



ROTTWEILER Update

A PURINA PRO PLAN PUBLICATION DEDICATED TO ROTTWEILER ENTHUSIASTS VOLUME 20 | SPRING 2022



IDIOPATHIC EPILEPSY Studies Focus on Etiology & More Effective Treatments



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IDIOPATHIC EPILEPSY RESEARCH

MAY ADVANCE TREATMENT FOR AFFECTED ROTTWEILERS

“In the beginning, I wanted to put a bubble around Dice, but now I want him to enjoy life and to keep doing the things he loves.”

Rottweiler owner Raquel Burke of South Plainfield, New Jersey

The perplexing nature of idiopathic epilepsy can be as challenging for owners to deal with as having an affected dog. The toll from seizures that occur for no apparent reason affects owners and dogs. Sadly, some dogs never respond to anti-seizure drugs.

Rottweiler owner Raquel Burke of South Plainfield, New Jersey, was dumbstruck when her 2-year-old male “Dice” had a seizure in May 2021. The minute-long episode took down the 90-pound dog. He fell over, his stiff body convulsing as foamy saliva oozed from his mouth.

“As he came to, Dice was a bit aggressive and disoriented for about 20 seconds. After that, it was as

though nothing had happened,” says Burke, describing her first seizure experience after 35 years’ sharing her life with Rottweilers.

When Dice had a second seizure hours later, worse than the first one, it put him into a cluster seizure category, having had more than one seizure within 24 hours. “This seizure lasted a bit longer than the first one, and Dice lost control of his bladder,” Burke says. “What we thought was a one-time freak occurrence became terribly concerning.”

An emergency visit to the local veterinary specialty clinic involved a thorough examination by a veterinary neurologist who would not release Dice to go home until he was seizure-



PHOTO: CAM MORLEY

“Dice,” a 2-year-old male Rottweiler, had his first seizure last May. Antiseizure drugs are helping to manage his idiopathic epilepsy.

SWEDISH EPIDEMIOLOGICAL STUDIES FIND EPILEPSY IS COMMON IN ROTTWEILERS

As in the U.S., the Rottweiler is a popular breed in Sweden. Although epilepsy has not been studied extensively in Rottweilers, the most revealing epidemiological information about disease incidence and mortality has come from Sweden.

Veterinary epidemiologist Linda Heske, PhD, of the Norwegian University of Life Sciences, was the lead investigator of a study [published in 2014 in *The Veterinary Journal*](#) that ranked Rottweilers seventh among 35 breeds with the most dog-years-at-risk (DYAR) receiving veterinary care for epilepsy. DYAR represents the time period from when a dog is first insured, typically at 8 weeks of age, until exiting the insurance database due to death, becoming an epileptic case or the end of the study.

The report tapped into the Swedish animal insurance database to learn about the incidence and mortality rates of epilepsy in a large population of insured dogs representing 197 breeds. Dr. Heske, a doctoral student at the time of the research, evaluated veterinary records from 1995 to 2006 that accounted for more than 2 million DYAR data.

The findings showed that Rottweilers had an epilepsy incidence rate of 24.3 cases per 10,000 DYAR compared to an average of 18 cases per 10,000 DYAR for all dogs. The breed's mortality rate of 21.5 deaths per 10,000 DYAR placed Rottweilers as the fourth most common breed to succumb to the disease.

"The higher-than-average incidence and mortality rates of epilepsy for Rottweilers mirrors the observations of veterinary practitioners and Rottweiler breeders and owners in Sweden that epilepsy has

seemed to increase in the breed over the last decades," Dr. Heske says. "Although epilepsy appeared to be common in the breed, there was little published research describing the disease in Rottweilers."

Thus, Dr. Heske led a follow-up study gathering information from a questionnaire sent to owners of Rottweilers diagnosed with epilepsy that were registered in the Swedish or Norwegian kennel clubs between 2007 and 2013. The purpose was to learn about the clinical characteristics of the disease in the breed. The [findings were published](#) in 2015 in the Swedish journal *Acta Veterinaria Scandinavica*.

"Clinical Characteristics of Epilepsy of Unknown Origin in the Rottweiler Breed" shared insights learned from 37 epileptic dog cases, 23 females and 14 males.

