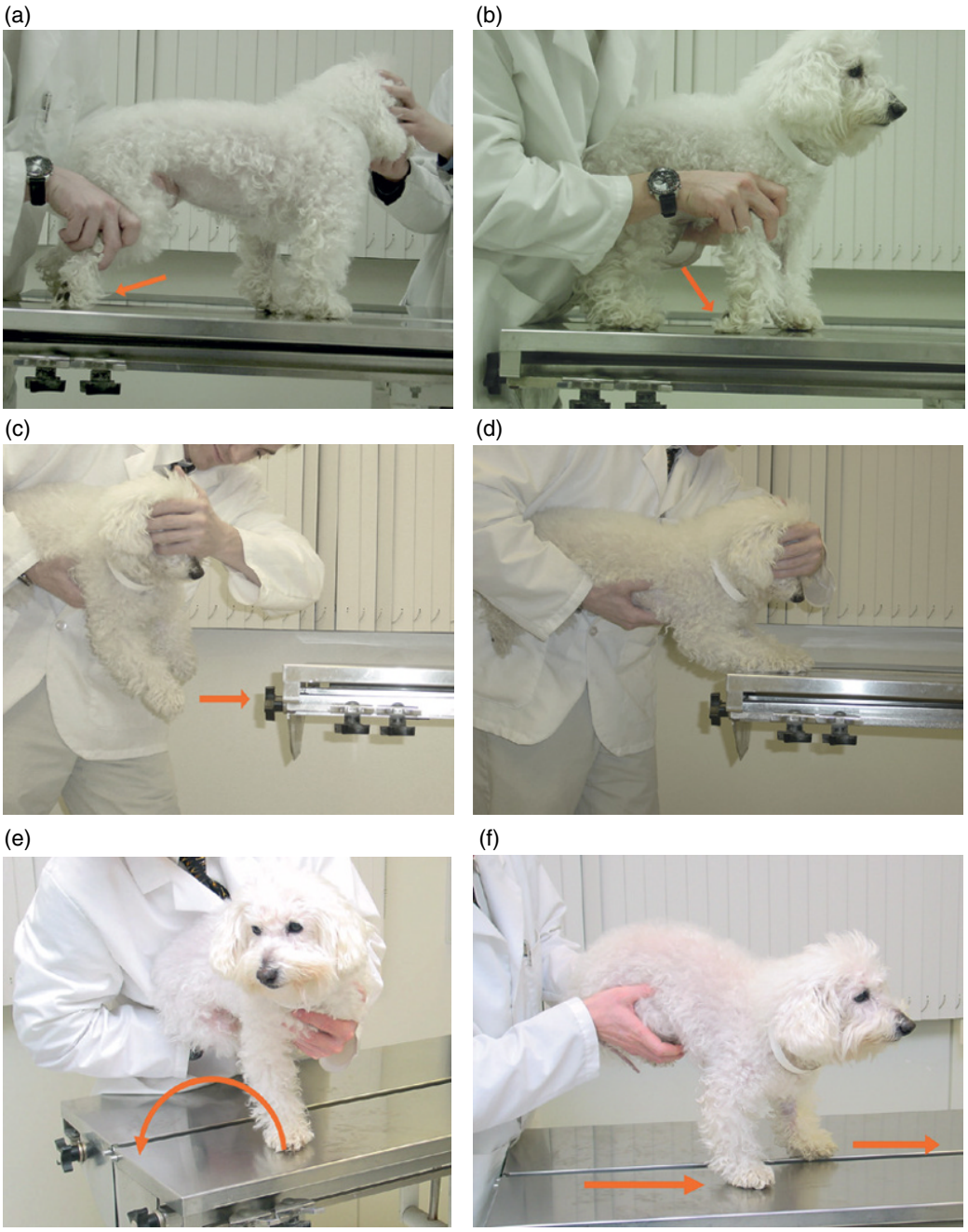


FIGURE A2.7 Various postural reaction testing (not all of them). (a) Placing of the rear paw (arrow). (b) Placing of the front paw (arrow). (c) Placing an animal blindfolded (or not) held near a table (works well for cats). (d) As the animal nears the table, if visual, it will extend its paws to support itself on the edge of the table. If the animal is blinded, as soon as the dorsum of the paw touches the table, it will extend and try to support itself. (e) Hopping. The animal is supported and as it is moved sideways, it will hop on its support limb to keep from falling. (f). Wheelbarrow. The rear limbs are supported, and the animal is moved forward. It will walk in order to prevent faceplanting.



FIGURE A2.8 Testing cranial nerve I (Olfactory) with a delicious treat. The pet's nose should twitch, and it should sniff for the treat when blindfolded. Avoid a noxious stimulus, which could irritate the nasal mucosa (testing CN V).



FIGURE A2.9 Testing cranial nerve II (optic). The menace test. With the nontested eye covered, a slow gesture is made toward the eye. The patient should blink. If it cannot blink (CN VII deficit), the eyeball should retract into the socket (via CN VI).

cotton ball in front of the animal and watching for tracking movements of the eyes and head. The pupils should be equal in size (Figure A2.10). Try to always perform a funduscopic examination. This examination usually requires assistance and will become easier the more it is performed. Assess the size and shape of the optic disk and retinal vessels, as well as the presence of chorioretinitis, hemorrhage, and abnormal or discolored areas of the retina. Discoloration of the lens may be due to the incidental finding of lenticular sclerosis (nuclear sclerosis) or the pathological condition of cataracts. With cataracts, the retina will not be visualized unless the cataract formation is early.

CRANIAL NERVES III, IV, AND VI: THE OCULOMOTOR, TROCHLEAR, AND ABDUCENT NERVES

These nerves function as motor to the extraocular muscles and assist in eyeball movement. In addition, the oculomotor nerve is also responsible for pupillary constriction. They are tested by observing normal eyeball movements, moving the head up and down and side to side to induce a physiologic nystagmus, and looking for strabismus (Figures A2.10 and A2.11). The nuclei making up these nerves and the peripheral portions of the nerve themselves are all in a similar location in the brain and peripheral nervous system. Because cranial nerve III innervates the vast majority of

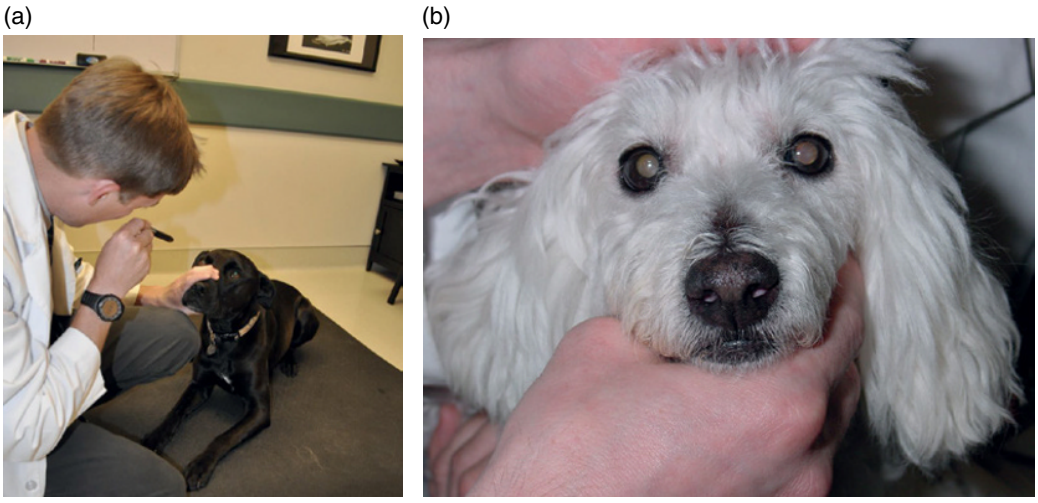


FIGURE A2.10 Checking pupil size. (a) Use a bright light and try to look at both pupils at the same time. (b) Pupils should be bilaterally symmetrical and of appropriate size for the light conditions. You will also asses for any abnormal resting strabismus.

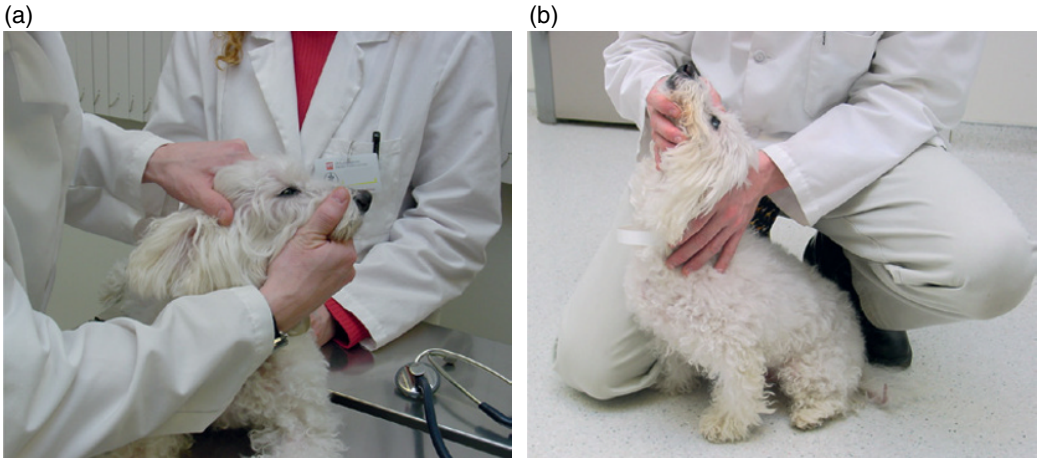


FIGURE A2.11 Testing CN III by moving the head side to side (a) and looking up (b) while assessing the eyeballs for normal physiological nystagmus (a) and the presence of any abnormal positional strabismus (b).

extraocular muscles, a lesion affecting all of the nuclei will usually be manifested clinically as a strabismus affecting cranial nerve III (ventral lateral strabismus).

The trochlear nerve acts to rotate the eyeball medio-ventrally (toward the nose). An abnormality of this nerve exclusively would be unusual. In a cat, it is relatively easy to detect owing to the asymmetrical shape of the pupil. In a dog, however, one would notice an abnormality through funduscopic examination and outward rotation of the retinal vessels.

The abducent nerve functions to retract the eyeball. It can be observed working normally in a patient with an absent palpebral (CN VII deficit) and normal vision. As the menace response is elicited, the patient can see the hand but cannot blink the eye. The eyeball will retract, and the nictitating membrane will passively flash up (Figure A2.12).

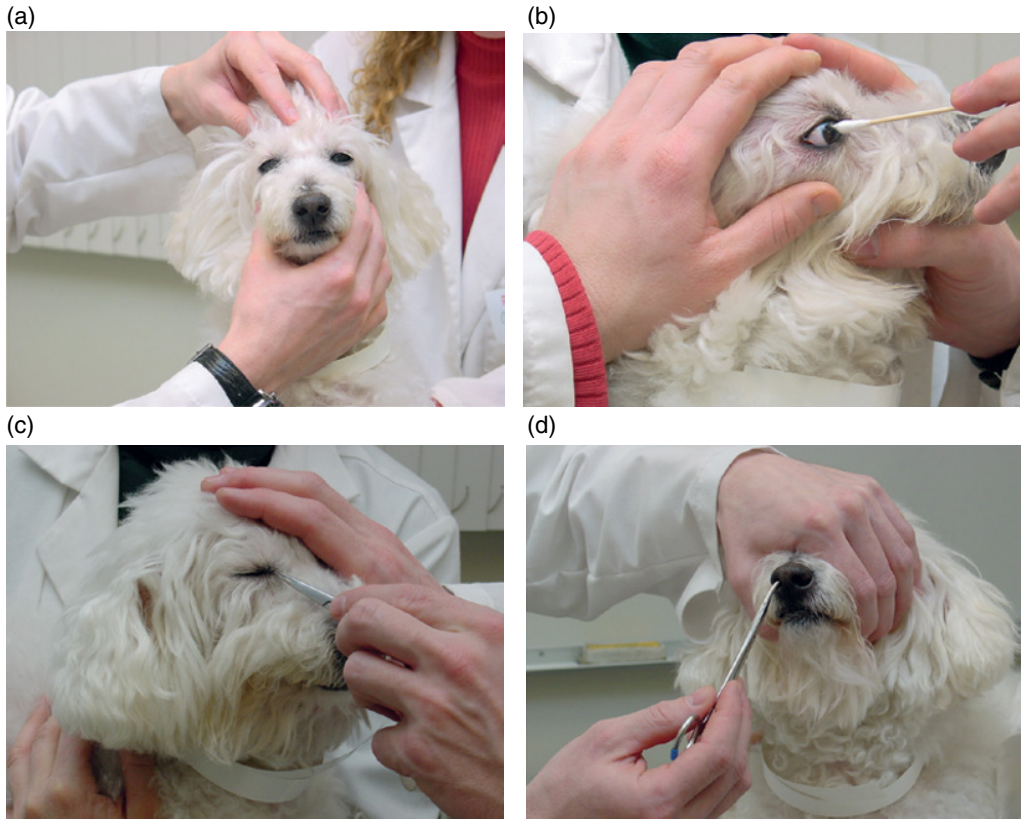


FIGURE A2.12 (a) Palpating the muscles of mastication for appropriate mass and symmetry—evaluating the mandibular branch of CN V. (b) Using the teased fibers of a cotton tip applicator to gently touch the cornea—evaluating the ophthalmic branch of CN V. If you hold the eyelid open you can also evaluate the abducens nerve—CN VI. (c) Touching the medial canthus of the eye also evaluates the ophthalmic branch of CN V. (d) Tickling the inside of the nostril, while the patient is blinded—evaluating the maxillary branch of CN V.

CRANIAL NERVE V: THE TRIGEMINAL NERVE

The trigeminal nerve is divided into three branches. The mandibular branch is the only motor portion of the nerve. It serves the muscles of mastication and skin sensation of the lower lip. To test the mandibular branch, palpate the muscles of mastication (temporalis and masseter) for any atrophy, swelling, or asymmetry. To test sensation, touch or pinch (ideally tickle) the lower lip lateral to the canine and look for an eyeblink or wrinkling of the face. The ophthalmic branch is sensory from the cornea and medial canthus of the eye. To test this branch, touch the medial canthus of the eye and observe the normal palpebral (blink) response, which is dependent upon the facial nerve (CN VII) for the motor portion of the blink. The final branch, the maxillary branch, is sensation from the upper lip. Touching the inside of the nostril with a hemostat (tickle) and observing an eyeblink or facial twitch test the maxillary branch. Ideally, this test should be performed with the eyes covered. Warn clients that you are about to tickle their pet's nose or they may think you just stabbed them when the patient will undoubtedly react with a rapid withdrawal from the stimulus (Figure A2.12).

CRANIAL NERVE VII: THE FACIAL NERVE

This nerve has many functions. In addition to controlling the muscles of facial expression, the facial nerve also mediates tearing and salivation through innervation of the lacrimal and salivary glands, as well as portions of the tongue for taste sensation. It is best evaluated by the palpebral reflex and observation of the face for a drooping ear, widened or narrowed palpebral fissure (depending on the length of time since dysfunction occurred), or drooping upper eyelid (Figures A2.9 and A2.12).

CRANIAL NERVE VIII: THE VESTIBULOCOCHLEAR NERVE

This nerve functions in both hearing and balance. It is the only cranial nerve that does not exit the cranium. Signs of vestibular dysfunction include a head tilt, a broad-based stance, and abnormal positions of the eyes. Hearing can be evaluated by the response of an animal to its name or being aroused from sleep by a loud noise. Unilateral or partial deafness is extremely difficult to assess clinically and is best left to testing through the brainstem evoked potential (BSEP).

CRANIAL NERVES IX AND X: THE GLOSSOPHARYNGEAL AND VAGUS NERVES

These two nerves are usually considered together and serve both motor and sensory functions of the pharynx and larynx. They are evaluated through the gag reflex. They are also involved in taste sensation. Abnormalities may be described in the history as dysphagia, inspiratory stridor, and regurgitation. The vagus nerve will continue to innervate many of the abdominal organs (Figure A2.13).

CRANIAL NERVE XI: THE SPINAL ACCESSORY NERVE

This nerve is motor to the trapezius muscle and parts of the brachiocephalicus and sternocephalicus muscles. A lesion of this nerve would result in atrophy of the trapezius muscle. Abnormalities associated with the spinal accessory nerve are rarely recognized.

CRANIAL NERVE XII: THE HYPOGLOSSAL NERVE

The hypoglossal nerve provides motor innervation to the tongue. An abnormality of this nerve will usually result in atrophy of the tongue. The atrophy is ipsilateral to the side of the lesion. Early in a disease process, the tongue will deviate away from the side of the lesion. As the tongue atrophies

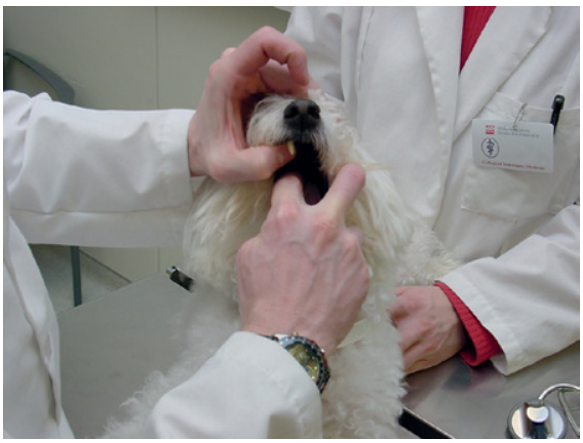


FIGURE A2.13 The gag reflex can be tested by touching your finger to the back of a patient's tongue and seeing if they swallow/gag.



FIGURE A2.14 Observing the tongue for CN XII dysfunction. (a) Normal dog. (b) In the acute phase of damage, the tongue will be deviated away from the lesion (right brainstem). Note, this dog's tongue is deviated to the left, the opposite side as the miotic pupil (lack of sympathetic innervation on the affected side). (c) With chronic denervation, the tongue is deviated toward the lesion (left brainstem). This dog has atrophy on the affected side of the tongue causing a constriction. Note—the tongue is deviated toward the miotic pupil and to the same side as the facial paresis (drooped upper lip). It is also firm and slightly discolored compared to the normal side (right).

and the muscle is replaced by fatty infiltrates and scar tissue, the tongue will crinkle up and deviate toward the side of the lesion (Figure A2.14).

REFLEX TESTING

Reflex evaluation is essential for the localization of a lesion of the spinal cord. Evaluating reflexes allows the clinician to determine if the lesion is affecting upper motor neurons or lower motor neurons. This not only helps with localization but may also provide some insight into possible prognosis. For instance, a fibrocartilaginous embolic (FCE) lesion affecting the thoracic or pelvic intumescences (and therefore the lower motor neuron to the limb) carries a much more guarded prognosis than FCE affecting other segments of the spinal cord (C1–C5 or T3–L3).

