Seizures are a common and potentially devastating clinical problem in small animal practice. Epidemiologic studies indicate that epilepsy affects approximately 5% of the canine population, and 60% of canine epileptics will experience status epilepticus (SE) or other emergent seizure semiology in their lifetime.¹ Seizures disorders, including status epilepticus, are among the most common presenting signs in animals admitted to veterinary hospitals on an emergency basis.

There is compelling evidence that epilepsy negatively affects the quality of life of both affected animals and the owners.² In addition, 25-33% of epileptic dogs that experience SE will die as a direct result of their seizure disorder, and the mean lifespan of canine epileptics with SE is 8.3 years versus 11.6 years for epileptics that do not experience SE.³,⁴ This session will review some novel therapeutic approaches to veterinary patients with emergent seizure disorders, and introduce some new developments in the management of seizure disorders that have the potential to revolutionize the way seizures disorders are diagnosed and treated in veterinary medicine.

Definitions of Status Epilepticus and Other Emergent Seizure Syndromes
Various working definitions of SE exist, but it is practically and most commonly defined as a series of generalized seizures without intervening periods of consciousness lasting ≥ 5 minutes. Status epilepticus is a medical emergency. Cluster seizures (≥ 2/day; also called acute repetitive seizures), multiple seizures with brief periods of interictal consciousness, or any seizure lasting longer than two minutes should also be considered emergent seizure manifestations, as they predispose the patient to SE. Failure of an animal to regain consciousness within 30 minutes to one hour of a seizure should be considered another emergent condition, as this may be indicative of brain edema or non-convulsive SE.

Treatment Strategies for Animals without Vascular Access
Manual Vagal Maneuver
The anti-convulsive effects of vagal nerve stimulation have been recognized for decades, although the mechanism by which vagal nerve activation exerts its beneficial effects is incompletely understood. Manual vagal maneuvers are technically easy and potentially effective techniques that can be performed in the actively seizing patient while vascular access is obtained. Both carotid massage and ocular compression are well described manual vagal stimulation procedures.⁵ This author prefers carotid massage, as it is less likely result in any injury to the person applying the treatment.
Percutaneous Electrical Vagal Nerve Stimulation
Surgically implanted electrical vagal nerve stimulators have been demonstrated to be of benefit to some humans and canines with epilepsy refractory to other therapies. Recently, portable, hand-held device capable of repeated percutaneous vagal nerve stimulation has been developed and is currently being evaluated in multicenter clinical trials for use in dogs to treat medically refractory epilepsy and as an adjunct therapy for emergent seizures.

Rectal Zonisamide and Levetiracetam
Rectally delivered zonisamide has been shown to rapidly attain plasma concentrations that are effective at seizure suppression in rodent models.\(^6\) Although published pharmacokinetic studies investigating rectal zonisamide in dogs are currently unavailable, there are some preliminary reports that suggest it may be effective per rectum when delivered at a dose of 40 mg/kg. The optimal vehicle for rectal administration of zonisamide is also unknown. A pharmacokinetic study in dogs has also recently shown that rectally delivered levetiracetam rapid achieves serum concentrations within recommended therapeutic ranges.

**Alternative First Line Anticonvulsant Drugs for Patients with Vascular Access**
Benzodiazepines are the primary drug choices for patients with SE. I administer all benzodiazepines as a bolus, and if bolus therapy controls the seizures, the boluses may be repeated up to three times. If three boluses fail to stop the seizure activity, another anticonvulsant with a rapid onset of action should be administered. As all benzodiazepines discussed below have relatively short duration of action, seizures may resume once plasma benzodiazepine levels fall.

*Lorazepam-* It is more expensive than diazepam and requires refrigeration, but is efficacious in stopping seizures when administered as an IV bolus. The initial IV dose is 0.1-0.2 mg/kg, but its anticonvulsant effects last longer than diazepam. The CRI dose of lorazepam is 0.1-0.4 mg/kg/hr.

*Midazolam-* Another benzodiazepine that is effective at seizure suppression. Its primary advantage is that it is water soluble and thus can be given IV or IM (0.5 to 2.0 mg/kg) if vascular access is a problem. The CRI dose of midazolam is 0.5 to 2.0 mg/kg/hr.