The median age of the onset of seizures was 36 months, though seizure onset ranged from 8 to 84 months. Twenty-four of 37 dogs were on antiseizure drugs, yet owners reported limited improvement in seizure frequency. All the affected dogs had relatives with epilepsy. Seven dogs were neutered after the onset of seizures, but none experienced reduced seizure frequency or intensity.

"The majority of cases were idiopathic epilepsy in which no morphological cause can be found," Dr. Heske says. "Over half of Rottweilers with epilepsy were reported to have cluster seizures, or two or more in a 24-hour period, and their responses to antiseizure treatment were variable. This retrospective study provides the first detailed characterization of epilepsy of unknown origin in the Rottweiler breed."

free for 24 hours. He was started on the antiseizure drug phenobarbital, which worked magic, giving Dice six months without seizures.

Burke recalls hearing someone say early in Dice's treatment journey that Rottweilers are predisposed to idiopathic epilepsy, something she had never heard.

Although breed prevalence has not been studied extensively in the U.S., an [epidemiological study in Sweden](#) found that Rottweilers have an epilepsy incidence rate of 24.3 cases per 10,000 dog-years-at-risk (DYAR) based on insurance data from 1995 to 2006 compared

to an average of 18 cases per 10,000 DYAR for all dogs. The study also found that with a mortality rate of 21.5 deaths per 10,000 DYAR, Rottweilers rank as the fourth most common breed to die from epilepsy. (See "Swedish Epidemiological Studies Find Epilepsy Is Common in Rottweilers" above.)

Dice had a mild breakthrough seizure last October even with his regular doses of phenobarbital, followed by another one a couple of weeks later in early November. A second antiseizure drug, levetiracetam (Keppra®), was prescribed. Since then, two more mild seizures

prompted his veterinarians to make dosage adjustments based on Dice's bloodwork.

"Treating idiopathic epilepsy is basically trial and error since it is not known what causes the seizures," Burke says. "In the beginning, I wanted to put a bubble around Dice, but now I want him to enjoy life and to keep doing the things he loves. It's easy to feel like it's your fault your dog has seizures, but you shouldn't be too hard on yourself."

Lisa Wingerter of Evansville, Indiana, blamed herself when her first Rottweiler, "Pagan," a female, had a seizure in 1992 at age 4 following spay sur-

Purina and the AKC Canine Health Foundation have worked together since 1997 to support canine health research to benefit all dogs.



PHOTO: LISA CLARE

“Pagan,” a female Rottweiler, was treated for idiopathic epilepsy starting at 4 years of age until she died from cancer five years later.

gery. “I thought I had brought her home too soon after the surgery,” she says.

Heavily medicated on phenobarbital, Pagan could hardly function and Wingerter had no choice than to stop taking her to obedience shows. “Adding potassium bromide and reducing phenobarbital made all the difference,” she says. “After a couple of years working with my veterinarian, the seizures stopped almost completely and Pagan started traveling with me again. The experience is vivid even today though it’s been 30 years. Pagan died at age 9 not from epilepsy but from cancer.”

EPILEPSY INITIATIVE PRIORITIZES RESEARCH

Idiopathic epilepsy [affects about three-fourths of epileptic dogs](#), of which [20 to 30 percent are refractory](#), or resistant, to antiseizure drugs. A veterinarian diagnoses idiopathic epilepsy after ruling out other brain diseases that can cause seizures. Bloodwork is typically performed first to evaluate a dog’s complete blood count, chemistry profile and bile acid levels for signs of organ dysfunction. If these are normal,

magnetic resonance imaging and/or cerebrospinal analysis may be used to rule out a brain tumor or other structural abnormalities.

Idiopathic epileptic dogs may likely have a genetic predisposition, and environmental factors may play a role in their disease. Seizures occur when abnormal brain functioning causes excessive or synchronous neuronal activity that goes beyond a normal threshold. Affected dogs require lifelong antiseizure drug therapy, though the drugs don’t generally eliminate all seizures. There is no “one size fits all” protocol, thus it takes time and experimentation to find the right combination and dosage for individual dogs.