Reflex testing should be performed consistently, and the subjective evaluation of an elicited reflex should be based upon those myotatic (muscle stretch) reflexes, which can be consistently

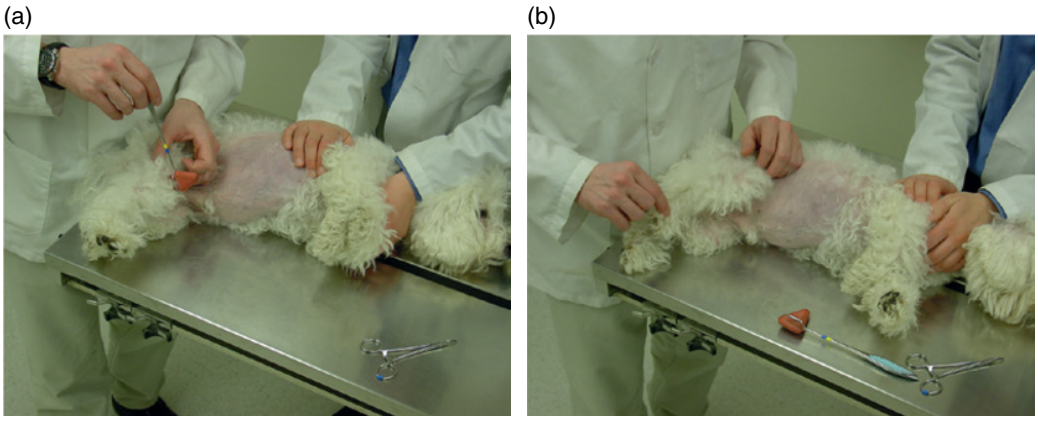


FIGURE A2.15 Reflex testing. (a) The patella reflex. The dog is in lateral recumbency and relaxed. (b) The withdrawal reflex. The toe is lightly pinched. Front and rear limbs are tested.

demonstrated in a normal dog or cat (Figure A2.15). Those reflexes which are typically repeatable and easy to demonstrate are the withdrawal or toe pinch reflex in the thoracic limbs and the patellar and withdrawal reflexes in the pelvic limbs. The reflex arc tests both the sensory and motor reflex pathways, and both must be intact in order to demonstrate a normal reflex.

A consistent method for evaluating reflexes is essential in order to develop a subjective sense of what is decreased, normal, exaggerated, or clonic (alternating flexion and extension after a single stimulus). To develop this sense, a reflex hammer (plexor) should be used for the patellar reflex, and the handles of a hemostat should be gently squeezed on a toe for the withdrawal reflex. Fingers can be used to evaluate the withdrawal reflex by pinching the toes just enough to elicit a response. If no response is elicited, the clinician can place the toe between the *handles* of a hemostat (not the tips) and gently squeeze. Obviously, a pet owner may also react negatively to this method. Reflexes should be evaluated prior to the evaluation of pain sensation.

The myotatic reflex involves the muscle stretch receptor, the afferent sensory neuron, the dorsal spinal root, the cell body of the sensory neuron, the spinal cord segment or segments of the reflex being tested, the cell body of the motor neuron, the efferent motor neuron, the neuromuscular junction, and the muscle.

A decreased reflex may therefore be caused by any abnormality in the aforementioned reflex arc. A rare but possible cause of a decreased reflex is the syndrome, more commonly recognized in humans suffering severe spinal trauma, known as "spinal shock." Spinal shock is usually short-lived in animals suffering from spinal trauma. It typically does not last longer than 30 min following injury (although the author has seen it last hours). Spinal shock is also characterized by a lack of sensation caudal to the lesion and paralysis. An artifactual cause of decreased reflex function is excessive extension of the muscles secondary to excitement or a decreased range of motion of the muscles or limbs due to orthopedic or skeletal muscle pathology (fibrosis or ankylosis). Decreased reflexes are usually accompanied by a decreased tone of the muscle. Decreased reflexes imply a lower motor neuron lesion.

Upper motor neurons inhibit the action of the reflex arc, and therefore, a lesion of an upper motor neuron will lead to exaggeration of the reflexes. Exaggerated reflexes may also be caused by a reflex muscle contraction, which is not inhibited by its accompanying antagonistic muscle. This is commonly seen with lesions in the L6–S1 spinal segments. In this case, the patellar reflex is exaggerated due to a lack of innervation to the antagonistic muscles normally serving to diminish stifle extension. This is commonly referred to as a "pseudo-hyperpatellar reflex." Usually, the withdrawal reflex in the same limb is decreased. A lesion of the sciatic nerve (L7) may also result in a pseudo-hyperpatellar reflex.

THE PATELLAR REFLEX

The patellar (or knee jerk) reflex is the most easily demonstrated myotatic reflex. It is performed with the animal in lateral recumbency and relaxed. Ideally, the limb should be midway between flexion and extension. The straight patellar tendon is struck using the weight of the head of the hammer itself, with no external force other than gravity applied to the hammer. A single brisk extension of the stifle should be seen. The patellar reflex is mediated by the femoral nerve, which is made of L4, L5, and L6. Therefore, a decreased patellar reflex implies dysfunction of those spinal nerve roots or spinal cord segments. An upper motor neuron lesion may produce a normal or increased reflex and would imply a dysfunction cranial to the L4–L6 spinal segments.

THE WITHDRAWAL REFLEX

The withdrawal (flexor) reflex is assessed in both the pelvic and thoracic limbs. Once again, the patient should be placed in lateral recumbency with the leg to be tested closest to the examiner (the up leg). The patient should be relaxed. The author prefers to use the space between the handles of a pair of mosquito hemostats or my fingers. The hemostats are opened, and a toe is placed between the handle. The handle is gently closed, and the reflex withdrawal is evaluated. It is very important to not squeeze the handle too tight. You are only trying to elicit a reflex withdrawal, *not a response to a painful stimulus*. The complete, intact reflex should show flexion of the coxofemoral joint, stifle, and tarsal joints in the pelvic limb and flexion of the shoulder, elbow, and carpus in the thoracic limb. Spinal nerves originating from L4 to L7 are necessary for the complete and intact withdrawal reflex in the pelvic limbs and C6–T2 in the thoracic limbs. Oftentimes, a lesion of the L7 spinal segment or sciatic nerve will show normal flexion of the coxofemoral and stifle joints but weak flexion of the tarsus. This is commonly seen with lumbosacral disease.

If extension of the contralateral limb is observed at the same time as flexion of the limb being tested, this is referred to as a *crossed extensor reflex*. Upper motor neurons will descend in the spinal cord to inhibit this contralateral extension, and therefore, the presence of the crossed extensor reflex implies an upper motor neuron lesion.

In the thoracic limbs, the C6–T2 spinal segments and nerves make up the withdrawal reflex. This reflex may be difficult to assess in animals with lesions in the C6–T2 spinal cord segments as they often have severe extensor rigidity of the forelimbs, secondary to a compressive lesion.

An intact withdrawal reflex does not imply deep pain sensation. One of the most common mistakes made during the neurological exam is the misinterpretation of a withdrawal reflex. Flexion of the limb in response to a light stimulus is a reflex action only and not a conscious recognition of a pain stimulus. Even if the spinal cord were severed cranial to the L4 spinal segment, there would still be a withdrawal reflex but no deep pain sensation.

THE CUTANEUS(EOUS) TRUNCI REFLEX (RESPONSE)

This test was formerly known as the panniculus reflex. This reflex arc tests the integrity of sensory neurons in spinal nerve roots along paraspinal muscles, the spinal cord pathways of the ascending nerves, and the efferent portions of the reflex arc in the C8–T2 spinal segments, as well as the efferent peripheral nerves. The reflex is tested by gently pinching the skin, lateral to the spine, with a pair of hemostats. The sensory signal enters the spinal cord approximately 1–2 segments cranial to the pinch and ascends the spinal cord to the C8–T2 spinal segments where the ventral horn motor neuron is excited, stimulating the lateral thoracic nerve and causing bilateral contraction of the cutaneous trunci muscle on the lateral thoracic wall. The test is started in the region of the L6 vertebral body, or just cranial to the wings of the ilium. This reflex pathway is diffuse with many crossover points as it ascends the spinal cord. An immediate contraction of the lateral thoracic

muscles should be seen when tested in the vicinity of the L5–L6 vertebral bodies. If no contraction is seen, the light pinch is continued cranially until the contraction is seen. A lesion is typically present two vertebral segments cranial to the point where the reflex was first seen. For instance, if the test is performed and a reflex response is not seen until the approximate level of the L1 vertebral body, then the lesion would likely be in the vicinity of the T11–T12 vertebral body. If a contraction is seen on one side but not the other, then the lesion has to be in the region of the C8–T2 spinal segments, or brachial plexus on the ipsilateral side being tested. This test may be difficult to elicit in some normal animals and can be particularly difficult to assess in cats. The absence of the reflex, therefore, does not imply pathology.

THE PERINEAL REFLEX

This reflex tests the S1–S3 spinal cord segments and peripheral nerves. It is performed by lightly touching the lateral wall of the perineum. A normal response is contraction of the anal sphincter and possible flexion of the tail. A decreased response, or flaccid anus, implies a lower motor neuron lesion affecting the S1–S3 spinal cord segments or peripheral nerves. An exaggerated response would be difficult to assess.

PAIN SENSATION

Testing for deep pain sensation *is only* necessary if there is a lack of voluntary movement (i.e., paralysis). Let me repeat that. If there is movement, it is not necessary to test for deep pain. That being said, the author has observed a single case of a canine where a central lesion from an FCE resulted in a temporary loss of deep pain to the pelvic limbs, but the patient still had motor function to the pelvic limbs. Because of the location of the deep pain pathways (more central in the spinal cord than superficial pain and voluntary motor pathways), a severe injury must take place in order to affect their function. It is extremely important not to confuse deep pain sensation with the reflex withdrawal of a limb as it is tested. The flexion of a limb as it is tested is only verifying the integrity of the peripheral nerve and reflex arc in the specific segment of the spinal cord. A positive deep pain response must include a conscious awareness and reaction by the animal in response to the deep pain test.

This evaluation is very important, as it is the single most important indicator of prognosis once voluntary movement is lost.

Superficial pain is occasionally tested when there is evidence a particular spinal or peripheral nerve may be injured (such as in brachial plexus avulsion). To test superficial pain, a pair of hemostats is used to gently grasp the area of the skin to be tested. After the piece of the skin is isolated, the hemostats are closed further to elicit a response. This "two-pinch" method allows only the area of interest to be evaluated.

LESION LOCALIZATION

Once you have determined the neurologic dysfunction, the next goal is to localize the lesion. The nervous system can be broken down into manageable packages based on the typical clinical signs manifested through disorders of each particular package:

- **Supratentorial or forebrain**
  - *Seizures*
  - Altered behavior or mentation
  - Circling (usually large circles, toward the lesion)

- Head tilt (usually toward the lesion)
- Cranial nerve deficits (CN I–II)
- Spinal reflexes increased (upper motor neuron—UMN) or normal
- Tetraparesis or hemiparesis (contralateral)
- Decerebrate rigidity

- **Infratentorial or brainstem**
  - Altered consciousness
  - Altered sleep patterns
  - Abnormal cardiac or respiratory patterns
  - Gait abnormalities
  - Head tilt
  - Circling (usually small, tight circles)
  - Tetraparesis or hemiparesis (ipsilateral)
  - Spinal reflexes increased (UMN) or normal
  - Cranial nerve deficits (CN III–XII)
- **Cerebellum**
  - Head tilt (usually away from the lesion)
  - Ataxia
  - Hypermetria
  - Tremor—intention
  - If pure cerebellar disease, no weakness
  - Decerebellate rigidity
- **Vestibular**

Clinical sign	**Peripheral**	**Central**
Head tilt	Present	Present
Nystagmus (spontaneous)	Horizontal	Horizontal
	Rotary	Rotary
		Vertical
Nystagmus (positional)	Constant	**Changing**
Horner's syndrome	May be present	May be present
Cranial nerve dysfunction	CN VII or CN VIII	**Any**
Conscious proprioception	**Normal**	**Altered**

- **Spinal cord**
  - Weakness or conscious proprioceptive deficits caudal to the lesion.
  - Spinal pain (often).

- Reflex abnormalities (UMN or lower motor neuron—LMN).
- Lack of localizable pain suggests intraparenchymal or chronic lesion.
- Loss of pain may also suggest a more severe lesion.

- **C1–C5 spinal segments**
  - Tetraparesis—common to tetraplegia (rare)
  - Ipsilateral hemiparesis or hemiplegia
  - Normal to increased reflexes to all limbs
  - Ipsilateral Horner's syndrome (possible)
  - Altered respiratory patterns
- **C6–T2 spinal segments**
  - Tetraparesis/tetraplegia
  - Ipsilateral hemiparesis/hemiplegia
  - Decreased or absent withdrawal reflex in thoracic limb(s)
  - Normal to increased pelvic limb reflexes
  - Hypotonia and rapid muscle atrophy (one or both forelimbs)
  - Ipsilateral Horner's syndrome (possible)
  - UMN bladder
- **T3–L3 spinal segments**
  - Normal thoracic limbs
  - Paraparesis or paraplegia
  - Ipsilateral monoparesis or monoplegia (rare)
  - Normal to increased pelvic limb reflexes
  - Possible loss of cutaneous trunci reflex caudal to the lesion
  - Schiff–Sherrington posture (severe cases)
  - Loss of deep pain sensation (severe cases)
  - UMN bladder
- **L4–S3 spinal segments**
  - Paraparesis or paraplegia
  - Ipsilateral monoparesis or monoplegia
  - Decreased pelvic reflexes
  - Hypotonia and rapid muscle atrophy (one or both pelvic limbs)
  - LMN bladder and fecal incontinence
- **Peripheral nerves**
  - Weakness and proprioception deficits.

- Motor and sensory deficits.
- Possible loss of pain sensation.
- Decreased to absent reflexes.
- Cranial nerves may be affected.
- Polyneuropathy—deficits in all limbs.
- Mononeuropathy—deficits in the area innervated by the affected nerve.
- May be painful or nonpainful.

- **Muscles**
  - Weakness.
  - Easily fatigued.
  - Gait abnormalities (usually stiff).
  - Painful or nonpainful.
  - Tremor of affected muscle.
  - Muscle may atrophy or enlarge (i.e., infiltrative disease).
  - Proprioception usually preserved.
  - Reflexes usually present but may be decreased.

NEUROLOGICAL EXAMINATION

Date:_____ **Time:_____** **Patient: _____**

Complaint:_____

History:

Mentation:	(circle)	
Alert	Depressed	Demented
Disoriented	Stuporous	Comatose

Posture:	(circle)	Normal
Head turn (L/R)	Head tilt (L/R)	Falling (L/R)
Decerebrate	Tics/twitches	Torticollis
Decerebellate	Schiff–Sherrington	Tremor

Gait:	Normal		Unable to assess	
Ataxic	Truncal	Pelvic	All	
Paretic	Para	Tetra	Hemi (L/R)	Mono (L/R) (T/P)
Lame	LT	LP	RT	RP
Short strided/stiff	Thoracic		Pelvic	
Long/lopey	Thoracic		Pelvic	
Unable to stand	Thoracic		Pelvic	All

Postural Reactions:

0 = absent,

1 = reduced,

2 = normal,

3 = exaggerated

		L	R
Conscious proprioception	Thoracic	_____	_____
	Pelvic	_____	_____
Hopping	Thoracic	_____	_____
	Pelvic	_____	_____
Wheelbarrow	Thoracic	_____	_____
	Pelvic	_____	_____
Hemistance/walk	Thoracic	_____	_____
	Pelvic	_____	_____
Placing	Thoracic	_____	_____
	Pelvic	_____	_____
Extensor postural	Thoracic	_____	_____
	Pelvic	_____	_____

Spinal Reflexes:

0 = absent, 1 = reduced, 2 = normal,
3 = exaggerated, 4 = clonus

Thoracic Limb:		L	R
Biceps	(C_6–C_8)	_____	_____
Triceps	(C_7–T_2)	_____	_____
Extensor carpi radialis	(C_7–T_2)	_____	_____
Withdrawal	(C_6–T_2)	_____	_____

Pelvic Limb:		L	R
Patella	(L_4–L_6)	_____	_____
Cranial tibial	(L_6–S_1)	_____	_____
Gastrocnemius	(L_6–S_1)	_____	_____
Withdrawal	(L_6–S_1)	_____	_____
Perineal	(S_1–S_3)	_____	_____

Cutaneous Trunci: **Normal**

T_2 T_3 T_4 T_5 T_6 T_7 T_8 T_9 T_{10} T_{11} T_{12} T_{13} L_1 L_2 L_3 L_4

Urination:

Voluntary	Yes	No
Bladder distended?	Yes	No
Easy to express?	Yes	No

Atrophy:

Pain:

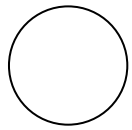
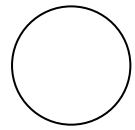
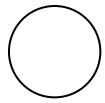
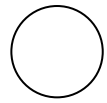
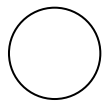
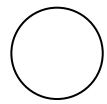
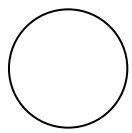
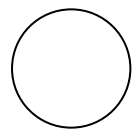
Orthopedic/Musculoskeletal:

Current Medications:

Cranial Nerves:

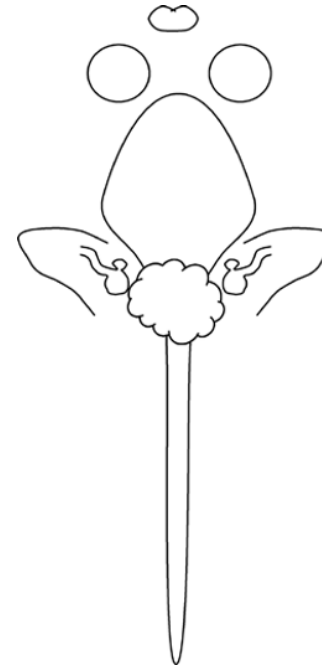
0 = absent, **1** = reduced,ww

2 = normal, **3** = exaggerated

	Right	Left
Smell (CN I)	_____	_____
Menace response (CN II + VII)	_____	_____
Pupil size (at rest)	Right	Left
Pupil response to light		
Light in the left eye		
Light in the right eye		
Fundic exam		

Strabismus, *resting* (III, IV, VI)	_____	_____
Strabismus, *positional* (III, IV, VI, VIII)	_____	_____
Nystagmus spontaneous (VIII)—(circle) none	**R**	**L**
	Horizontal	Horizontal
	Rotary	Rotary
	Vertical	Vertical
Positional	Yes	No
Changing	Yes	No
Oculovestibular (VIII, II, IV, VI)	_____	_____
Facial sensation (V)	_____	_____
Ocular sensation (V)	_____	_____
Facial symmetry (VII)	_____	_____
Palpebral (V + VII)	_____	_____
Swallowing (IX + X)	_____	_____
Trapezius muscle (XI)	_____	_____
Tongue (XII)	_____	_____

Deep Pain: Thoracic +/– Pelvic +/– Tail +/–



Neuroanatomical Localization:

	L	R
Forebrain		
Brainstem		
Cerebellum		
Vestibular central/peripheral		

Spinal Cord Segments

C_1–C_5	Generalized neuromuscular
C_6–T_2	Peripheral nerve(s) (name)
T_3–L^3	**Differential Diagnoses:**
L_4–S_1	**Recommended Diagnostic Tests:**
S_1–S_3	
Caudal	**Signature:**

INTERNATIONAL VETERINARY EPILEPSY TASK FORCE EPILEPSY QUESTIONNAIRE

Case No.:		**Name:**	
Breed:		**Name of animal:**	
Sex:	M/F	**Reproductive status:**	**Entire/Neutered**
Age:		**Body Weight:**	
Diet:			
Date:			
There are many possible causes of the episodes that your pet is experiencing, and unfortunately disorders of several body systems can all cause very similar signs. Please take the time to fill in this questionnaire, as the information it contains can be very helpful for us in interpreting the events you are witnessing, and thereby help us to focus our diagnostic investigations.			
If several options are available, please select all that are appropriate.			
The word "fit" in this questionnaire refers to episodes your pet is experiencing.			

