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Dr Kendal Williams (Host): Welcome everyone, to the Penn Primary Care Podcast. I'm your host, Dr. Kendal Williams. So as you get later in your career like me, you're challenged by some things you thought you knew very well. Definitions change, the classifications change, some of the names of the conditions change. And then, there's a whole new set of medications that come out that you have to get to know. And probably, nowhere have I found that to be true than in the arena of seizures and epilepsy. And so, I wanted to bring on a guest to talk about the modern management and classification of seizures and epilepsy. And we were lucky to find a great expert. Dr. Mindy Ganguly is here. Dr. Ganguly is an Assistant Professor of Neurology here at Penn. She has a special interest in epilepsy and is involved in the clinical trial work done here at Penn in epilepsies. Dr. Ganguly, Mindy, thanks for coming.

Dr Mindy Ganguly: Yeah. My pleasure. Excited to be here.

Host: So, I'm going to ask a lot of just sort of basic questions, because I want to start from the basics. Since I was in medical school, I graduated in 1995, I guess. And so, we were doing Dilantin and phenobarb. And some of the meds were the same. We had this, I think, fairly complex classification system. You could have a focal partial seizure or a complex partial seizure, which seemed redundant. But things have been updated to some degree. And I actually wanted to start just with the classifications this is a common thing. 5-10% of people will experience a seizure in their lifetime, a much lower percentage will actually be determined to have epilepsy. But we in the primary care field or in hospitalist medicine are going to be frequently encountering this. So, we need to kind of understand how it's classified. So, I guess, in a broader sense, we're still thinking about this as focal onset versus generalized onset. Is that right?

Dr Mindy Ganguly: Absolutely. Yeah. You're right. The classification has changed quite a bit, and I think it's more straightforward and easier to explain to patients and easier to think about as providers as well. So, the classification primarily depends on where the seizure starts in the brain. So, a seizure is an abnormal surge of electricity in the brain. And whether it's coming from a specific spot or focus in the brain determines whether it's focal epilepsy, or if it involves the whole brain at once, or rapidly involves the whole brain at once, means that it would be generalized epilepsy.

So now, when we talk about seizures, we talk about focal onset versus generalized onset. And within focal onset, there's focal aware seizures and focal impaired aware seizures. And that means exactly what it sounds like. You either

have a seizure that starts in a specific spot or focus. And the patient retains awareness or the patient has impaired awareness during the seizure. If they have generalized onset seizures, that means this is a seizure that's typically under a genetic generalized epilepsy and rapidly involves both hemispheres of the brain. And there's several different types of seizures that fall under generalized onset seizures as well.

Host: And so, you have seizures that can sort of be motor, like tonic-clonic. And then, you can have, you know, like we talk about the absence variety, which my understanding is it's a generalized onset, but is a non-motor seizure, but somebody is obviously having a seizure, but just not manifesting it.

Dr Mindy Ganguly: Right, exactly. So, generalized onset seizures, there's motor and non-motor. When we think of big shaking convulsions, we think of tonic-clonic seizures. Generalized tonic-clonic seizures are the motor onset seizure that a lot of us think about, whereas non-motor seizures are something like absence seizures, which can be typical or atypical. You can also have myoclonic seizures.

One distinction is that you can have tonic-clonic seizures that are generalized onset or focal onset, and the distinction is just where in the brain it starts. Ultimately, it looks like a convulsion, and you don't really know until you know what kind of epilepsy syndrome the patient has, whether it's a generalized tonic-clonic seizure or a focal to bilateral tonic-clonic seizure.

Host: So, I imagine history is really critical here in terms of figuring out if it started out focal first.

Dr Mindy Ganguly: Absolutely. History, EEG, and MRI is really what we use to try to figure out if somebody has focal or generalized epilepsy.

Host: So, you hinted that generalized epilepsy, you said a genetic component, that a lot of these come in syndromes that manifest in childhood and somebody then knows they have epilepsy and they have generalized onset. Or do we see generalized onset in adults?

Dr Mindy Ganguly: So, we can absolutely see generalized onset in adults as well. So, I think the way that the paradigm is shifting a little bit in epilepsy is that we believe that most people with epilepsy have some kind of genetic predisposition to having seizures, and that it's something in the environment or something throughout their lifetime that triggers them to actually have that first seizure event.

Those with generalized onset epilepsy, they tend to have genes that we are currently able to identify more frequently than, let's say, a lot of the patients with focal onset epilepsy. A lot of the patients with focal onset epilepsy, sometimes we can actually see a structural lesion on an MRI or we can find something focal on an EEG.

Host: So, let's talk about focal seizures, and let's talk about the ones that have intact awareness. And so, those can start, often, I think with focal motor, or can be non-motor. But let's talk about the motor ones first. Do they mostly start distally in the hands or in the feet, and then you kind of get this Jacksonian march that we've heard about? Is that the most common way you see it?