Epilepsy is the most common canine neurologic disorder and is ranked as one of the top health concerns of dog breeders and owners. They worry about the impact of seizure frequency and severity on a dog’s quality of life, the side effects of antiseizure drugs and a potentially shortened life span.

In 2017, the AKC Canine Health Foundation began its [Epilepsy Research Initiative](#) to focus on better understanding epilepsy and support-

ing investigations of more effective treatments. Altogether since its beginning in 1995, the Foundation has invested more than \$2.8 million in support of 42 grants. In 2021, more than \$375,000 was invested in epilepsy studies.

Darin Collins, DVM, CEO of the Foundation, says, “Epilepsy is a complex disease that affects pure-bred dogs and mixed breeds. It is frustrating that many dogs’ seizures remain uncontrolled using the therapies available today. We believe that the research the Foundation is funding with support from donors and parent clubs will lead to innovative approaches to deal with this common disorder.”

Here are highlights of three studies that are part of the 2021 portfolio and an ongoing study.

A ‘REAL-TIME’ TEST TO UNDERSTAND SEIZURES

The oftentimes mismatch between the type of seizure a dog with epilepsy has and the antiseizure drug used to treat the disease has prompted [a study just begun at the University of Guelph in Ontario, Canada](#). Lead investigator Fiona James, DVM, DVSc, DACVIM (Neurology), associate professor, is using electroencephalography (EEG), a technology that evaluates brain function, to record the electrical activity of the brain of affected dogs and aid in determining the frequency of seizures and effectiveness of antiseizure drugs.

The four-year study will evaluate EEG recordings along with synchronized video of about 160 dogs. “EEG is the only real-time test that can confirm and classify different types of seizures because it picks up the pattern of electrical charge in a large population of neurons,” Dr. James says. “Using the EEG with synchronized video we can compare the patterns and frequency of seizures with the dog’s physical manifestation and then evaluate the antiseizure drug therapy.”

Types of seizures seen in dogs are generalized tonic-clonic seizures (GTCS), and non-generalized tonic-clonic seizures (non-GTCS). A GTCS seizure affects the whole brain and causes stiffening of the body (the tonic part), making a dog fall to the ground, and convulsing, or rhythmic jerking of the face and limbs (the clonic part). A non-GTCS seizure may be focal in nature affecting one-half or a small part of the brain and causing altered awareness, such as a glassy or frozen look, and/or affect the whole brain causing the tonic-clonic aspects of a GTCS seizure.

Dr. James explains that in veterinary medicine dogs are largely diagnosed with epilepsy based on their owners’ report of seizures and then prescribed antiseizure drugs in a standard of care order. This is unlike human epilepsy standard of care where antiseizure drugs are prescribed based on the seizure type.

Inconsistencies between owners’ subjective descriptions of their dogs’ seizure episodes and results from objective EEG testing create an underreporting phenomenon, particularly related to non-GTCS episodes, says Dr. James, citing a study she led that was [published in July 2021](#) in the *Journal of Veterinary Internal Medicine*.

“We want to confirm the underreporting phenomenon and learn how this impacts antiseizure drug therapy,” she says. “Our previous data suggests that if antiseizure drugs make GTCS seizures more mild, they could become non-GTCS seizures. Owners may then undercount seizures, which could mean we are overestimating the efficacy of antiseizure drugs when we evaluate them without EEG.”

The ultimate goal of the study is to move the standard of care for veterinary epilepsy patients closer to human epilepsy standard of care. “Identifying the best antiseizure drugs to use with particular seizure types in dogs potentially will lead to more accurate seizure control,” Dr. James

says. “Currently, it is unknown which antiseizure drug is more appropriate for which type of seizure in dogs.”

FUNCTIONAL MRI MAY EXPLAIN PHYSIOLOGY OF EPILEPSY

A new [three-year study at North Carolina State University](#) aims to better understand what causes idiopathic epileptic seizures in dogs using functional magnetic resonance imaging (fMRI) to evaluate brain activity and measure small changes in blood flow associated with increased energy demand. The study will include 10 epileptic dogs not receiving anti-seizure drugs and 10 neurologically normal dogs.