Regarding your pet's history:

Did your pet have birth complications?	Yes ☐	No ☐	Not sure ☐
Has your pet ever sustained head trauma?	Yes ☐	No ☐	Not sure ☐
Has your pet ever had meningitis or an infection that involved the brain, spine or nerves?	Yes ☐	No ☐	Not sure ☐
Does your pet suffer from any of the following?	Liver disease ☐ Kidney disease ☐ Low calcium ☐	Low blood sugar ☐ Low potassium ☐	
Do you know of any relatives of your pet that suffer from epilepsy?	Yes ☐	No ☐	Not sure ☐
If yes, please provide a copy of the pedigree to us			
How old was your pet when he/she had his/her first fit?	..... years	..... months	
How many fits does your pet usually have in a 24 h period?	.....		
What is the most your pet has fitted in a 24 h period?	.....		

If your pet fits more than once in a 24 h period, is this:	Once every month ☐	Once every 3 months ☐	Other frequency (specify) ☐
Has your pet ever had a status epilepticus (seizure lasting longer than 5 min) in his/her life?	Yes ☐	No ☐	Not sure ☐
How many fits does your pet have per month?	.....		
If your dog is intact female, does the fit frequency increase during heat?	Yes ☐	No ☐	Not sure ☐

Possible triggering events:

Do the fits occur:	In the morning ☐	In the afternoon ☐	At night ☐	Any time ☐
Do the fits occur:	At rest ☐	During sleep ☐	During exercise/excitement ☐	
	During stress ☐	Soon after a meal ☐	When a meal is due ☐	
	Following exposure to flashing lights ☐			
	Following exposure to loud sounds ☐			
	Following any other stimulus (specify) ☐			

Before the fit:

Can you tell that your pet is going to have a fit before the event?	Yes ☐	No ☐	Not sure ☐
If yes, how long before the fit?	Minutes ☐	Hours ☐	Days ☐
If yes, what signals the fit?	Fearfulness ☐	Aggressiveness ☐	Disorientation/ agitation ☐
	Wobbliness ☐	Clinginess ☐	Anti-social/hiding ☐
	Sleepiness/ lethargy ☐	Staring into space ☐	Fly-catching/ star-gazing ☐
	Sniffing ☐		

Other:

The fit itself:

Do all the fits look the same? Yes ☐ No ☐ Not sure ☐

Please describe the fit(s), elaborating on the above where appropriate. If your pet displays more than one type of fit, please describe the most common type first and then the other type/s:

During the fit:

What is the very first thing that happens? .....

.....

Is the head involved first?	Yes ☐	No ☐	Not sure ☐
Does your pet do chewing movements?	Yes ☐	No ☐	Not sure ☐
Are hindlimbs or forelimbs involved first?	Yes ☐	No ☐	Not sure ☐
Does the fit start on left or right side of your pet?	Yes ☐	No ☐	Not sure ☐
Is your pet's body stiff, floppy or normal?	Stiff ☐	Floppy ☐	Normal ☐
Does your pet fall to the floor?	Yes ☐	No ☐	
If yes, is it always to the same side?	**yes, to the**		no ☐
Does your pet make chewing movements?	Yes ☐	No ☐	Not sure ☐
Does your pet make paddling movements?	Yes ☐	No ☐	Not sure ☐
Does your pet shake?	Yes ☐	No ☐	Not sure ☐
Can your pet hear you?	Yes ☐	No ☐	Not sure ☐
Can your pet see you?	Yes ☐	No ☐	Not sure ☐
Does your pet:	Urinate ☐	Defecate ☐	Drool/froth ☐

Please describe the fit(s), elaborating on the above where appropriate. If your pet displays more than one type of fit, please describe the most common type first and then the other type/s:

How long do the fits last? .....

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

How long does it take for your pet to be standing and walking around? .....

How long does it take until your pet is back to normal? .....

After the fit:

Does your pet appear:

Fearful ☐	Aggressive ☐	Disorientated/agitated ☐
Wobbly/clumsy ☐	Clingy ☐	Anti-social/hiding ☐
Sleepy/lethargic ☐	Staring into space ☐	Fly-catching/star-gazing ☐
Sniffing ☐	Blind ☐	Normal ☐

Other:

Between fits:

Does your pet appear completely normal between events?	Yes ☐	No ☐	Not sure ☐
If no, how do they appear abnormal compared to before the fits started?			
Altered mentation? e.g., depressed, hyperactive	Yes ☐	No ☐	Not sure ☐
Unable to perform previously learned tasks?	Yes ☐	No ☐	Not sure ☐
Abnormal social interaction? e.g., clingy, hiding	Yes ☐	No ☐	Not sure ☐
Aggressive? e.g., toward dogs, toward people	Yes ☐	No ☐	Not sure ☐
Disobedient?	Yes ☐	No ☐	Not sure ☐
Abnormal behavior? e.g., staring into corners, pressing head against walls	Yes ☐	No ☐	Not sure ☐
Change in appetite	Yes ☐	No ☐	Not sure ☐
Eating of excrement/abnormal items?	Yes ☐	No ☐	Not sure ☐
Change in thirst?	Yes ☐	No ☐	Not sure ☐
Excessive licking or scratching themselves?	Yes ☐	No ☐	Not sure ☐
Destruction of property?	Yes ☐	No ☐	Not sure ☐
Difficulty settling? e.g., pacing, howling, barking	Yes ☐	No ☐	Not sure ☐
Change in sexual behavior? e.g., toward humans, masturbation	Yes ☐	No ☐	Not sure ☐
Change in sleeping pattern?	Yes ☐	No ☐	Not sure ☐
Change in exercise pattern?	Yes ☐	No ☐	Not sure ☐

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

If available, please provide us with:

- **Video footage of the fit**
- **A copy of the seizure and medication diaries.**
- **Results of previous investigations (blood tests, urine test, MRI, CT, CSF analysis, others).**

Thank you very much for your time.

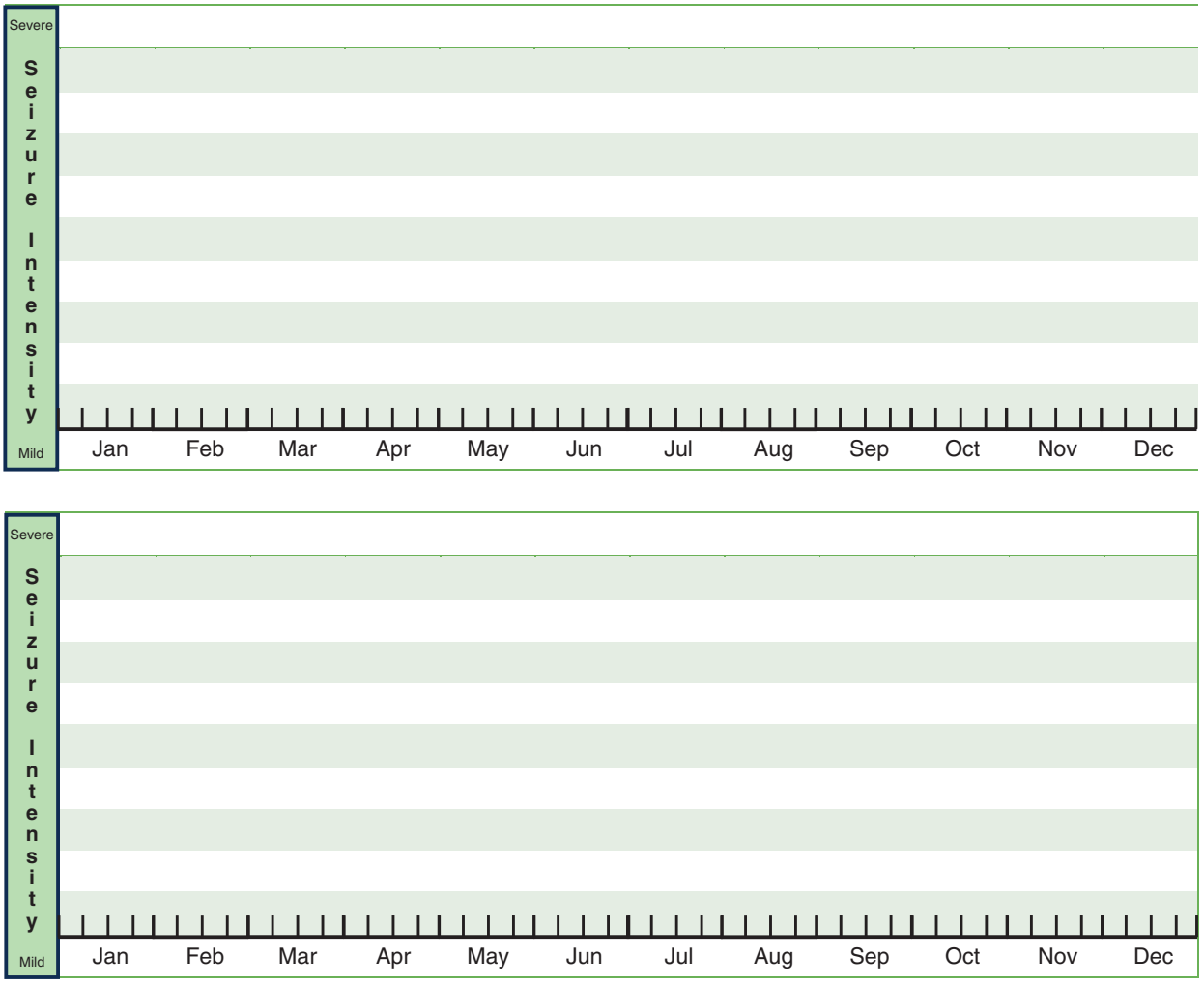


FIGURE A2.16 Example of *linear* seizure diary or log. For an example of how to use this log, see Figure 4.3. A blank log is also available on the companion website.

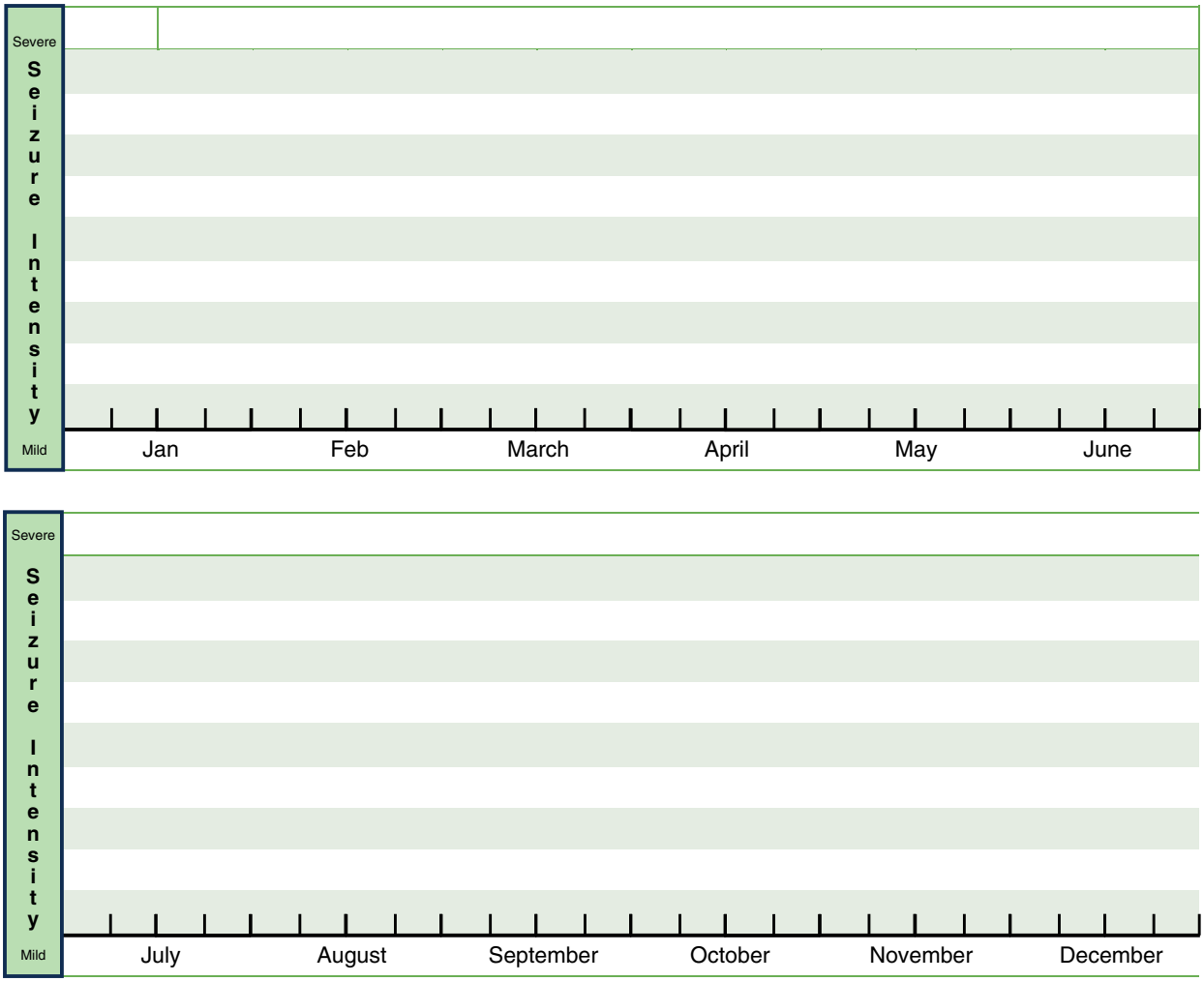


FIGURE A2.16 (Continued)

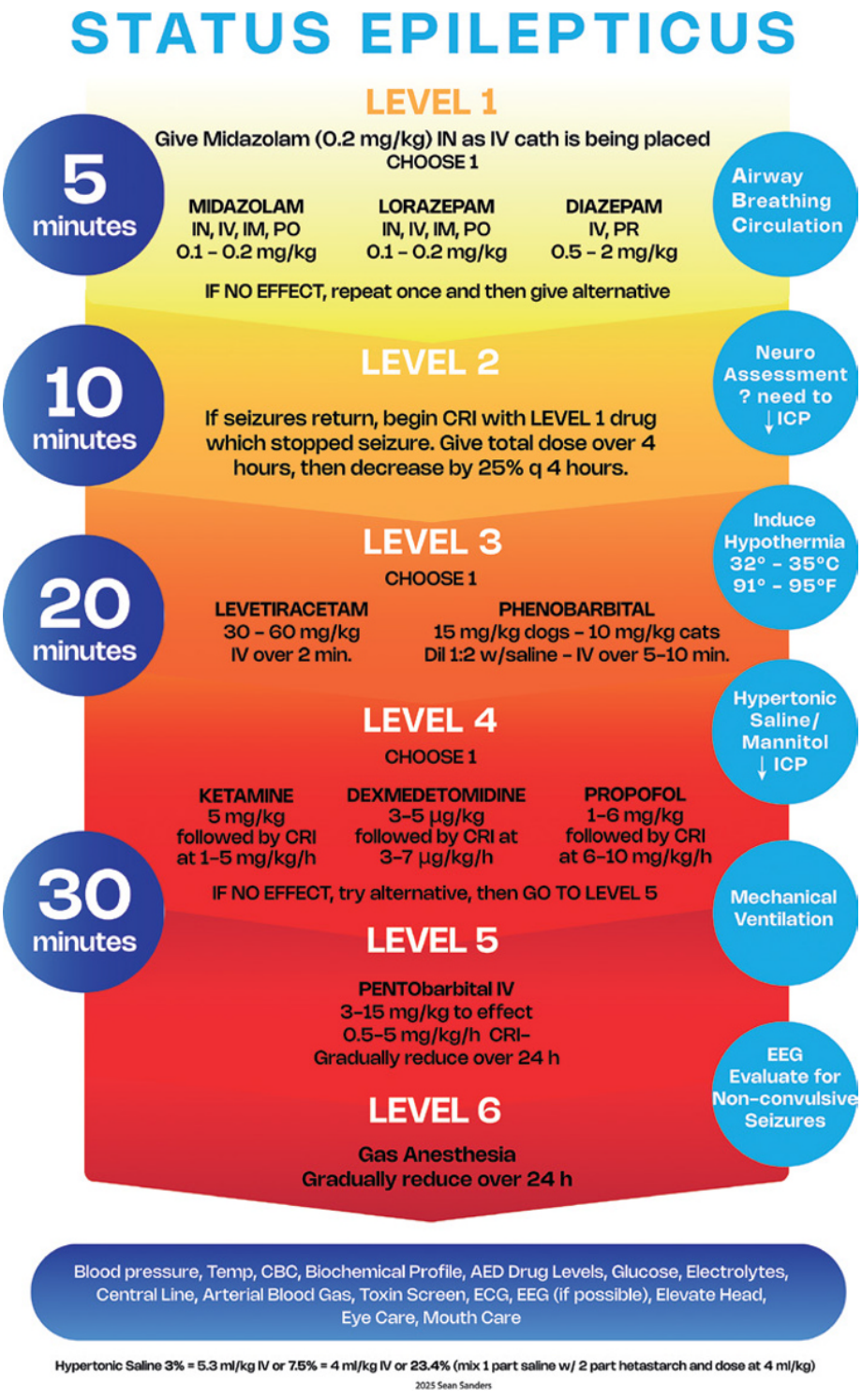


FIGURE A2.17 Flowchart for the management of acute seizure or status epilepticus. Source: Sean Sanders—www.theneurovets.com.

Antiseizure Medication Formulary and Common Formulas

APPENDIX 3

ANTISEIZURE FORMULARY

CARBAMAZEPINE (TEGRETOL®)



Pharmacokinetics

- Rapidly achieves peak plasma concentration within 1 h of oral dosing
- ~70% protein bound (~40% protein bound of the epoxide metabolite)
- Half-life of 0.63–0.73 h after repeated dosing (dogs)

Mechanism of Action

- Affects voltage-gated sodium channels
- Reduces sustained, repetitive firing of action potentials
- Stabilizes neuronal membranes
- May be an adenosine receptor antagonist
- May modulate GABA

Toxicity, Side Effects, and Interaction

- Transient sedation
- Humans report dizziness, sedation, nausea, and vomiting
- May cause abnormalities of the heart, liver, skin, and hematopoietic system in humans
- Many potential drug interactions. Use caution

Indications for Use

- Primarily used for behavior issues in dogs
- Not used commonly in veterinary medicine due to inability to maintain serum plasma concentrations in dogs
- May have a beneficial use in cats as a 5th-line antiseizure medication

Seizures in Dogs and Cats, Second Edition. Sean Sanders.
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Companion website: www.wiley.com/go/sanders/seizures2e

Dose

- 30 mg/kg PO q 8 h (anecdotal for neuropathic pain)
- 4–8 mg/kg PO q 6–8 h for behavior issues

Monitoring

- Safety and clinical efficacy
- Routine CBC, biochemical profile, and fasting and fed bile acids

CLONAZEPAM (KLONOPIN®) 

Pharmacokinetics

- The *strongest* benzodiazepine commonly used for dogs and cats
- 33% oral bioavailability (dogs)
- 82% protein bound
- Rapid metabolism. Half-life of ~2 h in dogs
- Tolerance develops in days (dogs)

Mechanism of Action

- Binds to $GABA_A$–chloride ionophore membrane complex
- Potentiates the flow of chloride through the ion channel
- Hyperpolarizes the plasma membrane
- More effective at stopping the propagation of an epileptic discharge, as opposed to suppressing the epileptogenic focus
- ~15× more potent than clorazepate, however, tolerance develops in days as opposed to months for clorazepate
- ~10× more potent than diazepam

Toxicity, Side Effects, and Interaction

- Transient sedation and ataxia possible
- Social disinhibition may lead to aggression
- Signs of drug withdrawal (lasting 1 week) possible after chronic use (listlessness, "wet dog shakes," tremor, hyperthermia, weight loss, tonic–clonic seizures)
- Caution with use in cats

Indications for Use

- Bridge medication
- Pulse medication

Dose

- Dogs: 0.5–2 mg/kg PO q 8–12 h
- Cats: 0.5 mg total dose PO q 8–12 h (use with caution)

Monitoring

- Adjust the dose to effect or side effect
- Routine CBC, biochemical profile, and fasting and fed bile acids (if used chronically in cats)

CLORAZEPATE (TRAXENE®) 

Pharmacokinetics

- The *weakest* benzodiazepine commonly used for dogs and cats
- Peak serum levels within 1–2 h after oral dosing
- Rapid metabolism. Half-life of ~4–6 h in dogs (compared to 2–4 h for diazepam)
- Tolerance develops in weeks to months (dogs) compared to days for clonazepam

Mechanism of Action

- Binds to $GABA_A$–chloride ionophore membrane complex
- Potentiates the flow of chloride through the ion channel
- Hyperpolarizes the plasma membrane
- ~15× *less* potent than clonazepam
- The active metabolite *nordiazepam* produced longer and at higher concentrations compared to diazepam

Toxicity, Side Effects, and Interaction

- Transient sedation and ataxia possible
- Social disinhibition may lead to aggression
- Withdraw slowly to prevent the development of withdrawal seizures if used chronically
- Caution with use in cats

Indications for Use

- Bridge medication
- Pulse medication

Dose

- Dogs: 0.5–1.5 mg/kg PO q 8–12 h
- Cats: 3.75–7.5 mg total dose, divided and given q 12–24 h (use with caution)
- Increase dose to 1 mg/kg if used concurrently with phenobarbital in dogs

Monitoring

- Adjust the dose to effect or side effect
- Routine CBC, biochemical profile, and fasting and fed bile acids (if used chronically in cats).