Dr Mindy Ganguly: Not necessarily. So, I would say that focal-onset seizures, if you think about the mechanism, you can kind of imagine how the seizure manifests itself. So if it's a focal seizure that stays in the spot where it originates and it kind of stays in that area and percolates, it might not spread enough to affect awareness. So, that can be if it starts near the motor strip, it might be motor onset. If it's somewhere else in the brain, it might cause non-motor symptoms. symptoms. So actually, focal aware seizures where the person is aware during that time is the same thing as auras. So, when we do see focal motor onset seizures, we do see that Jacksonian March because that seizure is migrating along the motor strip and you have that Jacksonian march where it can involve the hand, then it can spread to the arm, then it might spread to the leg, face, et cetera. But often, focal onset seizures are characterized by deja vu, funny smells, funny tastes, funny feelings in people's stomach. There's just really a vast array of what focal aware seizures can look like, which are pretty much synonymous with auras.

Host: Yeah, so, they can be motor. Your hand is doing something funny, and you're completely aware of it, and it never marches up or generalizes, and so that can be one thing. But, you know, I did want to get into this, because as I was sort of prepping for this, I realized that it's possible I've been missing patients who have auras, which is, as you said, a focal seizure, but it's not manifesting in a motor way, but rather in a sensation. And so, I'm going to give away a secret here. I usually read Harrison's Textbook of Medicine when I'm prepping for these podcasts because it always gives sort of the basic things. But they talked about hallucinations, vertigo, intense odors, various auras that we might miss in primary care, but maybe are being seen in our patients.

Dr Mindy Ganguly: Absolutely. I think that's one of the things that makes epilepsy so fascinating, is that everything that we do, when we see, when we speak, when we hear, those are all electrical communications between brain

cells. So if something goes awry with that electrical communication that causes a seizure, it can cause any of those symptoms. So, for example, if you have a seizure coming from the part of your brain that crystallizes memory, if something is malfunctioning there, you might have revisitation of that memory over and over again during a seizure. And that's what causes the classic aura of déjà vu with mesial temporal lobe epilepsy.

So, we actually see these non-motor sensory symptoms very often. And I have had many patients who've come to me with decades of being diagnosed with panic attacks or things or even syncope, where they have this feeling of fear suddenly, and then their heart is racing, and we put them on an anti-seizure medication, and suddenly their panic attacks are gone, because they were really focal aware seizures. The insula is a part of the brain that controls a lot of our autonomic functions, including if you have an insular seizure, you might have hypersalivation, you might have your heart racing, you might get sweaty, and that often gets conflated with syncope. But sometimes we have patients where we capture these seizures, we can start them on an anti-seizure medication and see improvement of these events that we assume are pre-syncopal.

Host: So, I had one patient who had this sense of depersonalization and we were trying to work through it and thought it might be psychiatric, but it sounds like it might have been seizures even.

Dr Mindy Ganguly: I think it's so hard to parse out sometimes these subjective symptoms that can be consistent with focal aware seizures. There's really bizarre symptoms that can happen. Out of body experience, we know actually where that localizes in the brain. People have Alice in Wonderland syndrome where their hands seem really big or small. And one of the features that suggests that something is a focal aware seizure rather than something that's psychiatric or psychogenic or something else is that stereotyped feature. So if somebody has this same exact symptom over and over and over, that suggests that maybe that is because of a specific short circuit that's happening in a specific part of the brain.

Host: So that's really fascinating and I think that helps me to raise my own awareness of that as I'm hearing histories from patients about what they're experiencing. So then, you do have these focal seizures in which awareness is impaired, where they can start with a staring episode and then there may be some stereotypical behavior associated with it. So, let's talk about that.

Dr Mindy Ganguly: Yeah, absolutely. So, you can imagine some patients do have an aura where they know that their seizure is coming on and then it

spreads from there and then it spreads enough that it impacts their consciousness. And some patients don't have an aura. It's still a focal seizure, but the first thing that they know is that they lose time and they wake up somewhere and they don't know how they got there. Those can be particularly disabling. Focal impaired aware seizures are those that are more likely to cause long-term cognitive and functional deficits compared to focal aware seizures. And they can look like anything. It just depends on the spread of the particular seizure and where it decides to go in the brain.

Host: I remember learning this in residency and, you know, it's not good to be in a seizure state for long. There's harm to the brain.