Lead investigator Karen Muñana, DVM, MS, DACVIM (Neurology), professor of neurology, says, “We hypothesize that these dogs with idiopathic epilepsy have alterations in the functional connectivity of the brain. Our goal is to better understand idiopathic epilepsy and potentially develop more effective treatment strategies.”

Whereas conventional MRI produces imagery of the anatomy of the brain revealing structural abnormalities, fMRI captures information about the brain’s activity. “Task-based fMRI is used widely in human medicine,” Dr. Muñana explains. “While an individual performs a task, he is being scanned to identify the corresponding regions of the brain that are involved. Although task-based fMRI has been used in dogs, it is challenging because awake dogs must lie still while unrestrained in the scanner as images are acquired.

“An alternative known as resting state fMRI can help identify structurally distinct but functionally related brain regions that are captured with dogs in the resting state while under anesthesia,” she continues. “Resting state fMRI allows us to study the functional architecture of the brain by detecting spontaneous fluctuations

in the brain's blood flow. These fluctuations can be analyzed for synchrony to identify anatomically distinct but functionally connected regions of the brain known as resting state networks (RSNs)."

In humans with epilepsy, alterations in RSNs are associated with disease progression, severity and treatment response. Thus, resting state fMRI has

become a powerful tool for investigating the underlying cause of epilepsy in humans.

"It holds similar promise in studying the disease in dogs," says Dr. Muñana.

CBD AS AN ADJUNCT DRUG THERAPY FOR EPILEPTIC DOGS

A [study showing the effectiveness of cannabidiol \(CBD\)](#) to significantly reduce seizures in idiopathic epileptic dogs that were also being treated with antiseizure drugs led to a new study underway at Colorado State University. The [latest study focuses on learning the amount of an effective dose of oral CBD](#) that will reduce monthly seizure activity by 50 percent or more when added to standard antiseizure drug therapy.

"Epilepsy is a violent, emotional and devastating disease," says Stephanie McGrath, DVM, MS, associate professor, who leads the study. "The worst part is that in many dogs we are not successful in treating this disease or their quality of life is not good. Sometimes we are successful controlling seizures, but dogs must be euthanized due to the medication side effects. Alternative therapies are desperately needed."

The potential benefits of oral CBD, a cannabis-derived product made from hemp that does not contain THC, the psychoactive compound in cannabis producing a high sensation, validates its use in clinical trials to assess its safety and efficacy and learn about safe dosages. Although not yet approved by the Food and Drug Administration for use in veterinary medicine, CBD is prescribed for humans as an adjunct therapy for many diseases and for pain management.

Enrolled dogs in this study will participate for three months during which three doses of CBD will be evaluated to learn which is most effective. Dogs will first receive milligrams of oral CBD per kilogram of body weight every 12 hours, then

OWNERS OF ROTTWEILERS CAN HELP ADVANCE EPILEPSY RESEARCH

Rottweiler owners are encouraged to participate in research that is part of the AKC Canine Health Foundation's [Epilepsy Research Initiative](#). Here is information about how to participate in the studies featured in this article.

- [EEG & Video Study at the University of Guelph](#) in Ontario, Canada: Recordings of 160 dogs will help to advance the accuracy of epilepsy diagnosis and best therapies for seizure control. Contact Dr. Fiona James at epilepsy@uoguelph.ca or by calling 519-823-8830.
- [fMRI study at North Carolina State University](#): Evaluations of 10 epileptic dogs not receiving antiseizure drugs and 10 neurologically normal dogs. Contact Julie Nettifee at janettif@ncsu.edu or by calling 919-513-6812.
- [CBD study at Colorado State University](#): Assessing dose protocol and efficacy in idiopathic epileptic dogs. Contact Dr. Stephanie McGrath at stephanie.mcgrath@colostate.edu or by calling 970-297-5000.
- [Gut dysbiosis study at North Carolina State University](#): Evaluations of fecal samples of 100 pairs of housemate dogs in which one is epileptic and the other is unaffected: Contact Julie Nettifee at janettif@ncsu.edu or by calling 919-513-6812.



5 milligrams per kilogram of body weight and finally 10 milligrams per kilogram of body weight. Participants will be rechecked at four-week intervals.