Stop Gaps with Longer Acting Anticonvulsant Drugs
I use the following drugs to provide a longer duration of serum anticonvulsant drug concentrations in patients that either respond to an initial dose of benzodiazepine but then resume seizure activity once blood concentrations of benzodiazepines drop or for those patients that fail to respond to benzodiazepines altogether.

*Fosphenytoin*
This drug is a phosphate ester prodrug of phenytoin that was developed in an attempt to avoid toxicity associated with IV phenytoin administration. Fosphenytoin works by blockade of
voltage-gated sodium channels, and is currently a second line anticonvulsant in people that is being investigated for use in dogs. A preliminary pharmacokinetic study in dogs has demonstrated that administration of 15 mg/kg of phenytoin equivalent fosphenytoin was well tolerated and resulted in serum concentrations of phenytoin considered therapeutic in humans. A multicenter, blinded and placebo controlled canine clinical trial investigating the efficacy of fosphenytoin in emergency canine seizure disorders is currently underway.

Levetiracetam
This drug offers several advantages over barbituates in that it is primarily renally eliminated, does not cause sedation when administered, and has a unique mechanism of anticonvulsant action that should be complimentary and synergistic to benzodiazepines and barbiturates. It can be administered in both dogs and cats at a dose of 15-40 mg/kg q 8 hours as a slow IV bolus over 5-10 minutes. In a recent study of levetiracetam in canine status epilepticus demonstrated a response rate of 56% in dogs receiving levetiracetam versus 10% in dogs receiving standard of care, although the difference in response rates between groups was not statistically significant.

New Second Tier Drug Choices for Refractory Seizures

Fospropofol
Fospropofol (FP) is a water-soluble propofol prodrug that is formulated as an aqueous solution. Following administration, FP undergoes hydrolysis by alkaline phophatases to produce propofol, phosphate, and formaldehyde. A principal advantage of fospropofol is that it reportedly causes less pain at the injection site than propofol emulsion formulations. Pharmacokinetic and pharmacodynamic studies of FP have been performed in normal dogs, and the pharmacokinetic parameters describing FP were not significantly different to those determined for propofol emulsion. Clinically, FP injection was well tolerated in normal dogs, although all dogs exhibited signs of excitability immediately prior to losing consciousness. In addition, the onset of sedation following FP injection was significantly delayed (mean 124 seconds) compared to propofol emulsion (mean 24 seconds), which is an expected consequence of the enzymatic conversion of FP to propofol. The duration of sedation following FP was also significantly greater than the duration after propofol emulsion.

Ketamine
There is experimental and limited clinical evidence that ketamine can be an effective anticonvulsant drug for patients with refractory seizures. However, there is controversy as to when in the course of SE ketamine therapy should be initiated. As ketamine antagonizes the NMDA ionotropic glutamate receptor, it theoretically possess anti-convulsant as well as neuroprotective properties through modulation of excitotoxicity. No evidence based data could be found for the optimal dosing protocol for ketamine usage in SE. However, typical dosing protocols in humans involve delivering a 1-3 mg/kg loading dose, and delivering
ketamine as a CRI at a rate of 0.5-5 mg/kg/hr. The author has used ketamine successfully at CRI doses from 0.5-2 mg/kg/hr.

**Ambulatory, Telemetric Electroencephalography (EEG)**

Pilot studies have been performed in which brain surface EEG recorders have been implanted in epileptic to allow for continual telemetric monitoring of brain activity. It is the ultimate goal of these studies to not only provide definitive electroclinical evidence that a seizure disorder exists, but also to implement computerized algorithms that allow for the early detection of an impending seizure. When a seizure risk is present, the owner can be alerted via mobile communication device so they can appropriately intervene, or the event recorder can function as an open biofeedback loop and directly activate a reservoir carried on the patient (similar to an insulin pump) that can infuse or titrate drugs when activated. Newer generation EEG recorders are being designed that will allow for transcranial EEG recording, which will greatly simplify the routine instrumentation of patients in the clinic.

**References**