

# Seizures

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## Objectives:

1. Define seizure, cluster, status epilepticus, and pharmaco-resistant/refractory epilepsy
2. Understand different ways to classify/describe seizures and the components of a seizure
3. Be able to list differentials for episodes that look like seizures but are not true seizures
4. Be able to list common anticonvulsants used in cats and dogs and understand when it is appropriate to use different medications
5. Understand essential principles of seizure management for non-urgent cases
6. Understand client management considerations

## Terms and definitions:

**Prodrome/preictal:** The interval immediately before the active seizure starts.

**Ictus:** The active seizure

**Post-ictal:** The interval immediately after the active seizure has resolved.

**Epilepsy:** Ongoing, recurrent seizure condition

**Idiopathic epilepsy:** This does not just describe a pet in which we cannot identify the underlying cause of the seizures. This is a specific syndrome that is suspected to be heritable or genetic. There is not one specific test for this disease – instead this is a “diagnosis by exclusion”. Animals must fit a certain set of criteria including:

-Appropriate age of onset (usually 1-5 years old)

-Normal behavior between seizures

-Normal neurologic exam between seizures

-Normal diagnostic workup including general body health blood and urine testing, MRI of the brain, and CSF analysis

-The seizure condition can be chronically managed without the pet developing new neurologic signs

-The diagnosis is further strengthened when there is a family history of seizures

**Pharmaco-resistant or refractory epilepsy:** Failure to achieve freedom from seizures despite adequate trials of two (or more) well-tolerated AED's

**Cluster:** 2 or more seizures within 24 hours

**Status epilepticus:** Seizure lasting longer than 5 minutes OR 2 or more seizures without full recovery to normal in between

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A seizure condition is one of the most common neurologic problems seen in veterinary medicine, and is therefore the disease I most frequently field questions about. I think what can be stressful for some veterinarians are a few things:

- Seizures are frightening for everyone involved
- There is not a single “best” approach for every seizure case – each patient is an individual
- Specialists might have strong, differing opinions on how seizure cases should be managed

Every neurologist may manage seizures a little differently. It is important to remember that there can be many ways to address the same problem. I encourage you to try not to worry about choosing the

“right” plan, but to instead follow some general principles. These notes reflect some of the guidelines I like to use when managing seizures in my patients:

- First and foremost, you must start managing client expectations from the beginning. Help them to understand the many different causes of seizures, the tests you can do to help rule out intra- and extracranial diseases, when a specialist referral is advisable, any relevant disease information, and what expectations they should have for treatment and seizure management in general. Be empathetic! It is natural for owners to be scared and stressed.
- I generally start medications when any of the following occurs:
  - animals have seizures more than once every 6 months – I am more forgiving in very mild partial seizure cases
  - seizure frequency is clearly accelerating over time
  - animals have an episode of cluster seizures, status epilepticus, or very violent seizures
  - animals have underlying disease like a brain tumor that predisposes to continued, progressive seizures
- My definition of success can be different for each patient/ family. While one seizure a week might be considered very frequent, it might be very good for a pet that was having several seizures a day. Adding or changing a drug is generally considered successful when seizure frequency is reduced by at least 50% (we certainly hope for more than that!). Remind clients that it is not common to totally eliminate seizures. We are instead trying to minimize frequency and severity and keep the condition stable.
- Use blood levels and clinical progress together to guide changes in the medication plan. Owners should keep a detailed diary of seizures and any unusual behavior to make this a more informed process. Video documentation by the owners of anything unusual is also very helpful.
- You may be tempted to increase seizure medications every time a pet has a seizure. When deciding if changes in the management plan are working, you need to look at the *trend*, not whether or not the animal has another seizure. If an animal only has a seizure once a month, it will take 3-4 months to know if the change is consistently helping (unless things are clearly accelerating before then). If an animal has seizures once a day, then you will know much sooner if your medication plan is working. Periodic seizures are typical and do not always necessitate more medication. So first ask yourself:
  - Is this seizure in the normal pattern/timeline for this pet?
  - Has there been more than one seizure occurring sooner than normal to indicate increasing frequency?
  - Are the seizures getting more violent?
  - Is there a new cluster or status episode that has not happened before?
  - Are there any changes to the neurologic exam or physical condition to warrant a reassessment of the entire case?
- I usually try to maximize the first medication the animal is on. I will increase the dose until seizures come under control, there are side effects (or a higher risk for side effects as in high phenobarbital blood levels), or the drug is cost prohibitive.
- If I have maxed out the usefulness of one drug (whether from high doses, side effects, cost, or failure to help with increased doses), then I will add a second drug.