“We need to home in on the appropriate dose for individual dogs, as it likely varies by age, seizure frequency and breed,” Dr. McGrath says. “Candidates for this study are dogs having two or more idiopathic epileptic seizures a month for a minimum of 12 weeks after being treated with a least one antiseizure drug. Participants will undergo a complete seizure workup that includes a neurological examination, bloodwork, brain MRI, and cerebrospinal fluid analysis.”

Besides determining CBD dosage protocol, Dr. McGrath says this study will continue evaluating the safety and tolerability of CBD in dogs with idiopathic epilepsy. “CBD has the potential to improve the quality and length of life for dogs with uncontrolled epilepsy while adding a much-needed tool for veterinarians treating canine epilepsy,” she says.

STUDYING GUT DYSBIOSIS IN EPILEPSY

A disruption of the delicate balance of the gut microbiota, known as gut dysbiosis, could play a role in canine idiopathic epilepsy. A study of 100 pairs of dogs living in the same household — an epileptic dog that is untreated or treated with the antiseizure drug phenobarbital and an unaffected dog — aims to learn if there are differences in the gut microbiome linked to idiopathic epilepsy.

Dr. Muñana of North Carolina State University, the lead investigator, says, “We believe there is an important interaction between the GI tract and the brain that is vital for maintaining normal homeostasis of the nervous system and that can influence a dog’s susceptibility to epilepsy.”

The [four-year study aims to better understand refractory epilepsy](#) in which 20 to 30 percent of dogs are resistant to antiseizure medications. Molecular genetic analysis, a method called 16S gene amplicon sequencing, is being performed on fecal samples from the pairs of housemate dogs to learn about differences in specific bacterial populations of epileptic dogs and the control dogs.

Participating dogs not only must live in the same household, they also must be fed the same diet. “By comparing results from pairs of dogs within the same household that are fed the same diet, we aim to minimize the effects of diet and environment, which have been shown to have an effect on the composition of the gut microbiome,” Dr. Muñana says. “This will provide a more accurate analysis of differences in the gut microbiome that may be due to epilepsy itself.”

The hypothesis is that dogs with idiopathic epilepsy have alterations in intestinal bacteria. “We want to determine if dogs with idiopathic epilepsy have shifts in their gut microbial populations such as the presence of *Helicobacter* and a decrease in *Lactobacillus* that result in inflammation associated with epilepsy,” says Dr. Muñana.

A common organism in the human gastrointestinal tract, *Helicobacter* in most cases does not cause clinical disease. When clinical signs are present with *H. pylori*, they most often cause stomach disease. In addition, in some people infection with *H. pylori* has been linked to the development of neurologic disorders, including Alzheimer’s disease, multiple sclerosis, Parkinson’s disease, and ischemic stroke. It is also believed that *H. pylori* may play a role in epilepsy.

Meanwhile, Dr. Muñana says, “*Lactobacillus* organisms, which also are typi-

cally found in the GI tract of humans, are believed to have a beneficial effect. Although not yet linked to epilepsy, a decrease in *Lactobacillus* populations is believed to contribute to the development of human neurologic diseases such as anxiety and depression, autism spectrum disorders, multiple sclerosis, and Alzheimer’s disease.”

The study will aid understanding of the complex signaling between the GI tract and the nervous system — the microbiota-gut-brain axis. “Our hope is that this study will advance understanding of epilepsy and drug resistance and guide the development of improved seizure control for dogs with epilepsy,” she says.

Collectively, these investigations that are part of the Epilepsy Research Initiative offer promise of better understanding this frustrating disease. Dice, the Rottweiler male who first experienced idiopathic epileptic seizures last May, may one day benefit from new treatments that come from these studies.

Meanwhile, his owner, Raquel Burke, says, “We’ve been diligent about the timing of Dice’s medications and monitoring his seizures. We have a camera that captures his movements so we can show video recordings of his seizures to our veterinarians.

“Dice is a lover boy who has never met a stranger. He loves to sit and be petted. I do barn hunt and trick dog with him. Most importantly, I’ve learned to let him enjoy life and take it a day at a time as is best with canine idiopathic epilepsy.” ■

Purina thanks the Rottweiler Health Foundation, particularly president Roberta Kelley-Martin, for helping us to identify this topic for the *Rottweiler Update*.

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