Dr Mindy Ganguly: Right, exactly. And in particular, when you have a seizure that spreads enough that involves both hemispheres of the brain and spreads into a focal to bilateral tonic-clonic seizure, that's when we're really worried about things like sudden risk of death in epilepsy. So, people who have convulsions, particularly at night, are at higher risk of having sudden risk of death in epilepsy, or SUDEP. And the mechanism of SUDEP is still under investigation, but we have seen that sometimes there's changes to the EEG; perhaps there's changes to the heart rate, where the heart rate slows; changes to the breathing, and that itself can be dangerous to the body, and the seizure itself can be damaging to the brain.

Host: I think you've gone over this already. But when you're taking a history, is there anything specific other than what you've mentioned that you teach your residents to look out for? Is there a seizure history script?

Dr Mindy Ganguly: Yes, absolutely. You know, it's very easy to take a seizure history if you know what to ask for. And one of the first questions that I ask my patients is, "Tell me what the first thing is that tells me that you're about to have a seizure. What's the first sign that you are going to have a seizure?" And often, people with epilepsy will say, "Well, I get this funny feeling in my stomach and then I get really sweaty and then it's hard to swallow." and if they're able to kind of lay out that progression of symptoms and it's the same every time, that's a very suspicious or seizure. Sometimes people aren't able to articulate all of that because these sensations are hard to describe. Sometimes they might just say, "I feel off or I feel weird." But if somebody comes to me with very stereotyped symptoms that I can map throughout the brain and kind of trace where that seizure is spreading, to me, that history is very consistent with a focal seizure.

Host: I'm curious about an overlap here, and that is the overlap with migraines. Because there's a lot in here that's sort of similar in terms of the aura and some of the other features. Is there more known in this area?

Dr Mindy Ganguly: It's so, so, hard to tell the difference between focal aware seizures and migraines. Migraines typically are followed by headache, which is primarily the feature, but there's also acephalgic migraines where you don't have head pain. And what I would say is that often people with focal aware seizures will quote "declare themselves", which means at some point they will lose consciousness, which is not typical of a migraine.

Beyond history, that's why we have additional testing. That's why we have EEG and MRI to try to see if we can supplement the history to try to make that distinction between migraines and focal seizures.

Host: So when a focal seizure generalizes, we all know the tonic-clonic seizures that everyone talks about, but they don't always happen as tonic-clonic. We talked about absence, where people just are not responsive, but what are some of the other ways that a generalized seizure can manifest other than the tonic-clonic?

Dr Mindy Ganguly: A focal impaired aware seizure can't necessarily become an absence seizure. An absence seizure, by definition, is part of the non-motor generalized seizures. So, generalized motor seizures are typically tonic-clonic seizures. And then, there's also myoclonic seizures, like we mentioned earlier. The non-motor generalized onset seizures are typical and atypical absence seizures and myoclonic seizures.

Host: And we know more about these epilepsy syndromes that often diagnosed in childhood. Can you take us through those?

Dr Mindy Ganguly: I think the arena of genetic epilepsies is exploding and we are finding more and more genes that correspond to specific syndromes in epilepsy. There are some common syndromes that we see that we are often taught like childhood absence epilepsy, there's juvenile myoclonic epilepsy. Those are probably some of the most common epilepsy syndromes that we see, and they're also pretty self-descriptive. So, childhood absence epilepsy tends to happen in early childhood, characterized by staring spells or absence seizures. A lot of those children with childhood absence epilepsy grow out of those seizures. Juvenile myoclonic epilepsy tends to in early to late adolescence. They often have the typical story for someone with juvenile myoclonic epilepsy, is that they're particularly clumsy in the morning. They'll wake up and they'll

throw their toothbrush because they have a myoclonic jerk in the morning. And they tend to have more seizures during sleep transition states or early in the morning once they wake up. They can often have tonic-clonic seizures as well. And then, they can also have staring spells. Those are the most common childhood epilepsy syndromes that we see.

Host: So, one of the names for the epileptic syndromes that I'm seeing on charts fairly frequently is Lennox-Gastaut syndrome. Can you tell us about that?

Dr Mindy Ganguly: So, Lennox-Gastaut syndrome is a syndrome that typically presents in childhood. There is actually a transition of syndromes, beginning with West syndrome, which is often diagnosed in infancy; Ohtahara syndrome, then it kind of progresses to a diagnosis of Lennox-Gastaut syndrome, which is typically a diagnosis made in early childhood. It's characterized by a pretty specific EEG pattern, which is 2 hertz spike-and-wave. And clinically, it's manifested by people who have multiple seizure types, intellectual impairment, and they're often medication refractory.

Host: So, patients who aren't born with a genetic profile or do not develop epilepsy as children, and acquire a seizure disorder, my understanding that's often due to head trauma, not exclusively, but some area of the brain has been damaged. And then, this results in a center of potential electrical focal impulse.