DIAZEPAM (VALIUM®) 

Pharmacokinetics

- Only 1–3% bioavailability when dosed orally in dogs
- Rapid metabolism. Half-life of ~2–4 h in dogs
- Tolerance develops in days to weeks (dogs)
- Half-life in cats ~15–20 h
- 94–96% protein bound
- Reaches serum therapeutic concentrations within 8–14 min of rectal administration
- 40% bioavailability when given intranasal
- Peak plasma concentration within 5 min of intranasal administration

Mechanism of Action

- Binds to $GABA_A$–chloride ionophore membrane complex
- Potentiates the flow of chloride through the ion channel
- Hyperpolarizes the plasma membrane
- At high doses (given intravenously), it may suppress repetitive firing
- Blocks arousal in CNS and centrally depresses spinal cord reflexes

Toxicity, Side Effects, and Interaction

- Transient sedation and ataxia possible
- Social disinhibition may lead to aggression
- Withdraw slowly to prevent the development of withdrawal seizures if used chronically
- Caution with use in cats—may develop acute fulminant hepatic failure
- Avoid chronic injectable use in cats as it may cause Heinz body anemia (propylene glycol preservative)

Indications for Use

- Treatment of status epilepticus (IV)
- Pulse medication at home use (PR or IN—but there are better choices such as midazolam and lorazepam)

Dose

- 0.5–2 mg/kg IV for treatment of status epilepticus (dogs)
- 0.25–0.5 mg/kg IV for treatment of status epilepticus (cats)
- 0.5–2 mg/kg intranasal or per rectum as pulse therapy
- 1–2 mg/kg per rectum as pulse therapy if concurrently taking phenobarbital
- 0.1–0.5 mg/kg diluted in D5W and administered as a CRI at normal fluid maintenance rate full strength for 4 h and then reduce dose by 25% every 2–4 h (adjust as needed)

Monitoring

- Adjust the dose to effect or side effect
- Avoid light exposure (wrap IV lines)
- Do not dispense in syringes
- Flush IV lines prior to use with diazepam solution

ETHOSUXIMIDE (ZARONTIN®)



Pharmacokinetics

- Half-life of 17–18 h (dogs)
- Peak plasma concentrations reached within 1–4 h after oral dosing (dogs)
- 1.5–9.5% protein binding in the dog

Mechanism of Action

- Blocks T-type calcium channels
- Primary action in the thalamus through prevention of spreading of characteristic 3-Hz spike and wave discharges

Toxicity, Side Effects, and Interaction

- No data available for dogs and cats
- Considered safe in humans. May cause psychosis and behavior problems in humans

Indications for Use

- Used to treat absence seizures in humans
- May be effective in dogs
- Considered a potential fourth- or fifth-tier drug

Dose

- Loading dose of 40 mg/kg
- Maintenance dose of 15–25 mg/kg q 8 h

Monitoring

- Monitor for safety and efficacy
- Plasma concentrations of 50–70 µg/ml is the target

FELBAMATE (FELBATOL®) 

Pharmacokinetics

- Half-life of ~6 h (dogs), <2.5 h in pediatric patients
- Half-life decreases with time and multiple dosing
- Well absorbed after oral dosing

Mechanism of Action

- Exact mechanism is unknown
- Potentially antagonizes intracellular calcium currents through interaction with glutamate subtype of the NMDA receptor
- Potentiates $GABA_A$-mediated inhibition similar to barbiturates

Toxicity, Side Effects, and Interaction

- Considered to be very safe in dogs
- Hepatotoxicity potential especially when used with phenobarbital
- May cause sedation, ataxia, GI distress, liver disease, and keratoconjunctivitis sicca
- May cause aplastic anemia in humans
- Levels of felbamate may *decrease* if phenobarbital is added
- Phenobarbital levels may *increase* if felbamate is added
- Safety not determined in cats

Indications for Use

- Maintenance drug as a fifth or sixth option
- May be a better choice in patients with structural brain disease as it tends to *not* exacerbate neurological deficits

Dose

- 15 mg/kg q 8–12 h

- Increase dose by 15 mg/kg increments every 2 weeks to effect or side effect
- Doses up to 70 mg/kg q 8 h may be necessary

Monitoring

- Monitor for safety and efficacy
- Plasma concentrations of 25–100 µg/ml is the target
- Monitor liver values, including fasting and fed bile acids

GABAPENTIN (NEURONTIN®) 

Pharmacokinetics

- Oral bioavailability of ~80% in dogs
- Oral bioavailability of ~90% in cats
- Peak plasma concentrations within 1–2 h of oral dosing
- Half-life of ~3 h in dogs and cats
- Steady state in approximately 1 day

Mechanism of Action

- Exact mechanism is unknown
- May increase the synthesis of GABA
- Its primary effect is thought to be mediated through its binding to the $\alpha_2\delta$ subunit of the presynaptic voltage-gated calcium channel (P, Q, and N types)

Toxicity, Side Effects, and Interaction

- May cause ataxia and sedation at high doses
- Considered very safe

Indications for Use

- Add-on therapy particularly for cats
- More commonly used to treat neuropathic sources of pain

Dose

- Start at 10–20 mg/kg every 8 h
- May be effective at every 12 h
- Increase dose to effect or side effect
- An extended-release formulation is available but no disposition studies have been performed in dogs or cats
- The commercially available oral solution (50 mg/ml) **contains xylitol**

Monitoring

- Monitor for safety and efficacy

IMEPITOIN (PEXION™) 

Pharmacokinetics

- Half-life of ~6 h (dogs)
- Less likely to develop tolerance and side effects commonly associated with $GABA_A$ receptor agonists
- Steady state in approximately 3 days (dogs)
- No tolerance/no withdrawal seizures

Mechanism of Action

- Low-affinity partial agonist to the benzodiazepine binding site of the $GABA_A$ receptor
- Blocks voltage-activated calcium channels in a dose-dependent manner
- Efficacy similar to phenobarbital (dogs)

Toxicity, Side Effects, and Interaction

- Considered very safe
- Contraindicated in patients with severe liver, renal or cardiovascular disease
- Limited safety data in animals <2 kg or <5 years old. Use caution
- May cause disinhibition of fear-based behaviors leading to aggression
- Common, reversible side effects include lethargy, ataxia, polyphagia, polydipsia, vomiting, and hyperactivity
- Less abuse potential for humans

Indications for Use

- As a primary prophylactic medication or an add-on prophylactic medication for dogs and cats
- Tier 1 anticonvulsant

Dose

- 10–30 mg/kg q 12 h (dogs and cats)
- Increase dose to effect or side effect

Monitoring

- Monitor for safety and efficacy

KETAMINE (KETAJECT®, KETASET®, KETA-STHETIC®, KETALAR®, VETALAR®)



Pharmacokinetics

- ~53% protein bound in the dog and cat
- Rapid distribution to all body tissues after IV or IM injection
- May be effective when given sublingually in cats
- Metabolized by the liver (dogs) and excreted unchanged in the urine of cats

Mechanism of Action

- *N*-Methyl-D-aspartate (NMDA) receptor antagonist
- May have neuroprotective effects through inhibition of intracellular calcium efflux

Toxicity, Side Effects, and Interaction

- May cause seizures
- May induce extreme muscle tone and spontaneous movement
- May cause apneustic breathing patterns
- Respiratory support may be necessary
- Increases cerebral blood flow and intracranial pressure
- May cause hypertension

Indications for Use

- To treat refractory status epilepticus as a *fourth*-line treatment after other antiseizure medications have failed (Figure 8.1)
- Generally used with prolonged status epilepticus (i.e., seizures lasting longer than 30 min)

Dose

- Titrate to effect
- 5 mg/kg IV bolus
- 5 mg/kg/h as CRI if seizures continue
- When used with dexmedetomidine **1 mg/kg IV bolus of ketamine over 5 min** followed by an IV bolus of **dexmedetomidine at 3 μg/kg over 5 min**, followed then by a CRI of ketamine and dexmedetomidine over 12 h (ketamine at 1 mg/kg/**h** and dexmedetomidine at 3–7 μg/kg/**h**)

Monitoring

- Careful monitoring necessary (i.e., respiratory depression, cardiac effects)
- May need mechanical ventilation

- Monitor blood pressure
- Monitor for increased intracranial pressure (pupils)
- Monitor ECG
- Ideally, monitor with EEG for effect

LACOSAMIDE (VIMPAT®) 

Pharmacokinetics

- ~15% protein bound in humans
- Half-life of ~3.5 h (dogs)

Mechanism of Action

- Very slow binding to the *fast inactivated* state of the sodium channel (same site as lidocaine)
- Binds to collapsin-response mediator protein 2 (CRMP-2), which has a range of effects on myelination, gene expression, axonal outgrowth, neural sprouting, and neuroprotection
- May provide neuronal protection

Toxicity, Side Effects, and Interaction

- Generally considered safe
- At high doses, it may cause reversible ataxia, reduced gastrointestinal motility, tremors, and seizures
- May lower blood pressure through reduced cardiac contractility
- Minimal drug interactions
- Caution should be used if hepatic impairment is present

Indications for Use

- As an add-on fourth-tier prophylactic antiseizure medication

Dose

- 50–100 mg (total dose) every 12 h (dogs)

Monitoring

- Monitor for safety and efficacy
- Routine bloodwork every 6 months
- The therapeutic range for humans is considered to be 10–20 µg/ml

LEVETIRACETAM (KEPPRA®) (KEPPRA XR®) 

Pharmacokinetics

- Well absorbed after oral dosing
- Peak plasma concentration in 45 min after oral dosing (dogs)
- Serum therapeutic concentrations maintained for 8 h after single IV dose of 60 mg/kg (administered over 2 min) (dogs)
- Serum therapeutic concentration reached within 10 min after a 20 mg/kg oral suspension given to cats
- Serum therapeutic concentrations achieved within 10 min after 40 mg/kg rectal dose (dogs)
- 100% bioavailability and peak serum concentrations achieved within 45 min if given intramuscularly at a dose of 20 mg/kg (dogs)
- Minimal hepatic metabolism. Excreted 50% unchanged
- Phenobarbital may increase clearance (by 50%) through induction of cytochrome P450
- Half-life ~3 h in cats and dogs. Extended-release about 1 h longer than immediate-release
- Extended-release form reaches therapeutic concentration within 200 min and is maintained for ~20 h
- Steady state in 2–3 days (dogs)
- Transdermal option for cats (400 mg/ml) dosed at 60 mg/kg to inside of pinna

Mechanism of Action

- Inhibits hypersynchronization of epileptiform neuronal burst firing by affecting neurotransmitter release while not reducing neuronal excitability
- Selectively binds to *synaptic vesicle protein 2a (Sv2a)*, which is involved in membrane transport functions
- Suppresses the spread of an epileptic seizure at the point of epileptogenesis
- Binds to an allosteric site of the GABA/glycine receptor and modulates its function through the inhibition of other allosteric inhibitors (disinhibition)
- Modulates voltage-gated Ca^{++} channels resulting in a decrease in glutamate release
- Inhibits calcium-induced calcium release in the hippocampus

Toxicity, Side Effects, and Interaction

- Generally considered safe
- Sedation at high doses (dogs and cats)
- Anorexia and transient lethargy (cats)
- No tissue damage if given extravascular

- Use caution in renal-impaired patients (may need to lower dose)
- "Honeymoon effect" anecdotally reported

Indications for Use

- As a third-tier prophylactic antiseizure medication (although not the most effective in dogs or cats)
- As an add-on prophylactic antiseizure medication
- As a second-tier antiseizure medication given intravenously for status epilepticus
- Home use for cluster seizures or status (rectal)
- Patients with compromised liver function
- Patients with portosystemic shunts (pre- and post-op). Of questionable value, but recommended

Dose

- 20 mg/kg PO q 8 h (dogs and cats)—increase up to 40 mg/kg q 8 h
- 30 mg/kg PO q 12 h if using extended-release form (note: patient must be greater than 15 kg to use the smallest extended-release pill form). Increase up to 60 mg/kg q 12 h
- 500 mg PO q 24 h of the extended-release form will reach therapeutic concentration in cats but *take caution pill is not broken*
- 60 mg/kg IV over 2–5 min for status epilepticus (ideally diluted 6:1 with 5% dextrose, lactated Ringer's or 0.9% sodium chloride)
- 40 mg/kg if used rectally (parenteral form)
- 60 mg/kg as a transdermal application (400 mg/ml) for cats
- Recommended to give with food to slow down absorption

Monitoring

- Monitor for safety and efficacy
- Routine bloodwork every 6 months
- The therapeutic range for humans is considered to be 5–45 µg/ml
- Increase dose to effect or side effect (fail at double the starting dose if no effect)
- Consider add-on if reached double the starting dose with ineffective seizure control

LORAZEPAM (ATIVAN®)



Pharmacokinetics

- Following IV dose at 0.2 mg/kg, maintains therapeutic levels (considered for humans) for up to 60–90 min in dogs
- Peak plasma concentration within 5 min of IV dose (dogs)

- Following intranasal dosing, peak plasma concentrations reached in 3–9 min (dogs)
- Half-life of ~1 h (dogs)
- Brain concentrations persist longer than plasma concentrations
- Extensive *extrahepatic* metabolism
- Is useful if given sublingually or intramuscularly to humans but has not been evaluated in dogs and cats

Mechanism of Action

- Binds to $GABA_A$–chloride ionophore membrane complex
- Potentiates the flow of chloride through the ion channel
- Hyperpolarizes the plasma membrane
- At high doses (given intravenously), it may suppress repetitive firing
- Blocks arousal in CNS and centrally depresses spinal cord reflexes
- Up to10× greater affinity for the benzodiazepine receptor site compared to diazepam

Toxicity, Side Effects, and Interaction

- Considered one of the safest drugs used to treat status epilepticus
- Sedation and ataxia
- Tolerance develops in hours to days
- Do not give intra-arterial
- Titrate to effect

Indications for Use

- Treatment of status epilepticus (IV, IN, IM, or sublingual)
- Pulse medication at home use (IN or sublingual)
- Do not use for rectal administration

Dose

- 0.2 mg/kg IV for treatment of status epilepticus (dogs). Repeat once
- 0.1 mg/kg IV for treatment of status epilepticus (cats). Repeat once
- 0.2 mg/kg IN, IM, or sublingually (dogs and cats)

Monitoring

- Titrate dose to effect or side effect
- Avoid light exposure (wrap IV lines)
- Does *not* bind to plastic. OK to dispense in preloaded syringes (see Table 6.9)

MIDAZOLAM (VERSED®) 

Pharmacokinetics

- Following IV injection, achieves very rapid CNS concentrations similar to diazepam and lorazepam
- Shorter acting compared to lorazepam or diazepam
- Faster onset of action when compared to diazepam
- Considered more effective than diazepam in stopping status epilepticus in some studies
- Peak plasma concentration following IV dose of 3 min (dogs)
- ~97% protein bound
- Peak plasma concentration achieved within 8–15 min of IM administration with 50–90% bioavailability
- Brain concentrations persist longer than plasma concentrations
- Effective if given IM, IV, IN, or sublingually
- Half-life of ~1 h in the dog

Mechanism of Action

- Binds to $GABA_A$–chloride ionophore membrane complex
- Potentiates the flow of chloride through the ion channel
- Hyperpolarizes the plasma membrane
- At high doses (given intravenously), it may suppress repetitive firing
- Blocks arousal in CNS and centrally depresses spinal cord reflexes
- Up to 5-6× greater affinity for the benzodiazepine receptor site compared to diazepam

Toxicity, Side Effects, and Interaction

- Weakness, sedation, and ataxia
- Use with caution in patients with compromised hepatic, renal, cardiac, or respiratory function
- May cause paradoxical agitation and excitation
- Titrate to effect

Indications for Use

- Treatment of status epilepticus (IV, IN, IM, or sublingual)
- Pulse medication at home use (IN or sublingual)
- Do not use for rectal administration
- Once dispensed, will expire in 30 days due to lack of preservative in the injectable solution
- Compounded form self-stable for up to 90 days. Undiluted form shelf-stable for up to 60 days (see Table 6.9)

Dose

- 0.1–0.2 mg/kg IV, IN, or IM for treatment of status epilepticus (dogs and cats). Repeat once
- 0.1–0.25 mg/kg/h as a CRI for refractory status epilepticus
- 0.2 mg/kg IN, IM, or sublingually (dogs and cats)

Monitoring

- Monitor for safety and efficacy
- Flumazenil may be used as a reversal if significant cardiac or respiratory depression is encountered

PHENOBARBITAL 

Pharmacokinetics

- Slow absorption from the GI tract in both dogs and cats with a bioavailability of ~90% in dogs and 100% in cats
- Food and GI disease will delay its absorption
- ~45% protein bound in dogs
- Reaches peak serum concentration within 4–8 h after oral dosing (dogs)
- Time to steady state in dogs and cats is 14–16 days (in beagles, may be as little as 7 days)
- Half-life of ~47–74 h in the dog (25–38 h in Beagles)
- Half-life of 34–56 h in the cat
- Induces its own metabolism. Half-life will decline with chronic use. Development of tolerance is common (more so in the dog)
- Cats may be able to maintain serum steady state with once-daily dosing
- Metabolized by the liver, primarily through oxidation to parahydroxyphenobarbital
- About 25% eliminated through a pH-dependent mechanism by the kidneys. Polyuria or alkalization of urine will increase its elimination
- Enhances elimination of many other drugs (e.g., benzodiazepines, levetiracetam, zonisamide)

Mechanism of Action

- Binds to $GABA_A$–chloride ionophore membrane complex at a different site than the benzodiazepines
- Potentiates the flow of chloride through the ion channel
- Hyperpolarizes the plasma membrane
- Creates an inhibitory postsynaptic potential
- Inhibits glutamate activity and decreases the conductance of calcium across the plasma membrane
- May alter sodium, potassium, and calcium conductance

- Decreases cerebral blood flow and cerebral metabolism to cause motor cortex depression
- Diffuse actions on the entire brain. Not specific for hypersynchronous neurons