- If seizures are not controlled, I tend to add to the drug protocol rather than switch suddenly. If the new drug successfully controls seizures, then I might brave reducing the other drug dose a little bit – if we are lucky, we might be able to reduce to as few drugs as possible to manage seizures.
  - Unfortunately taking away medications can increase the risk for break-through seizures. I always discuss the risk of increased seizures and subsequent increased difficulty in regaining control before reducing drug doses in refractory epileptic cases.
- If I want to try to wean off a seizure medication, I do this slowly over 6-8 weeks. You can do this more quickly with potassium bromide that has a natural slow weaning due to the very long half-life of elimination. In those cases I might decrease over a couple of weeks (to look for immediate break-through seizures) then just stop the medication.
- If I have a case that requires quicker drug conversion (as in a hepatic necrosis case), then I will make a plan to try to get quick coverage using other drugs. I will also warn the owners that breakthrough seizures are possible as well as increased difficulty in regaining control. You're between a rock and a hard place in these situations.
- It is always better to get medication a little early than to get it too late. An extra dose in a 24 hour period is not generally harmful.
  - If an owner is unsure if a pet got the medication, then it is better to give an extra dose than to skip it.
  - Similarly, if they will not be available to give the next dose on time, they can give an extra dose earlier in the day, then give that dose late, then return to the normal dosing schedule.
- I usually only monitor blood levels for phenobarbital and potassium bromide. These levels can help to direct treatment decisions. Zonisamide and Levetiracetam level tests are available, but the levels do not necessarily correlate with effectiveness. For both of those drugs, there is a relatively wide safety range so that higher recommended dose ranges can be exceeded if dose increases help the patient, there is not a problem with side effects, and costs are still manageable. I will more often test levels in cases where there is concern the animal is not taking the medication or there are owner compliance concerns – this is to try to document very low blood levels to support these concerns.
 

\*Recently compounding pharmacies have been making and selling transdermal formulations of anticonvulsants without evidence of effectiveness. I have used blood levels of zonisamide in poorly controlled patients to document very low absorption in the transdermal zonisamide product compared to the more reliable phenobarbital product. If you see that an animal has a change in seizure control when changing from a standard formulation of any drug to a compounded product, blood levels might document poor absorption from the new product – especially if returning to the standard formulation returns blood levels to a more therapeutic range.
- If I have a pet that has increasing seizure frequency or severity, I consider the following:
  - Is the animal getting the drug routinely?
  - Has there been a recent refill at the pharmacy? If so, are we confident that we have the correct dose?