Dr Mindy Ganguly: About two-thirds of the patients that we see have some identifiable cause for their epilepsy, and a third are cryptogenic, we don't really know why they have epilepsy. So, the two-thirds where we do find the reason, it might be structural, let's say, tumor, stroke, intracranial hemorrhage, something like that. It could be traumatic brain injury, encephalitis, meningitis. Those are all kind of things that can cause seizures later in adulthood. And then, a third of the patients, like I mentioned, we do all the testing, we do our best to figure it out, and we often don't have an answer.

Host: So, you have these patients who have acquired seizure disorders from, as you said, stroke or tumor. Are they considered to have epilepsy or is epilepsy somehow what you have when you don't have a structural reason?

Dr Mindy Ganguly: A seizure is an event that happens. A seizure is that abnormal surge of electricity. What epilepsy is a predisposition to having seizures, for whatever reason that is. So, there's a group that defines a lot of these terms for us. And they suggest that we define epilepsy as a 60% chance of

seizure over the next two years if you are off of medications. So, that could be because we have no reason for you to have a seizure or that could be because we have a structural something that we found on an MRI.

Host: And then, you have situational seizures, which we do not generally treat long term. I mean, the classic one is alcohol withdrawal. But I'm sure you see others that I can't think of right now, but that you don't necessarily treat long term. What are some others, maybe other than alcohol withdrawal that you'll see?

Dr Mindy Ganguly: If somebody has a seizure, that doesn't necessarily mean that they have epilepsy. But if they have epilepsy, that means that they are at risk for future seizures. So, the situations in which someone might have a seizure, but not epilepsy, might be if they have a single lifetime seizure. They don't necessarily have a high enough recurrent risk that would classify them as having epilepsy or if their seizure was provoked, which means like alcohol withdrawal in the setting of substance use is another one. If they're very sick or hospitalized, that might just lower the seizure threshold enough to cause a seizure without really conferring a long-term risk of epilepsy.

Host: So, we're not going to become EEG experts, but I think we should all have some idea of exactly what's going on and what's happening with that technology right now, because you mentioned it as a major tool for you to help sort all this out. How do you use it?

Dr Mindy Ganguly: I would say most patients who walk into my office will at least get a routine EEG. It is an imperfect tool. It actually takes a seizure or something to involve six square centimeters of your cortex, which is about the size of your palm, to actually be detected on EEG, which means that somebody could have one of those focal aware seizures or those auras that we were talking about and it wouldn't be picked up on EEG at all. And EEG itself, a routine EEG, is about 21 minutes. So, all it tells you is that, during those 21 minutes, there wasn't anything abnormal that took more than 6 square centimeters of cortex. However, it's the tool that we have. We can increase the yield of EEG by capturing sleep. People are more likely to have discharges or abnormalities in sleep. So, sleep-deprived EEG can be helpful, even if you're still getting that short study.

Then beyond that, some of the tools that we have in our back pocket is an ambulatory EEG, where we actually hook them up, send patients home for two or three days, monitor their EEG activity, and then review everything over those two or three days, including during sleep. And if that's not effective, then we

often bring them into the epilepsy monitoring unit, where we monitor their EEG, stress out their bodies with whatever tools that we have to try to capture an event or an abnormality.

Host: So, a sleep-deprived EEG, you deprive people of sleep and you try to get them to manifest something, right?

Dr Mindy Ganguly: Yeah. We tell them to stay up all night and then come in and get your EEG.

Host: And then, you have video EEGs. And this is, I think, where some patient is experiencing something that could be interpreted as seizures, and you really just want to see it happening at the same time you're doing the EEG.

Dr Mindy Ganguly: Yes. And so, that's what we do during the epilepsy monitoring unit. We have people who are monitoring on both video and EEG. There are situations where there's video EEG available as an outpatient with video ambulatory EEG where we can monitor patients at home. And that can be really helpful because if somebody's having events that aren't showing up on EEG or are on video, we can really clarify that difference.

In fact, there was a study done where Penn was involved, suggesting that there's a very, very high concordance of an epileptologist reviewing just a video and whether they have seizures or not once they're admitted into the hospital.

Host: So then, you're doing MRIs, and I assume these are just the normal MRIs that we all can order, or there are more sophisticated MRIs that you do?

Dr Mindy Ganguly: So, as epileptologists, we order MRI epilepsy protocol, which takes thinner slices through that mesial temporal lobe, which is one of the more common places that we find structural defects in patients with epilepsy. We order without contrast most of the time, unless someone has an abnormal exam, or if there's a special case that suggests that they might need contrast if you're worried about autoimmune disease, tumor, things like that.