Toxicity, Side Effects, and Interaction

- May cause idiosyncratic or dose-dependent hepatotoxicity
- May cause a nonpathological increase in alkaline phosphatase (ALP) and alanine aminotransferase (ALT)
- Increases over 5× normal of upper ALP value should trigger concern
- Increases over 2× normal of upper ALT value should trigger concern
- Increases in aspartate aminotransferase (AST) and persistent gamma-glutamyl transferase (GGT) should trigger concern
- May lower serum albumin and cholesterol values with chronic use
- Liver function tests may help distinguish induction of liver enzymes vs. liver damage
- May cause *transient* increases in gamma-glutamyl transferase and decreases in serum albumin
- Concern warranted if serum PB concentrations are increasing without dose increase
- More significant potential for hepatotoxicity if combined with primidone or phenytoin
- Concurrent use of cannabinoids may affect phenobarbital metabolism (slow down its elimination)
- May cause polyphagia, polydipsia, and polyuria
- Typical transient, sedation, ataxia, depression, and lethargy usually lasting 10–14 days
- Occasionally, a patient may have a paradoxical reaction becoming hyperexcitable and restless. This too may dissipate with time
- May cause thrombocytopenia, neutropenia, transient facial pruritus with dermatitis, and swelling of the paws
- Cats are much less susceptible to hepatotoxicity compared to dogs due to their reduced capacity of glucuronidation.
- May cause reversible bone marrow depression usually within 6 months of starting the drug
- May cause a hepatocutaneous syndrome in dogs after long-term use (superficial necrotic dermatitis)
- *Lowers* serum T_4 and free T_4
- Generally considered to *not* alter TSH levels
- No effect on the low-dose dexamethasone suppression test
- No effect on the ACTH stimulation test
- Has a wide variety of effects on other drugs (Table 7.1)
- May increase triglycerides and pancreatic lipase activity in dogs
- Recommended to dilute the injectable form with saline at 1:2 and give slowly over 5 min (no more than 60 mg/min)

Indications for Use

- First-line prophylactic treatment for seizures in dogs *and* cats
- As an add-on to other prophylactic treatments for seizures
- Treatment of status epilepticus (IV)
- Considered a broad-spectrum antiseizure medication
- Caution in patients who have hepatic compromise
- Generally preferred when structural brain disease is suspected or documented
- Indicated for the treatment of *idiopathic hypersialosis* in the dog

Dose

- 3–5 mg/kg q 12 h (dog)
- 1.5–2.5 mg/kg divided q 12 h (cat)
- Cats may be adequately controlled with SID dosing
- If hepatic compromise is suspected, decrease starting dose by 25%
- A loading dose of 12–15 mg/kg can be given to dogs
- A loading dose of 10–20 mg/kg can be given to cats
- Animals with a calculated half-life of <20 h may benefit from q 8 h dosing

Monitoring

- Monitor for safety and efficacy
- Serum reference range of 20–40 µg/ml (dog)
- Serum reference range of 15–40 µg/ml (cats)
- Titrate to effect or side effect
- CBC, biochemical profile, and urinalysis (ideally fasting and fed bile acids to establish "baseline") recommended prior to starting therapy
- CBC, biochemical profile, phenobarbital levels, and fasting and fed bile acids performed 2 weeks, 6 weeks, 3 months, and 6 months after starting therapy and then every 6 months thereafter (ideally)
- Not necessary to check a serum trough level unless calculating the serum half-life
- Do not collect in serum separator tubes
- Reference values >35 µg/ml in dogs should warrant increased surveillance and concern

POTASSIUM BROMIDE (K-BROVET®)



Pharmacokinetics

- Bioavailability of ~46% and reaches peak serum concentration within 30–45 min after oral dosing
- Distributed to all body tissues although concentrations are lower in CNS and muscle

- Primarily eliminated through the kidneys
- Half-life is 15–45 days (dogs)
- Time to steady state in dogs is several weeks to several months

Mechanism of Action

- Exact mechanism of action is unknown
- Hyperpolarizes the neuronal membrane, through interaction with the $GABA_A$ receptor much in the same way as the chloride ion but with greater effect
- Interferes with carbonic anhydrase resulting in extracellular acidosis with subsequent inhibition of epileptiform activity
- Influences the passive movement of other ions across cell membranes, particularly sodium resulting in membrane hyperpolarization

Toxicity, Side Effects, and Interaction

- Very broad-spectrum activity against all types of seizures
- Very effective in controlling seizure but has a very narrow therapeutic window
- Negative side effects often limit use
- Sedation and ataxia (i.e., bromism), typically dose-dependent but may be idiosyncratic
- May cause paradoxical hyperexcitability and "psychotic" behavior in dogs
- Polyphagia (can be dangerous), polydipsia, and polyuria
- May cause tetraparesis, paraparesis, cranial nerve deficits, ataxia, and generalized lower motor neuron signs
- May alter nerve conduction velocity, brainstem auditory-evoked potentials, electromyographic changes, and histopathological alterations to muscles and nerves
- May cause pancreatitis (although little support in the literature)
- Gastrointestinal side effects such as vomiting, anorexia, and diarrhea due to irritation of the salt compound on the GI tract
- Pruritic skin lesions reported in dogs similar to people
- High risk of developing lower airway disease in cats. May be irreversible and fatal
- High levels of dietary chloride will enhance the elimination of bromide and lower serum levels
- Diets used to manage crystalluria may lead to increased bromide elimination and loss of seizure control
- Avoid rapid changes of even maintenance diets
- Low levels of dietary chloride may lead to enhanced reabsorption of bromide and subsequent toxicosis
- Does not affect endocrine testing
- Use sodium bromide if a patient has hypoadrenocorticism (to help maintain normal potassium homeostasis)
- Will artificially increase serum chloride measurement, which is an artifact

Indications for Use

- First-line prophylactic treatment for seizures in dogs
- As an add-on to other prophylactic treatments for seizures in dogs
- Considered a broad-spectrum antiseizure medication
- Caution in patients who have renal compromise
- May be preferred if compliance is an issue as it can be dosed once a day and doses can be missed without any significant reduction in serum concentration
- Use *sodium* bromide if IV infusion is necessary. To create equal solutions of bromide, 211 mg/ml of NaBr would be used compared to 250 mg/ml of KBr
- May be more effective for "tail-chasing" bull terriers
- Not good if rapid control of seizures is desired or patients are elderly

Dose

- 20–30 mg/kg q 12 h
- 15–20 mg/kg q 12 h if used as an add-on therapy
- Loading dose of 65–90 mg/kg every 12 h for 5 days and then reduce to maintenance dose (see Table 7.3)
- Solutions of 250 mg/ml are generally well-tolerated
- **Do not use in cats**

Monitoring

- Monitor for safety and efficacy
- Serum reference range of 1–3 mg/ml
- Titrate to effect or side effect
- Measure levels 1 month after starting therapy (see text)
- Once steady state is achieved, monitor at 4 months and then every 6 months after starting therapy
- CBC, biochemical profile, urinalysis, and serum bromide concentration should be monitored every 6 months
- Laboratory measurement of bromide should be with spectrophotometry and not an ion-selective probe

PREGABALIN (BONQAT®, LYRICA®, PREGATAB®)



Pharmacokinetics

- Peak serum concentration after oral dosing achieved in 90 min (dogs)
- Serum therapeutic concentration maintained for ~8 h (dogs)
- Half-life of 6–8 h (dogs)
- Peak serum concentration after oral dosing achieved in 3 h (cats)

- Half-life of ~10 h (cats)
- The liver likely metabolizes a portion of pregabalin similar to gabapentin, but the majority is excreted through the kidneys

Mechanism of Action

- Exact mechanism of action is unknown
- Suspected to exert its effect by binding to the $\alpha_2\beta$ subunit of the voltage-gated calcium channel (P, Q, and N)
- 3–10 times more potent than gabapentin but with less sedation

Toxicity, Side Effects, and Interaction

- Sedation, ataxia, and "dizziness" (dogs)
- Sedation (cats)
- Generally regarded as very safe

Indications for Use

- Add-on prophylactic medication for generalized or focal seizures in the dog and cat
- For the treatment of neuropathic pain

Dose

- 4 mg/kg q 8 h (dogs). May titrate up or down as needed
- 1–2 mg/kg q 12 h (cats). May titrate up or down as needed

Monitoring

- Titrate to effect or side effect
- Serum monitoring not necessary
- Increase to effect, side effect, or double the dose (i.e., before failing)

PROPOFOL (RAPINOVET®, PROPOFLO®, AND PROPOCLEAR®)



Pharmacokinetics

- Rapidly reaches the CNS (within 1 min) after IV injection
- ~90–95% protein bound
- Effects are short-acting, lasting only minutes after single IV bolus
- Rapid hepatic metabolism with excretion through the kidneys

Mechanism of Action

- Exact mechanism of action is poorly understood
- Direct effect on inward hyperpolarizing chloride currents resulting in prolongation of inhibitory postsynaptic currents

- $GABA_A$ agonist but in way which differs from benzodiazepines and barbiturates
- Modulates inflammatory cytokines, impairing monocyte and neutrophil functions and altering the expression of nitric oxide
- Potent free radical scavenger (i.e., as potent as vitamin E)
- Significant neuroprotective effects through reduction of cerebral blood flow, decreased cerebral metabolism, and free radical scavenging effects, which may result in a significant reduction in intracranial pressure

Toxicity, Side Effects, and Interaction

- Apnea and cyanosis are possible if given too rapidly
- May require mechanical ventilation
- Cats susceptible to the development of Heinz body anemia
- Avoid successive or chronic dosing in cats
- Myocardial depressant may cause arterial hypotension
- Anaphylactic reactions are rarely reported
- May cause stereotypic movements which *appear* to be seizures
- May have synergistic effects with midazolam (increasing its serum concentration)
- Opioids may exacerbate propofol-induced bradycardia
- Use carefully if concurrently using medetomidine
- Concentrations may increase if used concurrently with inhalant anesthetics

Indications for Use

- Third or fourth-line agent to stop episodes of status epilepticus (Figure 8.1)
- May be used as a CRI for refractory epilepsy

Dose

- 1–6 mg/kg IV bolus administered slowly to effect
- 0.1–0.6 mg/kg/min as a CRI, titrated to effect

Monitoring

- Titrate to effect or side effect
- Monitor for respiratory and cardiac depression
- May require mechanical ventilation
- EEG monitoring is recommended

RUFINAMIDE (BANZEL®, INOVELON®) 

Pharmacokinetics

- Peak plasma concentration reached 18 h after oral administration (10 mg/kg; dog)
- Half-life of ~8 h in dogs
- Peak plasma concentration and half-life increase with higher doses
- Some variability exists in the elimination rate in dogs. Every 8-h dosing may be necessary

Mechanism of Action

- Exact mechanism of action is unknown
- Thought to modulate voltage-gated sodium channels through the *prolongation* of the inactive state
- Suspected broad-spectrum anticonvulsant activity

Toxicity, Side Effects, and Interaction

- Generally regarded as very safe
- Reported to increase QTc interval in humans
- Reported to increase serum phenobarbital levels in humans
- Phenobarbital may lower serum rufinamide levels

Indications for Use

- Considered a sixth-tier prophylactic antiseizure medication

Dose

- 20 mg/kg every 12 h (dogs)
- May start at 5–10 mg/kg every 12 h and titrate to effect
- Every 8 h dosing may be necessary

Monitoring

- Monitor for safety and efficacy
- CBC and biochemical profile recommended every 6 months
- A target of 10–45 µg/ml (extrapolated from human data) is a consideration

TOPIRAMATE (TOPAMAX®) (TROKENDI XR®), (QUDEXY XR®) 

Pharmacokinetics

- Oral *solution* is 2× more bioavailable than the capsules. There is a 27–59% difference in the bioavailability

- Time to peak plasma concentration following oral dosing is ~0.6–4 h in the dog (depending on the form given)
- Low plasma protein binding and distribution in the body similar to water
- No apparent induction or inhibition of liver enzymes
- Half-life of 3 h in dogs
- Cats given extended-release form (capsules opened and contents sprinkled on food) had a half-life of 8–14 h

Mechanism of Action

- Inhibition of voltage-activated sodium channels in a dose-dependent manner
- Increases the opening of GABA-mediated chloride channels
- Increases GABA content in the brain
- Decreases glutamate-mediated excitatory neurotransmission through interaction with the kainate and AMPA receptors
- Modulation of calcium current through a direct effect on L-type voltage-sensitive calcium currents
- May facilitate potassium channel function, thereby enhancing inhibitory effects
- Weak carbonic anhydrase activity suspected to be responsible for the creation of kidney stones in humans

Toxicity, Side Effects, and Interaction

- Generally regarded as very safe
- 1–2% of humans will develop kidney stones
- Side effects in dogs include gastrointestinal distress, anorexia, anxiety, and irritability
- Anorexia possible (cats)
- Anemia (subclinical reported) may occur in cats
- May decrease IOP in cats
- Serum levels may increase if used concurrently with amitriptyline and propranolol
- Use with caution if using other carbonic anhydrase inhibitors or CNS depressants
- Levels may be reduced if used with other drugs, which result in liver enzyme induction
- May increase the clearance rate of digoxin

Indications for Use

- Broad-spectrum prophylactic antiseizure medication
- Typically used as a third-tier prophylactic medication to treat epileptic seizures
- May have beneficial effects in treating neuropathic sources of pain
- May be an adequate once-a-day dosing medication for cats, who are difficult to pill (extended-release form—Qudexy *XR*®—can be opened and the contents sprinkled on cat food).

Dose

- 2.5–10 mg/kg every 12 h (dogs)
- May require every 8 h dosing
- 12.5–25 mg (total dose) q 8–12 h (cats)
- 10 mg/kg every 24 h extended-release form (cats). Capsule opened and contents sprinkled on food
- If using extended-release form give 5–20 mg/kg every 24 h (dogs)

Monitoring

- Monitor for safety and efficacy
- CBC, biochemical profile, and urinalysis recommended 2 weeks, 4 weeks, then every 6 months. Cats reported to develop subclinical anemia (50% in one study)
- Careful monitoring for crystalluria
- Periodic monitoring of IOP is recommended for cats
- Increase to effect, side effect, or double the dose (i.e., before failing)

VALPROIC ACID (DEPAKENE®)



Pharmacokinetics

- Good absorption after oral administration with 78–90% bioavailability (dogs)
- Peak plasma concentration reached within 1 h of oral dosing
- Half-life ~3 h (dogs)
- Half-life 5–7.5 h (cats)
- Concentrates in the CNS of dogs
- Pretreatment with probenecid or phenylbutazone enhances the rate of entry into the CNS
- Metabolized by the liver through glucuronidation and β-oxidation
- Excreted in the urine
- Major metabolites also have antiseizure activity

Mechanism of Action

- Increases the concentrations of GABA and enhances its release in the presynaptic axon terminals of CNS
- Demonstrated effects on amino acids other than GABA
- Causes a dose- and time-dependent reduction in the synaptic release of gamma-hydroxybutyric acid (GHB) in the brain, which may be why it is effective in the treatment of absence seizures in humans. Increased GHP causes absence-like seizures
- A postsynaptic effect of valproate through interaction with amino acidergic neurotransmitters is also considered to be a primary mechanism whereby it exerts its effects

- May affect sodium and potassium transport across neuronal cell membranes
- Various effects on antagonism of T-type calcium currents have been demonstrated in some areas of the brain
- Antagonizes dopamine and potentiates serotonin in the brain
- Indirect effects on cyclic GMP (i.e., reduced levels)

Toxicity, Side Effects, and Interaction

- Significant potential for hepatotoxicity, especially when combined with phenobarbital
- CNS depression, sedation, ataxia, gastrointestinal upset, alopecia, rash, hematologic abnormalities, pancreatitis, and edema
- Alters thyroid function tests in humans
- Affects platelet aggregation
- Phenobarbital increases the elimination rate of valproic acid
- See text for further possible interactions

Indications for Use

- Potential broad-spectrum prophylactic antiseizure medication
- Typically, not used in dogs or cats due to availability of other safer medications
- May have potential as a seventh-tier prophylactic antiseizure medication
- *One of the most broad-spectrum and most effective antiseizure medications at preventing experimentally induced seizures in animals*

Dose

- 60 mg/kg q 8 h as add-on medication (dogs)

Monitoring

- Monitor for safety and efficacy
- CBC, biochemical profile, and fasting and fed bile acids recommended every 6 months
- Careful monitoring for hepatotoxicity

ZONISAMIDE (ZONEGRAN®)



Pharmacokinetics

- Good absorption after oral administration with 70% bioavailability (dogs and cats)
- Peak serum concentration at 2.5 h (dogs) and 4 h (cats)
- ~40% protein bound
- Half-life ~17 h (dogs)
- Steady state of 3–4 days (dogs)

- Half-life ~33 h (cats)
- Steady state of 7–10 days (cats)
- Partial hepatic metabolism
- Up to 83% excreted in the urine

Mechanism of Action

- Exact mechanism of action is unknown
- Antagonism of voltage-gated sodium channels and T-type calcium channels in the thalamus and inhibition of potassium-mediated glutamate release
- Reduction of transient inward currents leading to the stabilization of neuronal cellular membranes
- Accelerates the hippocampal release of GABA and may possess *neuroprotective* actions
- Weak carbonic anhydrase activity, which may result in extracellular acidosis with subsequent inhibition of epileptiform activity
- Through inhibition of potassium-mediated glutamate release, also increases extracellular levels of dopamine and serotonin (which may be why anorexia is a side effect)

Toxicity, Side Effects, and Interaction

- Generally regarded as very safe
- Sedation, anorexia, and ataxia
- Single report of acute, idiosyncratic, fatal, hepatic necrosis
- Structurally similar to sulfonamides, which may result in hypersensitivity reactions (i.e., fever, skin eruptions, hepatotoxicity, blood dyscrasia, keratoconjunctivitis, and arthropathies)
- Potential for renal tubular acidosis (reported in one dog)
- Visual hallucinations possible (humans)
- Night terrors possible (humans)
- May lower circulating thyroid hormones (T3 and T4)
- Phenobarbital will increase the clearance of zonisamide (decrease phenobarbital dose by 25%, if used concurrently with zonisamide)
- Behavior changes (aggression, sudden rage, insomnia, restlessness/anxiety) (dog)
- Lymphadenopathy, hyperglobulinemia, neutropenia, lymphopenia, anemia (cat)
- May develop tolerance
- Zonisamide may increase serum phenobarbital concentration significantly (may need to lower phenobarbital dose)

Indications for Use

- Broad-spectrum prophylactic antiseizure medication
- Considered a second or third-level antiseizure medication
- May be helpful in treating tremors

Dose

- 3–7 mg/kg every 12 h, increasing up to 20 mg/kg BID (cautiously) (dogs)—Monotherapy
- 7–10 mg/kg every 12 h, increasing up to 20 mg/kg BID (cautiously) (dogs)—if added to concurrent phenobarbital therapy.
- 3–5 mg/kg every 24 h, increasing up to 15 mg/kg/day (cats)
- Consider BID dosing in cats if SID is not effective
- Increase to effect, side effect, or double the dose (i.e., before failing)

Monitoring

- Monitor for safety and efficacy
- CBC, biochemical profile, and urinalysis recommended 2 weeks, 4 weeks, then every 6 months
- Reference range of 10–40 µg/ml (dogs and cats), although probably not necessary to monitor serum levels

COMMON FORMULAS

FORMULA FOR CALCULATING A PHENOBARBITAL IV LOADING DOSE*

This formula will calculate the total mg of phenobarbital to give IV in order to achieve a serum concentration of 25 µg/ml. Essentially comes out to about 20 mg/kg.

$$\text{Total mg IV} = \left(\text{body weight}\left[\text{kg}\right]\right) \times \left(0.8\,\text{l} / \text{kg}\right) \times \left(25\,\mu\text{g} / \text{ml}\right)$$

FORMULA FOR CALCULATION OF NEW DRUG DOSE

This formula may be used to calculate dose increases to achieve a new target serum concentration of any drug where serum concentration can be determined:

$$\frac{\text{Desired serum concentration}}{\text{Current serum concentration}} \times \text{current dose in mg / day} = \text{new total mg / day}$$

Example: A 15 kg dog has a current serum therapeutic concentration of phenobarbital measured at 20 µg/ml. It has been at least 3 weeks since the initiation of phenobarbital or a change in the dose (i.e., the dog has achieved *steady state*). You want to attain a new serum concentration of 25 µg/ml. The dog is currently being dosed at 3 mg/kg every 12 h (45 mg BID) or 6 mg/kg every 24 h or 90 mg/day.

$$\frac{25\ \mu\text{g / ml}}{20\ \mu\text{g / ml}} \times 90\ \text{mg} = 112.5\ \text{mg / day}$$

For practical purposes, the dose would be increased from 45 mg every 12 h to 60 mg every 12 h.