- Did we change formulations (like from a standard tablet to a compounded liquid or transdermal form)?
  - Is there anything new like liver dysfunction, electrolyte imbalances, diet changes (for KBr), etc that might contribute to loss of seizure control?
  - Are there any new neurologic signs to raise the index of suspicion for progressing intracranial diseases?
  - Has there been a change in blood levels to reflect less circulating anticonvulsant.
- I advise going to the ER when seizures are longer than 5 minutes, when there are more than 2 seizures in 24 hours, if the seizures are very violent and the animal is having trouble recovering, or if the owner is very worried.
- For cluster/SE repeat offenders, I will have owners come in when seizures are more severe than usual, if they are not coming under control with typical measures, if the post-ictal period is more severe, or if the owner is having trouble managing the pet at home.
- Phenobarbital is still one of the more effective anticonvulsants (especially in large dogs with refractory epilepsy). Phenobarbital, zonisamide, and levetiracetam all can reach therapeutic blood levels within a few days - loading is usually tolerated well. Levetiracetam and Zonisamide might be good first choices in very old patients or otherwise more likely to experience serious side effects from Phenobarbital and bromide. Bromide takes much longer to reach stable blood levels and loading is not always tolerated well, so is not as good when quicker control is needed. Gabapentin and pregabalin may not be as effective and pregabalin is very expensive. We do not know as much about Topiramate side effect statistics yet, but some veterinarians have been happy using this drug as an affordable option with effectiveness similar to levetiracetam and zonisamide. Imepitoin (Pexion) is being used in Europe and has limited approval in the US – it is unknown when it might be widely available here.
- Remember some drugs are very expensive! Monitoring needs and emergency hospital visits also add up over time. Keep the long-term financial investments in mind when making your plan. Make sure owners are calling around for the best prices for drugs.
- Some specialists have very strong opinions on heartworm and flea preventatives - you might ask 3 neurologists for an opinion and get 3 different answers. Technically all flea, tick, and heartworm preventatives available today run the risk of "lowering the seizure threshold". This does not mean that it causes a normal dog to have seizures, but usually means there is a risk (usually small) of a seizure-prone dog to have breakthrough seizures easier. Some neurologists act on the small risk and insist that preventative medications need to change. Fipronil, Imidacloprid, and Selamectin might be some of the "safer" options. If seizures are controlled, then I don't worry about switching drugs.
- I think the truth is that MOST epileptics will tolerate most of these products similarly, but there will always be a handful that can be more sensitive. You must always weigh the risk of affecting seizure frequency with the problem of parasites and heartworm disease. I have practiced in heartworm endemic areas and with very prevalent resistant flea populations in which I feel it is a greater risk to not help manage those diseases – most of the time, I don't see a big difference when using the more "risky" preventative products. HOWEVER, if you notice that there is a change in seizure frequency after changing flea preventative, then don't ignore the correlation – especially if it is repeatable.

- Owners will ask you about diet, herbs, supplements, acupuncture, and many other potential treatments. I have certainly been in the position of reaching for acupuncture or referring to a trained herbalist in really tough refractory epilepsy cases. You must remember that these are *never a substitute* for conventional medication in violent seizures. While some modalities can be helpful, most of the “alternative” options that owners might ask you about have little to no evidence and some things may be harmful (as in owners who don’t understand the difference between CBD oil and more toxic marijuana).

## Suggestions for Cluster Seizure and Status Epilepticus Cases

These patients can have much scarier seizures that are often harder to control at home. There is usually a two-pronged approach to seizure management. The first is adjusting the long-acting medications (phenobarbital, KBr, levetiracetam, zonisamide, etc) to try to make the cluster episodes as infrequent and mild as possible. As clusters get closer together or more severe, these are the drugs you adjust as needed. The second is to try to help on the day of the seizures. Visits to the ER get costly after a while and financial depletion can become life-limiting to the pet. I will therefore make certain recommendations for things owners can do at home in an effort to prevent an ER visit.

This can include:

1. If dogs are prone to long and severe seizures or if they have clusters that are so close together that they cannot take oral medications (and have time for them to work), I will send home liquid or compounded gel diazepam to use rectally to help interrupt the seizures. As an alternative, you can use intranasal midazolam (not absorbed well rectally). This method may work more quickly in some patients, but also comes with greater risk of the owner being accidentally bitten, so choose the medication and route based on the owner and pet.