Host: What information does the MRI give you? By that I mean, I suppose if you're working up somebody for a seizure, there's three sort of categories I'm thinking of right now. One is you're not sure that they had a seizure and you're trying to figure out if there's a focus that potentially could cause a seizure. The second category are folks that clearly seized and you're trying to do some sort of prognostic evaluation as to whether or not they need to be on anti-seizure medications moving forward. And then, the third category may be folks that

their seizures are uncontrolled and you're trying to tell is there a focus that could potentially benefit from surgery.

Dr Mindy Ganguly: I think that sums it up pretty well. Yeah, I think that's pretty good. If you're trying to figure out, whether someone is at increased risk of seizure because they have something structural, you know they have something structural and you're trying to see if you need to intervene on that, or if there's a change in their epilepsy and you're trying to see if anything has changed with their brain.

Host: So, the other area that I find very confusing now that we've sort of gone through classifications, diagnosis, some of the tools you use, this whole arena of medications. So, when I grew up, it was Dilantin and phenobarb. We didn't really use phenobarb, it was almost always Dilantin, I think, in many cases, the folks I see. And I think I'm probably seeing a lot of acquired seizure disorders just in my practice, in my history doing a lot of inpatient medicine. Oftentimes, I see Keppra as the first drug that's used levotiracetam. Maybe you can educate us on what are the drugs you're most commonly using. And I want to go through each of those so that we at least have some familiarity with it, what's being used in modern practice.

Dr Mindy Ganguly: There's pretty interesting work done on how many medications patients have to go through before they're controlled. So, there was a study done in the '90s that suggested that about just under 50% of patients will be controlled by the first anti-seizure medication you put them on. An additional 15-20% will be controlled by the second medication you put them on. The third medication, it drops; the fourth, the fifth, it gets progressively less and less. So, about two-thirds of patients who come in will be controlled by their first or second medication. And by the time you're trying the third, fourth, fifth, the chance that they'll respond to medications is low. They redid the study with all of our new medications recently, and the seizure response rates despite all of our new medications is about the same. We still say that two-thirds are medication-responsive. And the last third, you should consider non-medication options.

The difference between some of the classic medications and the newer iteration of medications is tolerability and side effects. I think people are doing much better better on some of the newer medications compared to the Dilantin and the phenobarbital and the primidone. And we do less monitoring because we're not as worried about liver function or about bone density and things like that.

So when we select anti-seizure medications, we are primarily selecting for efficacy and for side effect profile. There was a study done a couple of years ago that suggested out of a lot of the first-line medications, lamotrigine tends to be the best tolerated. And the way we see that is by seeing how long patients actually stay on the medication. Lamotrigine tends to be pretty well-tolerated; however, it takes a while to be started on lamotrigine. You have to up-titrate slowly, because there's a risk of a dangerous rash. If lamotrigine is not an option, we often go to Keppra. Both of these medications, Keppra or levotiracetam, both lamotrigine and levotiracetam are great first-line medications. And they work for all kinds of seizures. So if you're still trying to figure out whether someone has focal epilepsy or generalized epilepsy, both lamotrigine and levotiracetam are safe bets. Once you figure out their epilepsy syndrome, or let's say if they're not tolerating lamotrigine or levotiracetam, that's when you start to think about other options.

I would say if you know that somebody has generalized epilepsy, valproic acid actually, even though it is one of those older medications, tends to be quite effective for people who are assigned male at birth with epilepsy. We do avoid that in people with childbearing potential, just because it is a known teratogen. And it comes with a lot of potentially undesirable side effects for people of childbearing potential.

Host: Can we just go back through those a little bit? So, lamotrigine, you mentioned, I haven't used this in a while. And when I have, it's usually been one of you folks putting in a schedule of how to do it on the chart. But how do you start it?

Dr Mindy Ganguly: So, it's a slow uptick, it's been over seven weeks. The reason we do that is because when we start at a lower dose, we are able to monitor more closely for Stevens-Johnson syndrome. It's a very, very rare, but very feared effect of lamotrigine. So, we typically start at 25 milligrams daily. And then, we go up to 25 milligrams twice a day for a week and then, we keep escalating from there. It really does take close to two months to get to the minimum effective dose. Lamotrigine is a fantastic medication in so many ways. But in other ways, it interacts with a lot of other medications. If somebody's also on valproic acid, there's a totally different titration schedule. If somebody's on birth control, that can, you know, very much lower the serum levels of lamotrigine. So, I would say medication titration, and epilepsy is quite complex overall.

Host: It sounds a lot of what I experienced with Dilantin. So, let's talk about Keppra, because when Keppra first came out, all of a sudden everybody was on

Keppra because we were so eager to get away from Dilantin mostly. But let's talk about it. How do you use it?

Dr Mindy Ganguly: I think levetiracetam is a great first-line option. It is very well-tolerated, so it's not associated with some of the feared consequences of long term anti-seizure medication usage. So, we're not really worried about someone's liver, kidneys, or bones, which is what we think about with a lot of other anti-seizure medications.