* Podell, M. 1996. Seizures in Dogs. *The Veterinary Clinics of North America. Small Animal Practice*. 26(4):779–809.

CALCULATION OF DRUG HALF-LIFE (WWW-USERS.MED.CORNELL.EDU/~SPON/PICU/CALC/HALFCALC.HTM)

The half-life of a drug ($t½$) refers to the time it takes for the concentration of plasma levels of a drug to decrease by ½ (50%). Because we are dealing with first-order kinetics, the rate of elimination is directly proportional to the concentration in the plasma (C_p). A linear relationship exists between the rate of elimination and the plasma drug concentration. Even though the amount of drug eliminated in a first-order kinetic model changes with concentration, the *eliminated fraction* of the drug remains constant. Therefore, the elimination rate constant (K_{el}) represents the fraction of drug eliminated per unit of time. The value 0.693 is the ln 2, which is calculated from the slope of the concentration of drug in the plasma at time 1 and the concentration in the plasma one half-life later (time 2), which would be 50%. Great news, this is a constant and you can just plug this into the formula—here it is:

$$\ln\left[\frac{C_p}{1}\times\frac{2}{C_p}\right]=\ln 2=0.693$$

The half-life can be calculated from the formula:

$$t\,{}^{1}\!/_{2}=\frac{0.693}{K_{el}}$$

K_{el} is the slope of drug concentration versus time; therefore:

$$K_{el}=\frac{\ln\left[\text{concentration 1}/\text{concentration 2}\right]}{\text{time 2}-\text{time 1}}$$

Concentration 1 is the *peak level* and concentration 2 is the *trough level*. The time to max concentration in the blood of the dog is between 4 and 8 h, so the time value in the denominator is going to vary a bit depending on what you pick (I usually choose 6 h). You can work through this formula as in the example below (pro tip – turn your phone sideways for this one) or use the drug calculator website found in this appendix, at the top of this section.

Example: Calculation of phenobarbital $t½$

Sample 1 at time 1 (6 h after dose = peak concentration in blood—note: range in dogs is 4–8 h) = ex. 30 µg/ml

Sample 2 at time 2 (12 h after dose = trough concentration in blood) = 20 µg/ml

$$K_{el}=\frac{\ln\left[30/20\right]}{12-6}=\frac{0.41}{6}=0.07$$

$$t\,{}^{1}\!/_{2}=\frac{0.693}{0.07}=9.9\,\text{h}$$

In this case, because the $t½$ of phenobarbital is <24 h, dosing every 8 h may result in better seizure control. Also note, if you alter what you think might be peak level (i.e., time 1) between 4 and 8 h, you will get wildly different results.

$$4\,\text{h}=6.86\,\text{h}$$

$$6\,\text{h}=9.9\,\text{h}$$

$$8\,\text{h}=13.86\,\text{h}$$

- Drugs with a higher volume of distribution will have a longer elimination half-life than a drug with a lower volume of distribution.
- Drugs that are more alkaline will tend to have a higher volume of distribution and therefore a longer elimination *t*½.
- Drugs that are more acidic will tend to be more highly protein-bound and therefore stay in the plasma (bound to albumin) leading to a lower volume of distribution and shorter *t*½.
- The more lipophilic a drug, the more likely it is to leave the circulation, have a higher volume of distribution and a lower *t*½.
- The more hydrophilic a drug, the more likely it will stay in the circulation, have a lower volume of distribution and a higher *t*½.
- Plasma proteins (like albumin) like to bind to lipophilic drugs, countering the effect of the higher volume of distribution. In these cases, the volume of distribution becomes more dependent on the acid/base characteristics of the drug (is it acidic or basic?).
- Steady state is met after 5.5 half-lives.

POTASSIUM BROMIDE LOADING DOSING EXAMPLE

The *loading* dose for potassium bromide in the dog is ~15 rapidly given maintenance doses:

If used as a monotherapy, begin with 30 mg/kg every 12 h by mouth. If used in combination with phenobarbital, initially give 20 mg/kg once a day. The dose range is anywhere from 15 to 80 mg/kg once a day. The drug is only given in divided doses to alleviate some of the gastric irritation that may be present from ingestion of a large amount of a salt at one time (think—gastric mucosal irritation). Gastric irritation may also be alleviated by giving the medication in a liquid form and with food. If tolerable, the entire daily dose can be given at once. Remember it is not the actual dose the animal gets but the serum concentrations the animal attains which is important.

A loading dose of 400–600 mg/kg can be given. Typically, the maintenance dose will be figured followed by an appropriate loading dose of the same capsule size (or amount of liquid), which can be given over several days. For example:

A 20 kg dog would need (30 mg × 20 kg = 600 mg every 12 h) as a maintenance dose.

A loading dose would be in the range of 8,000–12,000 mg (400–600 mg × 20 kg).

If 600 mg capsules are obtained, then the loading dose would be 14–20 capsules (8,000/600 = 13.3 capsules, 12,000/600 = 20 capsules).

The loading dose can be given as quickly as possible as long as there are no adverse side effects. Usually, 1–2 capsules are given every 4–6 h until the loading dose is achieved, followed by the maintenance dose 12 h after the last portion of the loading dose.

In the above example, the maintenance dose would be 600 mg every 12 h. The same dose or capsules can be used for the loading dose. Regardless of the capsule size calculated for the maintenance dose, if you give 15 "maintenance" doses over a short period of time (1–2 days), you will have *loaded* the patient.

Index

Note: Page numbers in *italics* refer to Figures; those in **bold** to Tables

A

abducent nerves, 480–481, *481–2*
absence seizure *see* epileptic seizures
acepromazine and seizure activity, 35
acetazolamide, function of, 54
acetylcholine, 32, *50*
  acetylcholinergic neurons, 49
  effect on epileptogenicity, 50
  and theta rhythm, 53
acidosis, effect on neurons, 54
Acorus calamanus, 397
action potential, *22,* 25, 27–31, *28–31*
  definition, 20
  patterns of discharge, 32
acupuncture/acupressure, 393–4
acute seizure, *499*
adenosine
  antagonism by methylxanthine derivatives, 399
  and hypothermia, 432
  role in stopping seizures, 354
  valerian and, 401
adenosine triphosphate (ATP), as an extracellular messenger, 46
Aethusa cynapium, 417
affective syndrome, 90
afterdischarges, 203
afterhyperpolarization (AHP), 32, *32*
Agaricus muscarius, 417
Albertoni, Pietro, 10, 292
alkaline phosphatase, 406
alkalosis, effect on neurons, 54
alpha-linolenic acid, 392
alternative therapy, definition, 385
alvear path of hippocampus, 52
American College of Veterinary Internal Medicine (ACVIM), 257
American College of Veterinary Internal Medicine (ACVIM) Consensus Statement, 202
American hellebore, 408
amnesia, 90
amygdala
  definition, 48
  and epileptogenicity, 46
  and hippocampus, 51
  and kindling, 48
  and limbic seizures, 91
amygdalohippocampectomy, 453
anosmia, 89, 478
antašubbû, 4
anticonvulsant effect of CBD, 405
antiepileptic drug (AED), 198
Antiepileptic Drug Development Program (ADD), 324
antiseizure formulary
  carbamazepine (Tegretol®), 501–2
  clonazepam (Klonopin®), 502–3
  clorazepate (Traxene®), 503–4
  diazepam (Valium®), 504–5
  ethosuximide (Zarontin®), 505–6
  felbamate (Felbatol®), 506–7
  gabapentin (Neurontin®), 507–8
  imepitoin (Pexion™), 508
  ketamine (Ketaject®, Ketaset®, Keta-sthetic®, Ketalar®, Vetalar®), 509–10
  lacosamide (Vimpat®), 510
  levetiracetam (Keppra®) (Keppra XR®), 511–12
  lorazepam (Ativan®), 512–13
  midazolam (Versed®), 514–15
  phenobarbital, 515–17
  potassium bromide (K-Brovet®), 517–19
  pregabalin (Bonqat®, Lyrica®, Pregatab®), 519–20
  propofol (Rapinovet®, Propoflo®, and Propoclear®), 520–521
  rufinamide (Banzel®, Inovelon®), 522
  topiramate (Topamax®, Trokendi XR®, Qudexy XR®), 522–4
  valproic acid (Depakene®), 524–5
  zonisamide (Zonegran®), 525–7
antiseizure medication choices
  for cats, 233, *236,* **237,** 237–8
  for dogs, 231, 233, **234,** *235, 236*

Seizures in Dogs and Cats, Second Edition. Sean Sanders.

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apasmara, 4
apigenin, 402
apneustic breathing, 363
aquaporin-4, 45
aromatherapy, 396, *412*
arrest reaction, 91
arsenic, 414
Artemisia absinthium, 417
ashwagandha, 413
asomatognosia, 89
ASPCA National Poison Control Center, 153
association fibers, *49*
  definition, 48
astrocytes, definition and function, 27, 45
Atharvaveda, 429
atonia, 88
ATP *see* adenosine triphosphate
attention deficit hyperactivity disorder (ADHD), 390
aura, 140
  definition, 67
autoimmune limbic encephalitis, 238
automatism
  definition, 67
  formation, 88
  reactive, 91
autonomic seizure, 471
autonomic signs, 90, 91
autoregulation, 361, *361*
  chemical *vs.* pressure, 366
axon hillock
  action potential and, 30
  definition of, 21
  sodium channels and, 30
Ayurveda, 4, 413–14

B

Bach flower therapy, 414
basal forebrain nuclei and cholinergic neurons, 49
basket cells of hippocampus, 52, *52*
BDNF *see* brain derived neurotrophic factor (BDNF)
beagle, 221, 283, 436, 455
  phenobarbital hypermetabolization, 226
belladonna (homeopathic treatment), 416
benign familial juvenile epilepsy, in Lagotto Romagnolo dog, 26
benign familial neonatal seizures, 26
benzodiazepines
  appetite stimulation, 262
  for cats, *263*
  for dogs, *259*
  introduction of, 13
  and status epilepticus, 355–6
Berger, Hans, 11
betony, 408
bile acids, 152
bilobalide, 399
bioavailability
  definition, 208
  related to bioequivalence, 212
biochemical profile, 149–50
bioequivalence, definition, 212
biofeedback, 417
biogenic amines, and seizure inhibition, 35
biomarkers, 186–7
  HFOs, 53
  and magnetic resonance spectroscopy, 185
biotransformation, in liver, 214
Biot's breathing, 363
blood brain barrier, and absorption of drugs, 212
bloodletting, 8
blood oxygen level-dependent (BOLD) fMRI, 178
blue cohosh, 408
Book of the Hunt, 7, *8*
Boothe, Dawn, 14
border cells (as in Schiff–Sherrington posture), 364
Bourgelat, Claude, 7
bovine congenital hypertonia *see* hyperekplexia
brain
  autoregulation, *361,* 366
  clinical signs, progression of, 128, 141–2
  development, 106
  herniation, 361
  numbers of neurons in, 20
  organization of, 46–53
  structural disease and treatment, 203
  traumatic brain injury (TBI), 368, 372–3
  "wireless network," 46
brain derived neurotrophic factor (BDNF), 43
brainstem evoked potential (BSEP), 483
brainstem locomotor network, 51
breed and genetic epilepsy, **84,** 103, 108
bridge therapy, 374
brivaracetam, 325
Brown-Séquard, Charles-Édouard, 9–11
bruxism, 88
buckthorn, syrup of, 13
burst firing
  CA3 neurons, 53
  subiculum, 53

C

caffeine, 398–9
calcium
  and burst firing, 47
  and epileptogenicity, 53
  and high-frequency oscillations (HFOs), 47, 53
  and long-term potentiation, 45
  and t-type currents, 47
  and waves, 46
calcium/calmodulin-dependent kinase II, 355
CAM *see* complementary and alternative medicine (CAM)
camphor, 397
cannabidiol (CBD), 404–7
cannabidivarin, 405

Cannabis sativa, 402–4
capnograph, 366
carbamazepine (Tegretol®), 314, 501–2
  dose, 316
  indications for use, 316
  introduction of, 13
  mechanism of action, 315
  monitoring, 316
  pharmacokinetics, 315
  toxicity, side effects, and interactions, 315
carbenoxolone, 39, 48, 325
carbonic anhydrase
  buffering function, 54
  inhibitors of, 54
CA1 region of hippocampus
  anatomical connections, 52
  burst firing, 53
  and gap junctions, 39
  and long-term potentiation, 45
CA3 region of the hippocampus
  anatomical connections, 52–3
  burst firing, 53
  and long-term potentiation, 45
cataplexy, **72**
cataracts, 480
catnip, 411
CAT scan *see* computed tomography
causticum, 417
centrencephalic theory of epileptogenesis, 51
cephalic signs, 90
cerebellum effect on epileptogenicity, 50
cerebral perfusion pressure, 360–361
cerebral spinal fluid (CSF), 166–9
  reduction of, 368
chamomile, 402
Charaka Samhita, 4, 413, 429
Cheyne–Stokes respiration, 363, *364*
Chinese Clubmoss *see* huperzine
chiropractic, 417
chloral hydrate, 10, 11
chloroform, 11
chocolate, 398
choline and magnetic resonance spectroscopy, 183, 185
chronic AED therapy, 229–239, 374
chrysin, 401
  supplements, 401
Cicuta virosa, 417
cineole, 397
cingulate gyrus and hippocampus, 51
cingulum and hippocampus, 51
clobazam, 322–3
clonazepam (Klonopin®), 502–3
  discontinuation, **248**
  indications for use, 260
  mechanism of action, 259
  monitoring, 260–261
  oral dose, 260
  pharmacokinetics, 260
  toxicity, side effects, and interactions, 260
clorazepate (Tranxene®), 503–4
  as a bridge therapy, 126, 241, *242*
  discontinuation, **248**
  indications for use, 262
  mechanism of action, 261
  monitoring, 262
  oral dose, 262
  pharmacokinetics, 261
  as a pulse therapy, 140
  toxicity, side effects, and interactions, 261
cluster seizure
  in classification, 82
  definition, 70, 82
  and tonic–clonic seizures, 94
  treatment, initiating, 203
Cobb, J.M., 14
cocoa, 398–9
coconut oil, 387
Codex of Eshnunna, 4
coffee, 398–9
cognitive enhancers, 399
cola (kola), 398
color therapy, 414
commissural fibers, *49*
  definition, 48
communication
  analogy, use of, 127, 130
  anti-seizure medications, choosing, 129–33
  bedside manner, 124
  disease progression curve, 128, *128*
  exam and discussion, 127–9
  exam and history, 124–5
  goals, 122
  models, 120–124, *121*
  narrative, 127–9
  patterns, **121**
  whiteboard, 130, *130, 131,* 132
    dose–response curve, 132, *133*
complementary and alternative medicine (CAM), 383
  acupuncture/acupressure, 393–4
  aromatherapy, 410–413
  ayurveda, 413–14
  herbal-and plant-based remedies, 394–6
  homeopathy, 414–17
  marijuana and hemp, 402–7
  potentially dangerous, 407–10
  potentially harmful, 396–400
  potentially helpful, 400–402
complementary therapy, definition, 385
complete blood count, 149
computed tomography (CT or CAT scan), 166, *167*
  introduction of, 14
conductance (G), definition, 22
connexins, *38,* 39
connexons, *38,* 39

conscious proprioception, 478, *479*
contraversive movements, 91
convulsive agents, 396
corpus callosotomy (CC), 454, 456–7
corpus callosum, transection of (callosectomy), 51
cortical spreading depression, 298
corticosteroids, 257–259
  epileptogenesis, 399
  intracranial pressure (use of to manipulate), 368
  limbic encephalitis, 371
  post status epilepticus, 371
  traumatic brain injury, 373
cranial nerves
  deficits of, 148
  facial nerve, 483
  glossopharyngeal and vagus nerves, 483
  hypoglossal nerve, 483–4
  oculomotor, trochlear and abducent nerves, 480–481, *481–2*
  olfactory nerve, 478
  optic nerve, 478, 480
  spinal accessory nerve, 483
  trigeminal nerve, 482
  vestibulocochlear nerve, 483
cranioplasty, *449*
creatine + phosphocreatine (CR), 183
crossed extensor reflex, 486
cryptogenic, 103
cryptogenic epilepsy *see* epilepsy, cryptogenic
CSF *see* cerebral spinal fluid
CT scan *see* computed tomography
cuprum, 417
current (I), definition, 22
Cushing reflex, 362
cutaneous stimulation, 437
cutaneus(eous) trunci reflex, 486–7
cytochrome p450, 215
  and microsomal enzyme induction, 215
cytotoxic edema, 362

D

dacanoic acid, 387
dacrystic, 67
dangerous herbal sedatives, **407,** 407–10
death, status epilepticus and, 352
decerebellate posturing, 364
decerebellate rigidity, 477
decerebrate posturing, 363, 364
decerebrate rigidity, 477
deep brain stimulation (DBS), 433–4
de Foix, Gaston, 7, *8*
de Lahunta, Alexander, 14
dentate gyrus, *52*
  anatomy, 52
2-deoxy-D-glucose, 327
derivation (related to EEG), 171
dexamethasone, 368
  traumatic brain injury (following), 372, 373
diabetes mellitus, and drug selection, 222
diagonal band of Broca *see* subcallosal area
diary *see* seizure diary
diazepam (Valium®), 504–5
  cluster seizures, 244
  CRI, 369
  distribution as effectiveness, 215
  dose, 266–7
  first pass effect, 215
  home kit, 243, *245*
  indications for use, 265–6
  intranasal, 244
  mechanism of action, 263
  monitoring, 267
  pharmacokinetics, 263–4
  as a pulse therapy, 140, 243, *244*
  rectal, *245*
  toxicity, side effects, and interactions, 264–5
diencephalon and epileptogenicity, 46
diet, 386–9
  dietary considerations, 389–90
    medium chain triglycerides, 390–391
    omega-3 fatty acids, 391–2
  gluten-free, 389
  ketogenic diet, 386–8
    for cats, 388–9
    for dogs, 388
  raw, 389
diffusion tensor imaging *see* magnetic resonance imaging, diffusion tensor imaging
diffusion tensor imaging MRI (DT-MRI), 372
  dexamethasone effect, 258
Dioscorides, 6
  and mugwort, 409
  and valerian use, 401
disconnection surgery, *453*, 456–60
disease
  definition, 99, 110
  progression curve, 128, *128*
docosahenaenoic (DHA), 391–2
dopamine, *50*
  effect on epileptogenicity, 50
  neurons, 49
dopaminergic *see* dopamine
doshas, 413
Drélincourt, Charles, 7
drug *see* medications
drug-resistant epilepsy (DRE), 456
dynorphin, 355
dysmnesia, 90
dyspraxia, 90
  definition, 67