This therapy is a diversion risk so you must trust that your owners will use the drug appropriately. Alternatives include a human suppository gel (expensive), and capsule-type suppositories. I don't feel the capsule-type suppositories work well in cases that need a quick stop to severe seizures because the absorption is much slower than the gel or liquid formulations. I generally send home 3-5 doses (depending on the relative risk and patient size) at a time in an amber glass vial (because injectable solution is light sensitive and binds to plastic) with syringe-adapter cap so that the owners don't need to use needles.

Tutorial videos for clients including rectal diazepam administration and midazolam intranasal administration:

<https://vetmed.illinois.edu/hospital/veterinary-teaching-hospital/veterinary-specialties/medication-dispensing/client-tutorials/>

2. If dogs have clusters that allow recovery between the seizures to safely take oral medications (like 5 seizures in one day, rather than 5 seizures in 20 minutes), then I don't usually send home the liquid diazepam. Instead, I focus on using oral medications to help limit seizures as well as possible.
  - a. First I will tell owners to give an additional dose of the maintenance medication(s), even if they just gave the last dose in the last hour.
  - b. Next I will increase the dosing of the maintenance medications. This might mean going from BID phenobarbital and zonisamide to TID. Since Keppra/ levetiracetam is already a TID drug, I'll double the dose instead. I continue these for 1-2 days before going back to the normal dosing schedule if the dog is doing well.
  - c. I might also prescribe diazepam tablets (0.25-0.5mg/kg per dose) to give immediately after the first seizure, then every 4-6 hours after that for 12-24 hours. Clorazepate 0.5-1.0mg/kg PO Q8H is an alternative.
3. If owners know that certain triggers can cause a seizure event (like fireworks or a ride to the vet), I'll have owners give extra medications as described above.

4. The extent to which we follow these recommendations and the duration of time that owners follow these instructions depends on the nature of the seizure events, over what period of time they typically occur, and how difficult they are to get under control. If the pet stops having clusters with this plan, owners can start to back off the extra medications with subsequent seizures in case the dog doesn't need as much medication.

## Approach to the Pet that Presents to Your Hospital with New or Active Seizures

- Remember to keep calm. Seizures are stressful to the owner (especially in cases of first-time seizures) and often distresses the staff. Being calm, empathetic, and assisting the owner quickly are the most important first steps.
- Approach a seizing pet as you would any medical problem. Consider the signalment, get a good history, perform a thorough physical and neurological exam, and make a management plan.
- Refer to the decision tree included in this document to help with stopping the seizures. Don't overlook checking simple things like blood glucose levels to look for problems that area easily corrected (and need more than just an anticonvulsant).
- Educate your client on the differentials and diagnostic options. I encourage at least CBC, chemistry, urinalysis, and blood pressure in first time cases. Older pets should also have thoracic radiographs, T4, and sometimes belly ultrasound. Younger animals or pets with liver function concern should also have bile acids testing.
- Animals with intracranial signs should have a discussion of referral for advanced brain testing. *Remember that lack of intracranial signs on the exam does not fully rule out intracranial disease!*
- You will need to make a decision for whether or not to start an ongoing anticonvulsant. I start medication if the first time seizure was very violent, if the animal had a cluster of seizures, or if there is a high suspicion for intracranial disease.
- Once seizures are under control, you will need to make a plan for ongoing treatment, monitoring, and follow up with you (which might also include follow up with specialty services).
- Do not forget to start educating your client and managing client expectations from the beginning. Be empathetic! It is natural for owners to be scared and stressed

While there are many choices available for managing seizures, the general principles remain the same. And while this outline is meant to make decisions a little less stressful, there are always cases that don't follow the rules or situations in which a second opinion can be comforting. Know your local specialty options – most of us are very happy to help answer your questions and try to guide you through next steps in the more challenging cases.

### **References**

Podell, et al. "2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs". *Journal of Veterinary Internal Medicine*. Vol 30, Issue 2, March/April 2016. pp. 477-490. *Open access online*.