The initial studies showed that about 5% of patients on the maximum recommended dose of Keppra have irritability or mood side effects. I think in my clinical practice, it's probably a lot more than 5% and on lower than the maximum recommended dose. So, it's probably not your go-to medication if someone has a diagnosis of depression or mood disorder. But otherwise, I think it's a great first-line medication if you have to get someone on a medication right away.

Host: I've had some issues with it in older patients with sedation, that they feel just sleepy and tired.

Dr Mindy Ganguly: One of the other side effects of Keppra and actually most anti-seizure medications is sedation. There's a little bit of an art to this. So, the minimum recommended dose of Keppra is 500 twice a day, the maximum is 1500 twice a day. But often in people who are older, whose metabolism is a little bit different, sometimes we will put people on 250 twice a day of Keppra because of that sedation piece.

Host: But the side effect profile is reassuring as you noted otherwise. Let's talk about maybe newer ones. I know Lamictal, it was definitely used for bipolar disorder and some other things. And we're familiar with valproic acid and now Keppra. What are some of the newer ones out there that you actually use beyond those?

Dr Mindy Ganguly: I would say that some of my personal favorites, not that I'm endorsing any of these, but I do tend to like clobazam and cenobamate. The reasons for that, clobazam is a benzodiazepine, which we all know are very effective for shutting down seizures. But what's unique about clobazam is it doesn't have those peaks and troughs that you have with some of the more rapid-acting benzodiazepine. So, people don't get dependent or used to clobazam like they might with lorazepam, clonazepam, et cetera. So, it's typically a once-daily medication. And there was a study that also came out of

Penn that suggested it's maybe a more effective add-on medication than some of the other options.

So, I do like clobazam. I also really like cenobamate. Their initial trial data was very, very promising in patients who've tried many other medications. They still had a significant proportion of patients who achieved greater than 50% seizure reduction, which is tough because a lot of these patients have been on five, six, seven other medications in the past and have not had success. The problems with both of those medications is they tend to be very, very sedating and difficult to tolerate. They also have pretty complex pharmacokinetics with some other medications.

Host: Do you mean by that clobazam and cenobamate or just cenobamate as sedating?

Dr Mindy Ganguly: both clobazam and cenobamate can be pretty sedating. What's difficult is clobazam and cenobamate interact with each other, interact with other medications. Cenobamate can also make people pretty dizzy. If cenobamate interacts with clobazam, it can increase a metabolite of clobazam, which will also make people dizzy, so you have to proceed with caution if you're going to prescribe either of those.

Host: So, that's a benzodiazepine then. I'm not sure I ever realized that. Does it have some of the side benefits of benzodiazepines? I mean, I use those for anxiety and insomnia and some other things occasionally.

Dr Mindy Ganguly: I think the dosages that we prescribe it for are too low to have any meaningful impact on mood disorders though.

Host: Is it a benzodiazepine that you would use? Typically, we would use Ativan in the setting of acute seizure, when somebody's actually seizing. Has that changed or is that still what you would use in acute seizures?

Dr Mindy Ganguly: Typically, we use a more rapid onset or a more rapid-acting benzodiazepine. My favorites are the rescue sprays. So, there's both intranasal midazolam and intranasal diazepam as rescue sprays. They're much easier to administer than trying to get a tablet into a patient's mouth when they're having a convulsion. It's much more convenient for everyone than a rectal administration. So basically, it's the same kind of bottle as a Narcan spray. You hold it up to their nose, it's dosed for their weight, just deliver it. And they are designed for rapid administration of benzodiazepines.

There are still situations where you use an oral benzodiazepine, dissolvable tablets typically, like clonazepam. And then, you can use Onfi or clobazam as a rescue medication. You typically use it in a setting where you want long-term benefit because that clobazam has a half-life of about 50 hours. And so, it hangs out in the system for a long time.

Host: So Mindy, you mentioned that two-thirds of folks are going to be controlled with two medications. And then, sort of the odds of the third, fourth, fifth, there's a law of diminishing returns, so you really don't get the benefit. So, you're probably going to end up with about a third of people that are really hard to control, or that you're going to need multiple medications if you can succeed at all. So, let's talk about that population, the folks that are on multiple seizure medications and are not really controlled. I understand there's some real advances in that area.

Dr Mindy Ganguly: Once someone has tried two medications, they should be referred for epilepsy surgery. That doesn't necessarily mean you walk into a neurologist's office and you leave with a surgery. That just means that you do an evaluation to see what your options are. And there's so many different options out there. The options might be just the right medication cocktail, and titrating a few of these more complex medications that might get somebody under control. Or it might mean something that's quite minimally invasive, a 20-minute procedure like a vagal nerve stimulator, which sits in the chest, stimulates a vagus nerve, and it just goes off as often as the provider programs it. It's open loop stimulation. You might have a device that's implanted or has leads implanted in the brain, like a responsive nerve stimulator, or a deep brain stimulator. And those targets are basically decided by the provider based on where seizures are coming from in the brain and then, if those device options are meant to be palliative, which means that they reduce the severity and frequency of seizures.