E

Edward of Norwich, 7
EEG *see* electroencephalograph (EEG)

eicosapentaenoic (EPA), 391–2
elastogram, 185
ELB 138 *see* imepitoin (Pexion™)
electrical synapse, 37, *38,* 39 *see also* gap junctions; synapse, electrical
electrocerebrogram, 11
electrocorticography (ECoG), 447–52
electroencephalograph (EEG), *18,* 170–177, *172*
  ambulatory EEG, 170, *171*
  burst suppression, 176
  definition, 170
  development, 11
  electroclinical syndromes, 172–3
  epileptiform, 67
  and high-frequency oscillations (HFOs), 47
  incidence of abnormalities, 71
  paroxysmal depolarization shift and, 31–2, *32*
  sensitivity, 170
  during slow-wave sleep, *18, 175*
  "spike and wave," 171
  surgical planning, 173
  theta rhythm, 53
  when to use, 174
electroencephalography, 447–52
electrolytes and epileptogenicity, 54
elimination half-life calculation, **219,** 528–9
emergency management
  home setting, 374–6
  hospital setting, 356–60, *357*
"enclothed cognition," 124
endocrine disease and drug selection, 222
endorphins (acupuncture), 393
entorhinal cortex, *52*
  anatomy and connections, 51–3
entourage effect, 405
ephedra, 398
ephedrine, 399, 418
epigastric signs, 89–90
"epilambanein," 63
epilepsia partialis continua, 64
epilepsy
  biomarkers, 186–7
    HFOs, 53
  catamenial, 109
  classification, 71, **71, 75**
    approach to, 80–86
    etiological, 70, 74
    goals, 103
    historical perspectives, 70–72
    importance of, 72
    phenomenological, 73, **77–8,** 86–100
    syndromic, **83,** 84
  cryptogenic, 75
  definition, 18, 66, 102
  earliest record, 4
  etiology, 142
    age based, **143–5**
    genetic (cats), 102
      and breed correlation, 108
    genetic (dogs)
      breeds, **84,** 103, 108
    historical classification, 6
    idiopathic
      confusion of term, 75
      definition, 75
      incidence, 71
    maturational cessation of, 43
    metabolic, **75**
    paroxysmal depolarization shift and, 31
    primary, 75, **75**
    reflex epilepsy, 9, 11
    success, estimates of, 439
    surgery, *162,* 179, *180,* 438–52, *444–6*
    traumatic brain injury (following), 372
    treatment *see also* medications
      conservative *vs.* diagnostic approach, 129
      dosing, 205–8, 228–9
      success, estimates of, 200, 230
      when to treat, 201–5
      why treat, 199–201
epileptic seizures, 468
  absence, *81,* 96
    definition (historical), 76
  autonomic seizure, 471
  autonomic signs, 67
  cessation of, 354
  complex partial, definition (historical), 76
  conditions mistaken for, 19, 137
  dacrystic, 67
  definition, 17, 19, 63, **103**
  duration, 472–3
  elements of, 66–8
    aura, 140
    ictus, 140
    postictus, 141
    postictus and bridge medication, 141
    postictus deficits, persistence of, 141
    prodrome, 140
  etiological significance of, 72
  etiology, **138**
  factors contributing to, 20, **20**
  focal, 73, 87–92
    automatisms, 88
    definition, 67
    definition (historical), 76
    dyscognitive, 88
    elementary types, 89–90
    epidemiology, 91, 140
    incidence in population, 92
    interactive, 89
    treatment of, 90
    types, 87
      limbic, 90–91, 100
      neocortical, 87–8

epileptic seizures (*cont'd*)
secondary generalization, 92
gelastic, 67
generalized, **77,** 92–7
definition, 76
epidemiology, 93–4, 140
secondary generalized, 76
tonic–clonic, 92
types, 92–7
absence, 96
atonic, 96
atypical absence, 96
clonic, 96
myoclonic, 96
myoclonic absence, 96
myoclonic atonic, 95
myoclonic tonic-clonic, 95
tonic, 94
tonic–clonic, 93–4
grand-mal *see also* epileptic seizures, generalized
definition, 76
and head trauma, 203
ILAE classification of seizure types, **77–8**
incidence, 18
management, lifestyle changes, 141
motor
automatism, 469–70
elementary motor, 468–9
nonmotor, 470–471
partial and aura, 67
partial, definition, 76
petit mal, definition, 76
progression of, 141–2
reactive, 70, **75**
remission, 247
secondary generalization, 442
seizure timing, 472
sensory seizure, 89
simple partial, definition, 76
somatotopic modifiers, 471–2
spread, 87
stressor, 126
tonic-clonic, self-termination of, 69
treatment *see* epilepsy, treatment
unknown
definition, 76, 97–100
hyperekplexia, 99
idiopathic phenobarbital-responsive hypersialosis, 100
reflex seizures, **99**
rub epilepsy, 99
epileptic syndrome, 100–109
approach, 80
definition, 66, 68, 100
examples, 79–80
fingerprinting, 179
influencers, 104–9
types, 106
epileptiform, definition, 63
epileptogenesis
and brainstem connections, 51
cerebral circulation, 54
definition, 36, 53, 371
and epilepsy, 102
and glucose, 54
hepatic disease, 54
and hippocampus, 54, 371
hypertriglyceridemia, 54
and limbic system, 51
and neocortical connection, 47
and oxygen metabolism, 54
polycythemia, 54
renal disease, 54
and slow-wave sleep, 49–50
and subcortical connections, 49–50
epileptogenic lesion, 451
epileptogenic zone, 451
definition, 88
equilibrative nucleoside transporter (ENT_1), 404, *405*
essential epilepsy, 102
essential oils, 398, **398**
estrogen, as a proconvulsant, 109
ether, 11
ethosuximide (Zarontin®), 324, 505–6
absence seizures, 224
dose, 316, 317
indications for use, 316, 317
mechanism of action, 316
monitoring, 316, 317
pharmacokinetics, 315–17
toxicity, side effects, and interactions, 315, 317
eucalyptus, **398**
euthanasia
economic, 353–4
frustration, 266
ignorance, 120, 354
premature, 93, 199, 200, *206,* 207, 375
threatening, 204
experiential events, 90
ezogabine, 327 *see also* retigabine

F

facial nerve, *482,* 483
Fair, W.C., 12
the Falling disease, 4
the Falling sickness, 7, 11, 13
familial spontaneous epilepsy, 455
famotidine, 368
The Farmer's Veterinary Adviser, 11
fast ripples (pHFOs), 53
fecal analysis, 150
feedforward and feedback inhibition, *47*

and hippocampus, 52
and neocortical connections, 46–7
felbamate (Felbatol®), 304–5, 506–7
discontinuation, **248**
dose, 305
indications for use, 305
mechanism of action, 305
monitoring, 306
pharmacokinetics, 305
therapeutic drug monitoring, **156**
toxicity, side effects, and interactions, 305
fennel, **398**
Ferrier, David, 10, 11, *11*
^{18}F-fluorodeoxyglucose (FDG), 179
first pass effect, 215
FLAIR *see* fluid-attenuated inversion recovery
flaxseed oil, 413
flea control, essential oils, 398
fluid-attenuated inversion recovery (FLAIR), *157,* 158
flumazenil, 266
fluorofelbamate, 325–6
fly-biting, 89
focal motor seizure, 18
secondary generalization, 442
Fontana, Felice, 7
Food and Drug Administration (FDA)
and generic drugs, 212–13
formulary, 501–27
Fritsch, Gustav, 10, 433
functional deficit zone, 451
functional tolerance, 223
fundic exam, 148
furosemide
increased intracranial pressure (use of), 366

G

GABA *see* gamma-aminobutyric acid
$GABA_A$ receptor, 27, *29,* 32, *33,* 34
and palmitoylation, 40
$GABA_B$ receptor, 34
GABAergic interneurons
and mistletoe, 408
and mugwort, 409
and synchronization, 46–7
gabapentin (Neurontin®), 507–8
discontinuation, **248**
dose, 268–9
indications for use, 268
mechanism of action, 267–8
monitoring, 269
pharmacokinetics, 268
toxicity, side effects, and interactions, 268
GABA reuptake transporter (GAT-1), 39
GABA transaminase (GABA-T), 39
gadolinium, 159
gait, 148
galanin, 355
Galen, 6
γ-aminobutyric acid (GABA), 20, 25, 390, 392
and magnetic resonance spectroscopy, 183, 185
ganaxolone, 326
gap junctions *see also* synapse, electrical
and calcium waves, 53
failure of disassociation, 39
and glial cells, 45
HFOs, 53
uncoupling, tonabersat, 327
gas anesthesia, 370
gastrointestinal disease and drug selection, 221–2
GAT-1 *see* GABA reuptake transporter
gelastic seizures, 67, 91
generalized motor seizure, 18
secondary generalization, 68
genetic epilepsy prone rats *see* GEPR-9
geniculohypothalamic tract, 107
GEPR-9
and centrencephalic theory, 51
model, 48, 51
ginko, **399**
ginseng, 399
ginsenoside Rg1, 399
glial cells
definition and function, 45
as an extracellular buffer, 54
glioma, prognosis, 82
glossopharyngeal and vagus nerves, 483
glucuronidation, 215
glutamate (glutamine), 32, 362
biomarker, 187
and huperzine, 402
and kavalactones, 400
and ketogenic diet, 387
and magnetic resonance spectroscopy, 183, 185
glutaminergic neurons
epileptogenesis, 371
and hippocampus, 52, 355
and hypothermia, 432
and status epilepticus, 355
glycine, and hyperekplexia, 99
G protein-coupled receptor 55 (GPR55), 404
gradient echo, 160, *161*
grand mal, 6
granule cells of hippocampus, 52, *52*
"The Great Sickness," 6
guarana, 398, **399**

H

Hahnemann, Samuel, 414
half-life calculation, **219,** 527–9
hallucinations, 89
hamartoma, *162*

Haupmann, Alfred, 12
"head bobber" *see* postural repetitive myoclonus
Hebb, Donald O., 43
Hebbian Theory, 43–4
hellebore (American), 408
hemispherectomy/hemispherotomy, 453
hemorrhage and MRI changes, 158–60, **160,** *162*
hemp, 402–4
herbal remedies, 394–410
herbal sedatives, **400,** 400–410, **407**
herbal stimulants, 398–9, **399**
high-frequency oscillations (HFOs)
  as biomarkers, 53
  definition, 47
  ripples, 53
hippocampal fornix, 51
hippocampal sclerosis, 53, 173, 439
  and mesial temporal lobe epilepsy, 441
hippocampus, *52*
  anatomy and connections, 51
  and appearance, 124
  cannabinoid receptors, 403
  and catamenial epilepsy, 109
  granule cells, 52, *52*
  and limbic seizures, 90
  and long-term potentiation, 45
  microscopic connections, 52
  mossy fibers, 52
  perforant path, 52
  and seizure types, 91
  and surgery, 453
  and toxic destruction of, 92
  traumatic brain injury, damage to, 371
Hippocrates, 6
  and appearance, 124
  and diet, 386
  and homeopathy, 414
history, 137–9
Hitzig, Eduard, 10
Hoerlein, B.F., 14
Holliday, Terrell, 14
Homeopathy, 414–17
honeymoon effect, 223
Horsley, Charles, 11
huperzine, 402
hydrocephalus
  breeds of dogs, 108
  cats, 108
hyoscyamus, 417
hyperekplexia, 99
hyperforin, 400
hyperkalemia and epileptogenicity, 54
hyperkinetic state, 88
hypernatremia and epileptogenicity, 54
hyperosmotic agents and lowering intracranial pressure, 365–6
hypersensitivity reaction, 223
hypersialosis (phenobarbital responsive), 100
hyperthermia and tonic-clonic seizures, 93
hypertonic saline, increased intracranial pressure (treatment of), 365
hyperventilation, increased intracranial pressure (treatment of), 366
hypnic jerks, 97
hypoacusis, 89
hypoalbuminemia and drug selection, 222
hypocalcemia and epileptogenicity, 54
hypochloridemia and epileptogenicity, 54
hypoglossal nerve, 483–4
hypokinetic state, 88
hypomagnesemia, and epileptogenicity, 54
hypothalamus, and limbic seizures, 91
hypothermia, 432
  status epilepticus, 360
hyssop, **398**

I

ictal onset zone, 179
ictus, definition, 68
idiopathic
  definition, 75
  epilepsy *see* epilepsy, genetic
  incidence of, 71
idiopathic phenobarbital-responsive hypersialosis, 100
ILAE *see* International League Against Epilepsy
illusions, 90
imepitoin (Pexion™), 269–70, 508
  dose, 271
  indications for use, 271
  mechanism of action, 270
  monitoring, 272
  pharmacokinetics, 270
  toxicity, side effects, and interactions, 270–271, *271*
imponderables, 415
insulin/glucose ratio, 153
integrative therapy, definition, 385
interictal
  deficits, 105
  definition, 68
International League Against Epilepsy (ILAE)
  1981 classification scheme (focal), 87
  2010 classification scheme (focal), 87
  mission statement, 62
International Veterinary Epilepsy Task Force (IVETF), 135, 231, 257
intracarotid amobarbital procedure (Wada test), 442
intracranial pressure, 360–371, *361*
  assessment of, 362–4
  treatment of increased ICP, 365–8
ion channels, *33*
  ligand-gated, *23,* 25, *33*
  voltage-gated, 25, 33
ion, definition, 24
ionotropic receptor, *27*

definition of, 32
ipsiversive movements, 91
irritative zone, 179, 451
isoflurane anesthesia, 370
isovalerate, 401

J
Jackson, John Hughlings, 10
Jacksonian march, 469
Jimson weed (stramonium), 13

K
Kahun Papyrus, 5, *5*
kainic acid and amygdala destruction, 49
kava, 400–401
kavalactones, 400
ketamine (Ketaject®, Ketaset®, Keta-sthetic®, Ketalar®, Vetalar®), 509–10
CRI (for status epilepticus), 370
dose, 307
indications for use, 307
mechanism of action, 306
monitoring, 307–8
neuroprotective effects, 306
pharmacokinetics, 307
toxicity, side effects, and interactions, 307
ketogenic diet, 386–8
for cats, 388–9
development, 12
for dogs, 388
kidney and drug elimination, 214
kindling
and amygdala, 49
definition, 43, 45, 48–9
and long-term potentiation, 45
and progressive brain signs, 141
and reactive/metabolic seizures, 371
and seizure treatment, 203
knee jerk reflex, 486

L
lacosamide (Vimpat®), 510
dose, 309
indications for use, 309
mechanism of action, 308
monitoring, 309
pain control, 308
pharmacokinetics, 308
toxicity, side effects, and interactions, 308
lactate, 183, 185
biomarker, 187
Lafora disease, 106
and myoclonic epilepsy, 95
Lagotto Romagnolo, 26
lamellipodia, 43
lamotrigine, 323–4
lateral dorsal tegmental area and cholinergic neurons, 49
laudanum, 13
Law, James, 11
Laws of Hammurabi, 4
lead, blood testing, 150, 153
lesion localization, 487–90
leucine-rich glioma inactivating factor 1 (LGI1), 371
levetiracetam (Keppra®) (Keppra XR®), 511–12
dose, 276
extended release weight limitations, 221
indications for use, 275–6
mechanism of action, 272–3
method of action, 37
monitoring, 276
pharmacokinetics, 273–4
therapeutic drug monitoring, **156, 248**
therapeutic "window," 231, *233*
toxicity, side effects, and interactions, 274–5
lidocaine, working of, 27
limbic encephalitis (felines), 371
limbic seizures *see* epileptic seizures
limbic system, *52*
connections, 51–3
definition, 51
liver
and drug elimination, 216
and drug metabolism, 214, **216**
altered with plant/herbal remedies, 395
and drug selection, 222
hepatic lipidosis (cats), 388–9
hepatotocixity, 215
"Livre de la Chasse," 7
localization, 82
Locock, Charles, 10, 292
locus coeruleus and noradrenergic neurons, 49
long-term memory, 199
long-term potentiation, *44,* 44–5, 141
lorazepam (Ativan®), 276–7, 512–13
dose, 278–9
indications for use, 278
mechanism of action, 277
monitoring, 279
pharmacokinetics, 277–8
as a pulse therapy, 140, 243, *244*
status epilepticus, chronic use, 369
toxicity, side effects, and interactions, 278
Lorenz, John, 14
Löscher, Wolfgang, 14
losigamone, 326
Luciani, Luigi, 10
"lunatic," 4
lysosomal storage disease *see* storage disease

M
magnetic resonance elastography (MRE), 185–6
magnetic resonance imaging (MRI), 157–66
diffusion tensor imaging, 53, 161
diffusion-weighted, 160, *163*

magnetic resonance imaging (MRI) (*cont'd*)
and edema, 160, *162*
fluid-attenuated inversion recovery (FLAIR), *157,* 158
functional, 178, *181*
definition, 53
gradient echo, 160, *161*
and hemorrhage, 158–60, **160,** *162*
introduction of, 14
magnetic susceptibility artifact, 158
scan protocol for brain imaging, **165,** 165–6
and stroke, *163*
and toxins, 157, *157*
magnetic resonance spectroscopy, *180,* 183–5
magnetoencephalography, 178
ma huang *see* ephedrine
mannitol, increased intracranial pressure (treatment of), 365–6
marijuana, 402–4
testing for toxicity, 150
toxicity, 403
Maté, 398
materia medica, 415
McGrath, J.T., 14
MDR1 gene *see* multi-drug resistant 1 gene
medications *see also* individual drug names
choosing, 146, **220,** 220–228, 230–231
corticosteroids, 257–9
discontinuing, 247–8, **248**
dosing, 205–8, 226
drugs not used in dogs and cats, 322–4
bromide (cats), 323
clobazam, 322, 323
ethosuximide, 324
lamotrigine, 323–4
nitrazepam, 324
phenytoin, 323
primidone, 323
reasons for, 323–4
tiagabine, 324
verapamil, 323
vigabatrin, 324
drugs under development, 324
brivaracetam, 325
carbenoxolone, 325
2-deoxy-D-glucose, 327
fluorofelbamate, 325–6
ganaxolone, 326
losigamone, 326
perampanel, 326–7
retigabine, 327 *see also* ezogabine
retigabine (ezogabine), 327
tonabersat, 327
drug working mechanisms, 257
failure, 142, 146
formulary, 501–27
generic *vs.* brand name, 212–13
half-life, *206, 209,* 217–18
calculation, **219,** 527–9
loading dose, *219*
definition, 219
memory enhancers, 399
narrative, 131, 132
newer or less common drugs
felbamate, 304–6
ketamine, 306–8
CRI, 370
lacosamide, 308–9
pregabalin, 309–11
propofol, 311–13, 370
paradoxical side effects, 312
rufinamide, 313–14
paradoxical reactions to, 223
pharmacological principles, 208–28, *209*
absorption, 211–13
distribution, 213–14
elimination, 216–17
metabolism, 214–16
protein binding, 213
pharmacoresistance
incidence of, 384
p-glycoprotein, 315
rarely used drugs
carbamazepine, 314–16
ethosuximide, 316–17
mephenytoin, 317
phenytoin, 317
primidone, 318
valproic acid, 318–22, 355
routes of administration, 208–11
standard drugs/medication
clonazepam, 259–61, 369, 374
clorazepate, 261–2, 369, 374
diazepam, 262–7
CRI, 369
home bridge/pulse therapy, 375
gabapentin, 267–9
imepitoin, 269–72
levetiracetam, 272–6
lorazepam, 276–9
home bridge/pulse therapy, 375–6
status epilepticus, chronic use, 375
midazolam, 279–82
home bridge/pulse use, 376
phenobarbital, 282–92
potassium bromide, 256, 257, 292–7
loading dose, **297,** 369
rectal, 369
sodium bromide, 295
topiramate, 297–300
zonisamide, 300–304
status epilepticus, 356–9, *357,* **358**
steady state, *206*

definition, 205, 218
strategies for treatment, 228–47, *229*
and acute disease, 222
bridge, 126, 239–43, *242*
home use, 374
loading doses, 241
status epilepticus, following, 369
withdrawal seizures, 240, 241
chronic/prophylactic, 125, 230
definition, 229
home use, 374
definition, 228
drugs
cats, **237**
dogs, **234**
home kit, 243, *245*
pulse, 140, 243–7, *244*
definition, 229
doses, **244**
home use, 375–6
therapeutic drug monitoring, 247, **248**
and bioequivalence, 212
and protein binding, 213
reference range, 205, 206, *207,* 227
therapeutic range, 205, 206, *207,* 227
medium chain fatty acids (MCFAs), 387, 390–391
medium chain triglycerides (MCTs), 390–391
epilepsy and cognitive dysfunction, **391**
meningioma
MRI appearance, *167, 180*
prognosis, 82
mental status, 475, *476*
Mentat, 413
mentation, 147, 148
mephenytoin, 317
meprobamate, 304
mesial temporal lobe epilepsy
clinical signs, 91
hippocampal sclerosis, 441
magnetic resonance elastography, 186
pathophysiology, 411
and surgery, 441
metabolic screen, for storage disease, 154
metabolic tolerance, 223
metabotropic receptor, *33*
definition of, 32
second messenger systems, 40
metaldehyde, 373
methylprednisolone sodium succinate (Solu-Medrol®)
increased intracranial pressure, treatment of, 368
traumatic brain injury (following), 372, 373
methylxanthine derivatives, 399
microglia, definition, 45
microsomal enzyme induction, 215
midazolam (Versed®), 514–15
dose, 281–2
indications for use, 281
mechanism of action, 279
monitoring, 282
pharmacokinetics, 279–80
pulse therapy, 244, **244**
stability, 244, **244**
toxicity, side effects, and interactions, 280–281
midazolam IV, 369
Miletus, 6
mimetic sign, 469
minimal database, 148–50, **149**
mirror focus, *49*
definition, 50
and seizure treatment, 203
mistletoe, 400, 408
Monro–Kellie doctrine, 360, 362
montage, 170
mossy fibers, of hippocampus, 52, *52*
MRI diffusion imaging *see* magnetic resonance imaging, diffusion tensor imaging
MRI scan *see* magnetic resonance imaging
mugwort *(Artemisia vulgaris),* 6, 409
multi-drug resistant 1 gene (MDR1), 154
multiple hippocampal transection (MHT), 458
multiple subpial transection (MST), 458, *458*
myelin, *22*
myoclonus
definition, 94
distinction from tremor, 97
myoinositol, 183, 185
myristoylated alanine-rich C kinase substrate (MARCKS), 319

N

N-acetyl aspartate (NAA), 183
biomarker, 187
narcolepsy, **72**
National Institute of Neurological Disorders and Stroke (NINDS) 2007 Epilepsy Research Benchmarks, 186
Neher, Erwin, 14
neonate
and drug metabolism, 215
and drug protein binding, 213
nepetalactone, 411
nerve growth factor (NGF), 43
netrins, 43
neurites, 43
neuroanatomical localization, 146, 492
neuroblasts, 42–3
cell differentiation, 43
neurokinin B, 355
neurological deficits, presence of, 147
neurological exam, 146–8
conscious proprioception, 478
cranial nerves *see* cranial nerves

neurological exam (*cont'd*)
description, 491–2
form, 475–99
lesion localization, 487–90
mental status, 475
pain sensation, 487
posture, 475–8
reflex testing, 484–5
neurons, *22*
afferent, 36
burst firing, 47
and high-frequency oscillations, 47
connection, 36–7
definition, 20
efferent, 36
environment, 40
function, 24
interneuron, 36
migration, 42
disorders of, 42
networks, 42–3
principle neurons and HFOs, 53
super-networks, 39
synapses, 36
synchronization, 45
threshold, 24
neuropeptides, anticonvulsant/proconvulsant, 355
neuropeptide Y, 355
neuropil, definition, 36
neurosteroids, 326
neurotransmitter, 31
neurotrophins, 43
NGF *see* nerve growth factor
nitrazepam, 324
nodes of Ranvier, 21
noninvasive vagal nerve stimulation (nVNS), 437
noradrenergic neurons, 49, *50*
effect on epileptogenicity, 49
nordiazepam, 261
nosodes, 415
nucleus subcoeruleus and noradrenergic neurons, 49

O

ocular compression, 437–8, *438*
oculocardiac reflex, 437
oculomotor nerves, 480–481, *481–2*
Ohm's law, definition, 22
olfactory nerve, 478, *480*
olfactory signs, 91
olfactory system, *412*
oligodendrocytes, definition, 45
omega-3 fatty acids, 391–2, 413
omeprazole
effects on cerebral spinal fluid production, 368
and gastrointestinal protection, 368
optic nerve, 478, *480*
The Organization of Behavior, 43
oroalimentary automatisms, 80, 87
Osler, William, 120
oxcarbazepine, 314
oxide of zinc, 13

P

pacemaker cells, neocortical, 47
pain (neuropathic)
deep (testing of), 487
medications
carbamazepine, 314
gabapentin, 323
lacosamide to treat, 308
perampanel, 326
topiramate to treat, 299
valproic acid, 318
superficial (testing of), 487
pain sensation, 487
Palmer, A.C., 14
pancreatitis and drug selection, 221–2
pantoprazole
effects on cerebral spinal fluid production, 368
and gastrointestinal protection, 368
paracusis, 89
paradoxical vestibular syndrome, 477
parageusia, 91
paraventricular nuclei and slow-wave sleep, 107
parosmia, 91
paroxysmal depolarization shift, 31–2, *32*
relation to gap junctions, 39
paroxysmal discharges, 171–2
paroxysmal microarousal, 97
paroxysmal dyskinesia (movement disorder), 19, 64, **72**, **84**, 139
diet, link to, 389
zonisamide for treatment, 303
passionflower, 401
patch clamp
discovery, 14
historical use, 14
phenobarbital, 14
patellar reflex, 486
pathological high-frequency oscillations (pHFOs)
definition, 47
fast ripples, 53
patient care, hospitalization, 373
pedunculopontine reticular and cholinergic neurons, 49
pennyroyal, 398, **398**
perampanel, 326–7
perforant path, 52
perineal reflex, 487
PET scan *see* positron emission tomography
p-glycoprotein, **143**
pharmacoresistance, 315
pharmacokinetics, 217–20
first order, 217, *218*
single-compartment model, 220

two-compartment model, 220
zero order, 217, *218*
pharmacoresistance
definition of, 439
p-glycoprotein, 315
pharmacoresistant human patients, 384
phenobarbital, 257, 282–3, 515–17
discontinuing, **248**
dose, 289–90, **290**
drug interactions, 285–6, **287–8**
effectiveness, 282
idiopathic hypersialosis, treatment of, 289
and idiopathic phenobarbital-responsive hypersialosis, 100
indications for use, 288–9
mechanism of action, 283
microsomal enzyme induction, 215, 224, 231
monitoring, 290–291
pharmacokinetics, 283–4
polyphagia, 223
side effects, 285
therapeutic drug monitoring, 155, **156, 248**
toxicity, side effects, and interactions, 284–6, **287, 288**
phenothiazines and seizure activity, 35
phenylbutazone and valproic acid, 321
phenytoin, 317
discovery of, 12
and idiopathic phenobarbital-responsive hypersialosis, 100
phosphenes, 89
physical exam, 146–8
Pipsissewa, 409
placebo effect, 415, 416
plant and herbal remedies, 394–410
pneumoencephalography, 14
Podell, Michael, 14
poison *see* toxin
poison control *see* ASPCA National Poison Control Center
pontine reticular formation and cortical excitability, 46
positron emission tomography (PET), 179–82
postictal phase and tonic-clonic seizures, 94
postural repetitive myoclonus ("head bobber"), 98
posture, 475–8
changes of, 148
potassium bromide (K-Brovet®), 256, 257, 292, 517–19
ataxia, 223
discontinuation, **248**
discovery of, 10
dose, 296
effectiveness
compared to phenobarbital, 282–3
compared to sodium bromide, 295
historical use, 10, 11, 13
idiosyncratic reaction, 223
indications for use, 295–6
loading dose calculation, 296
mechanism of action, 292–3
monitoring, 296–7, **297**
pharmacokinetics, 293
"spinning dogs," 225
therapeutic drug monitoring, **156, 248**
therapeutic "window," 231, *233*
toxicity, side effects, and interactions, 293–5
when to use, 227
potassium channel
KCNQ2 and KCNQ3, 26
KV7 gene family, 26
limbic encephalitis (felines), 371
M-current, 29
retigabine, effects on, 327
toxins, 29
Pravdich-Neminsky, Vladimir, 11
prednisone/prednisolone
and increased intracranial pressure, 368
structural brain disease, use of, 373
pregabalin (Bonqat®, Lyrica®, Pregatab®), 309, 519–20
dose, 311
indications for use, 310–311
mechanism of action, 310
monitoring, 311
pharmacokinetics, 310
stopping, **248**
toxicity, side effects, and interactions, 310
pregnane X receptor, 400
presurgical ECoG, *450*
primary care veterinarian, 198
primidone, 318, 323
and idiopathic phenobarbital-responsive hypersialosis, 100
probenecid (and valproic acid), 320, 321
prodrome
definition, 66
and tonic-clonic seizures, 93
progesterone, as an anti-convulsant, 109
projection fibers, *49 see also* neurons, principle neurons and HFOs
definition, 48
prophylactic (chronic) therapy, 230–239
cats, drug choices, 230–238, **236**, *237*
dogs, drug choices, 231–233, **234**, *235*
emergency, home treatment, 374
problems with, 238–239
propofol (Rapinovet®, Propoflo®, and Propoclear®), 520–521
CRI (for status epilepticus), 370
dose, 313
indications for use, 312–13
mechanism of action, 311–12
monitoring, 313
pharmacokinetics, 312
toxicity, side effects, and interactions, 312
proprioceptive deficits, 148
protein palmitoylation, 40

pseudoephedrine, 399
pseudoresistance, 198, 238
psychomotor seizure, 18, *85*
  and temporal lobe epilepsy, 442
  and toxins, 91
pulse therapy, 375–6
pyramidal neurons, of hippocampus, 52, *52*
pyruvate, biomarker, 187

R
rabies
  historical, 4, 7
  "running madness," 7
radiographs, 155
ragweed, 409 *see also* mugwort
Raphe nucleus
  and serotonergic neurons, 49
  and slow-wave sleep, 107
rapid eye movement (REM), 394
raw food diet, 389
reference range, definition, 205
reflex epilepsy, 65, 98
  stimuli, **99**
reflexes, 148, 484–7
  crossed extensor, 486
  cutaneus(eous) trunci reflex, 486–7
  patellar reflex, 486
  perineal reflex, 487
  withdrawal reflex, 486
refractory period (of action potential), 27
Reiki, 417
renal disease
  and drug elimination, 216
  and drug selection, 222
repetitive transcranial magnetic stimulation (rTMS), 438
resection surgery, 455–6
resistance (R), definition, 22
respiratory patterns and brainstem compression, 363
resting membrane potential, 24
  depolarization, 27
retigabine, 327 *see also* ezogabine
retinohypothalamic tract, 107
ripples (HFOs), 53
risk factors, 186
rosemary, 397, **398**
rostral and lateral tentorial craniectomy, *448*
rub epilepsy, 99
rufinamide (Banzel®, Inovelon®), 522
  dose, 314
  indications for use, 314
  mechanism of action, 313
  monitoring, 314
  pharmacokinetics, 313–14
  toxicity, side effects, and interactions, 314
Rush, Benjamin, 8, *9*

S
sage, **398**
Sakikku, 4
Sakmann, Bert, 14
saltatory conduction, *22, 31*
  definition, 21
sarcodes, 415
savin, **398**
Schaffer collaterals, *52*
  hippocampus, 52
Schiff–Sherrington posture, 364, 477, *478*
seizure *see also* epileptic seizures
  control, 384
  definition, 63
  diary, 125–7, *126,* 141, 497–8
    and bridge medications, 241, 242
    and chronic medications, 374
  reactive or metabolic and development of epilepsy, 371
seizure-like event, 71, 72
seizure-onset zone, 451
semiology, 467–73
sensory seizures, 67
serial seizures, 352
serotonin, *50*
  effect on epileptogenicity, 49
  serotonergic neurons, 49
  syndrome, 402
Shalihotra, 6, 413
Shalihotra Samhita, 6, 413
shen-men, 393
shoe-smelling, 410, *412*
short-term memory, 199
Sieveking, Edward, 10, 292
sign of disease, definition, 63
silicea, 417
silver nitrate, 9
single-photon emission computerized tomography (SPECT), 182, *183*
  and mesial temporal lobe epilepsy, 441
skullcap, 409–10
sleep
  behavior disorders, 97
  slow-wave and epileptogenicity, 107, *175*
  and unknown or unclassified seizures, 97
sodium bromide, 295
sodium/potassium ATPase pump, 25, *25*
  and hypothermia, 432
sodium valproic acid *see* valproic acid (Depakene®)
somatostatin, 355
spatial summation, 41, *41*
SPECT scan *see* single-photon emission computerized tomography
spike initiation zone, 30
spinal accessory nerve, 483

spinal epilepsy, 10
spinal shock, 485
spirit gate, 393
"stargazing," 89
startle epilepsy *see* hyperekplexia
status epilepticus, *357, 499*
  and burst suppression, 176
  in classification, 82
  complications of, 353
  definition, 69, 82, 352
  epidemiology, 352–4
  excitotoxic neuronal cell death, 33
  incidence of, 352
  nonconvulsive and EEG, 175, *176*
  pathophysiology, 354–6
  prognosis, 353
  receptor internalization/expression, 306
  supportive care, 360
  treatment timing, 203
stereotypic movement disorder, 97
steroids *see* corticosteroids; neurosteroids; individual names
St. John's Wort, **399,** 400
storage disease, **151–2**
  screening tests, 148, 150, 154
  treatment, 154
stramonium, 417
  ointment, 13
stress and epileptogenesis, 399
stroke, prognosis, 82
structural brain disease, 203
  and drug selection, 222
subcallosal area, anatomy and connections, 53
subiculum, *52*
  anatomy, 52
  burst firing, 53
substance P, 355
substantia nigra and dopaminergic neurons, 49
sudden unexplained death in epilepsy (SUDEP), 200
superconducting quantum interference device (SQUID), 178
superficial pain, 487
supportive care, hospitalization, 373
suprachiasmatic nuclei, 107
surgery, *444–6*
  in dogs and cats, 443–7
  EEG/ECoG, 447–52
  effectiveness in treating epilepsy (humans), 451
  justification for, 440–441
  presurgical evaluation, 441–3
  similarities between species, 438–40
surgical protocols, 452–4
  disconnection surgery, 456–60
  resection surgery, 455–6
surrogate biomarker, 186
Sushruta Samhita, 413
SV2a *see* synaptic vesicle protein 2a
symptomatic epilepsy, 102
symptomatic zone, 451
symptomatogenic zone, 88
symptom of disease, definition, 63–4
synapse, *23*
  chemical, 22, *23*
  definition of, 22, 37
  electrical, 37, *38,* 39, 46
synaptic capacity, 43
synaptic cleft, definition, 37
synaptic rearrangement, 43
synaptic segregation, 43
synaptic stabilization, 43
synaptic vesicle protein 2a (SV2a), 38
synaptotagmin-1 (Syt1), 37
synchronization, *48*
  and feedforward/feedback inhibition, 46–7
  and neuron, 45
synchronous excitatory discharge, 46, *48*
syncope, **72**
syndrome (as in disease syndrome)
  definition, 66
  epileptic, 100–109

T

tachykinins, 355
tansy, **398**
(99m) Tc-ethylcysteinate (ECD), 182
(99m) Tc-hexamethylpropyleneamine (HMPAO), 182
tea, 398
telencephalon and epileptogenicity, 46
temporal lobe epilepsy (TLE), 439
temporal lobe epilepsy, pharmacoresistance and, 439
temporal summation, 41, *41*
Δ^9–tetrahydrocannabinol (9THC), 403–4
thalamus
  arrest reaction, 91
  pacemaker activity of, 18
theobromine, 398
theophylline, 398
therapeutic drug monitoring, 154–5, **156**
  reference range, 155
therapeutic range, 205, 206, *207*
theta rhythm, formation of, 53
threshold
  definition of, 24
  depolarization, 27
  relation to action potential, 27
thuja, **398**
tiagabine, 324
titubation, 98
tolerance, 223
tonabersat, 327

toothache plant, 400
topiramate (Qudexy XR®, Topamax®, Trokendi XR), 297–300, 522–4
  dose, 299–300
  indications for use, 299
  and kidney stones, 298
  mechanism of action, 298
  monitoring, 300
  pharmacokinetics, 298–9
  toxicity, side effects, and interactions, 299
torticollis, 475
toxin, **153–4**
  agenized flour, 92
  blood testing, 154
  and psychomotor seizures, 91
tramadol, 402
transcendental meditation, 414, 417
transcranial magnetic stimulation (TMS), 177–8, 438
transcriptomics, 187
transcutaneous, 437
transient receptor potential vanniloid-1 (TRPV1), 404
traumatic brain injury (TBI), 368, 372–3
trazodone, 402
treatment
  conservative *vs.* diagnostic approach, 129
  for epilepsy, 438–52
tremor
  definition, 97
  intention, 97
  topiramate as treatment, 297
trigeminal nerve, 482, *482*
trochlear nerves, 480–481, *481–2*
turpentine, **398**

U

ultrasound, abdominal, 157
urinalysis, 150
urine and drug elimination, 217
Usui, Mikao, 417

V

vagal nerve stimulation (VNS), 434–8
  cutaneous stimulation, 437
  and drop attacks, 454
  implanted device, 435–7
  and inhibition of epileptogenesis, 411
  ocular compression, 437–8, *438*
valerian, 401
  and aromatherapy, 410
valproic acid (Depakene®), 524–5
  dose, 322
  indications for use, 321–2
  mechanism of action, 39, 318–19
  monitoring, 322
  pharmacokinetics, 319–20
  and status epilepticus, 355
  toxicity, side effects, and interactions, 320–321
vāyu vāta, 413
ventral tegmental area and dopaminergic neurons, 49
verapamil, 323
versive movements, 91
vertiginous signs, 89
vestibulocochlear nerve, 483
The Veterinary College of London, 7
veterinary patients, 395
vigabatrin, 324
vocalization, 89
voltage (V), definition, 22

W

Wada test *see* intracarotid amobarbital procedure
Wilder, Russell, 12, 386
Wilks, Samuel, 10
withdrawal (flexor) reflex, 486
withdrawal seizures, 109, 223
wogonin, 410
wormwood, **398,** 400

X

X-rays *see* radiographs
xylitol, 269

Y

yoga, 417

Z

zonisamide (Zonegran®), 300, 525–7
  anorexia, 224, 301
  discontinuation, **248**
  dose, 303–4
  hypersensitivity, 223
  indications for use, 303
  mechanism of action, 39, 300–1
  monitoring, 304
  pharmacokinetics, 301
  therapeutic drug monitoring, **156**
  therapeutic "window," 231, *233*
  toxicity, side effects, and interactions, **301,** 301–3
  tremors, treatment of, 303

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