But our primary goal with epilepsy surgery is actually seizure freedom and actually trying to cure epilepsy. Patients will probably need to be on long-term medications, but we try to get patients completely seizure-free by intervening on where their seizures are coming from in the brain. That might mean resection, so actually cutting out the part of the brain where the seizures are coming from or a laser ablation where we're able to actually burn where the seizures are coming from. And I think that there is a lot of fear around a surgery like that because it's an elective brain surgery, which can be really scary. But I think a lot of patients are also fatigued with being on numerous medications with multiple side effects and continuing to have seizures.

Host: You seem to have a lot in common with the cardiac electrophysiologists and their ablation procedures for various arrhythmias.

Dr Mindy Ganguly: I guess it's not too dissimilar.

Host: So, what's the success with ablation? I guess, you know, that location in the brain, it's a focal seizure, or at least it's something that you're able to clearly identify the source. How successful are these?

Dr Mindy Ganguly: We do have some non-medication options for patients with generalized epilepsy. They're primarily devices, so the vagal nerve stimulator or the deep brain stimulator we can use for generalized epilepsy, because it kind of stimulates the whole brain at once. For focal epilepsy, that's when we're talking about these other options. Success rate varies a lot from patient to patient. And so, that's why it really requires a risk-benefit discussion between the provider and the patient. Sometimes we quote patients as high a rate as 60-80% seizure freedom if we can see where their seizures are coming from and everything, all their testing, lines up and we're confident we have the seizure onset zone.

And then, sometimes if patients have seizures coming from multiple different parts of the brain or less well-defined parts of the brain, we might quote rates of 0-20% seizure freedom. And in that situation, we're just trying to reduce, again, the severity frequency of seizures rather than aiming for seizure freedom.

Host: I want to ask you more about these stimulators. So, you had mentioned deep brain stimulators and others. So, I guess you put some form of probe in the area that's most affected when it detects. And I think about this in a cardiac electrophysiological way. It sounds like an AICD, a cardiac defibrillator for the brain, right? Is it similar in its approach?

Dr Mindy Ganguly: So, somewhat, we have what we call open loop and closed loop stimulation. So, the vagal nerve stimulator and the deep brain stimulator are primarily open loop. The vagal nerve stimulator can stimulate more frequently depending on heart rate. About 85% of patients with seizures will have an increased heart rate during their seizures. So if it detects a tachycardia, it might deliver more stimulation. But I primarily think of deep brain stimulation and vagal nerve stimulation as open loop stimulators. The responsive neurostimulator is interesting, because we actually have EEG recording in the brain. It will detect a seizure based on what the provider programs. And then when it detects a seizure, it will deliver a stimulation in response to the seizure.

Host: And the idea is to try and shut it off before it gets going.

Dr Mindy Ganguly: Exactly. But it's supposed to try to stimulate the seizure before the patient is symptomatic, or at least reduce the severity of the seizure.

Host: So, there's two other areas I want to delve into for a primary care audience, and that's women with epilepsy and sort of the issues with childbearing and so forth. And then, there's this question that all primary care physicians have to deal with, and that is, "When can I drive, doc?" Let's start with the driving one first. this comes up a lot, So, I'll just throw it out there. I guess anybody who's had a seizure should not drive. And I believe in the state of Pennsylvania, it's a year. But educate me on that.

Dr Mindy Ganguly: You're absolutely right. It's very variable from state to state. Pennsylvania and New Jersey require that a patient with epilepsy is seizure-free for six months before they're able to drive. There are exceptions to that rule. For example, if it was a provoked seizure like in the situations we were talking about earlier, if they were very sick; if they have a pattern of having only nocturnal seizures for over two years. Some patients only have seizures during sleep. So if they're awake, they are good to drive. Or if a patient has a prolonged aura where they can tell, "You know what? I'm having a seizure. I'm going to pull over the car," or if the patient only has focal aware seizures that don't impact their driving. So if a patient just has a funny smell and that's their seizure, that doesn't affect their ability to drive.

There was a survey done that suggested that the inability to drive is the single most debilitating feature of epilepsy for patients with seizures. So, it's something that we take very seriously, and it's a hard discussion to have with our patients, especially because both New Jersey and Pennsylvania are mandatory reporting states, meaning that if a patient tells us that they have a seizure, we are mandated to report that to the driving authorities.

Host: And then if they're controlled on medications for six months, then you can release them to driving. I actually don't know how that process works. Does the DMV decide that or do you decide that?

Dr Mindy Ganguly: So, the DMV makes all ultimate decisions. All we do is report the information that we have, and the DMV decides one way or the other. The DMV makes it very easy to pull someone's license because if they get a report saying that someone has a seizure, they will pull the license and they make it very difficult to get the license back, which means patient has to go to the DMV website. They have to download the correct forms. They have to fill

out their portion. They have to get their physician to fill out the rest of the form. They have to submit it, follow up, et cetera. So, it's a little bit of a process.

Host: So, let's talk about seizures in women of childbearing age in particular, because it's a little more complicated there, right?

Dr Mindy Ganguly: Absolutely. So, the International League Against Epilepsy recommends that all people of childbearing potential with epilepsy take folic acid. There's two reasons. One reason is that people of childbearing potential with epilepsy have a slightly higher chance of having a fetus with neural tube or brain and spinal cord defects compared to people without epilepsy.

And also, a lot of epilepsy medications can reduce the amount of folic acid or folate in someone's body. So, because you have to have a store of folic acid for about three months to have this effect, to protect against neural tube defects, we recommend that all people of childbearing potential who have epilepsy take folic acid just in case something were to happen.

But realistically, within epilepsy, the best pregnancy is the planned pregnancy. So, we ask early and often what patients plans are with birth control, if they're using it, if they're trying to conceive, especially pregnancy can affect the body in many different ways with hormonal changes, that can affect anti-seizure medication levels. And it also suggests that if somebody does become pregnant, that we need to make sure we manage them appropriately, refer them to high-risk maternal care, and have a delivery plan for them.

Host: The last question I wanted to ask you was there are medications that we use that reportedly lower the seizure threshold. So, I like Welbutrin a lot. I find it very, successful with it as an antidepressant, prescribing it. But it does lower the seizure threshold. How much is that an issue we need to be concerned about?

Dr Mindy Ganguly: We've discussed provoked seizures a few times already. And if somebody is on Welbutrin and has a seizure, I would absolutely consider that a provoked seizure. There's many antidepressant that may be associated with a lower threshold for seizures. But the ones I really think about and the ones I would consider taking someone off of if they have epilepsy or have had a seizure are Welbutrin and clozapine, which we don't really see too much. Welbutrin, so at doses greater than 450, there's about a 10 times risk for seizure, but we don't really know the increased risk for seizure dose is lower than that. But Wellbutrin can absolutely lower that seizure threshold.

Host: And you wouldn't recommend it then in folks that already have a known seizure disorder.

Dr Mindy Ganguly: I would personally avoid it.

Host: Tramadol is another one, I think, that at least used to be thought to have this as well.

Dr Mindy Ganguly: Yeah, potentially. But a lot of these medications, I think, is also about risk benefit. So if someone's in pain, it's otherwise relatively benign. I think there's a lot of medications that we tell people to avoid if they can. For example, Benadryl is one of the more common medications that we tell people with seizures to avoid. Sudafed is another one. But if someone's having a major allergic reaction, they need to take Benadryl, then that's absolutely fine.

Host: One of the things you've really taught me here, well, you taught me many things, but one of the things is my takeaways is that if I see folks that are uncontrolled on two or more, medications, two or more, I believe is what you said, that they should really be referred down to the Epilepsy Center for consideration of advanced therapies. Can you tell us a little bit about the Epilepsy Center at penn?

Dr Mindy Ganguly: The Penn Epilepsy Center, I think, are a great group of people. I think every faculty member within the Penn Epilepsy Center has a special interest that they are working on trying to develop either for the department or within research. And I think we have a very collaborative environment and we tend to take a very multidisciplinary approach to some of these more involved decisions, which means that when we are discussing surgery or device for a patient, we have neurosurgery, neuropsychology, we have nuclear medicine, we have the entire Penn Epilepsy Center involved and confer on some of these decisions.

I think we have also worked really hard to make the Penn Epilepsy Center accessible, which means that patients should be able to get in pretty quickly if they need to be seen. Whether they go through a normal referral or if they need to be seen more quickly, we can always get them in with an urgent appointment. So, I think we try really hard to provide our patients the best care possible.

Host: So that's fantastic, Mindy. I really appreciate you coming on and talking about this. I'm going to leave it at that, because I think that's a good place to end in terms of things that the primary care community needs to know to get people to you. But updating all of us on this whole area and some of the older stuff that

has changed, but also the newer stuff that is really exciting. So, thank you so much for coming, Mindy.

Dr Mindy Ganguly: Yeah, no problem. It was my pleasure.

Host: Thank you everyone for joining the Penn Primary Care Podcast. Please join us again next time.

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