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ADOLESCENCE AND EPILEPSY - A FOCUS ON SEXUAL HEALTH

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[video transcript]

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Dr. Ina Hughes is an associate professor of child neurology and epilepsy at the University of Rochester. Dr. Hughes completed undergraduate studies at Williams College and graduated from Washington University in St. Louis School of Medicine. After completing the combined MD, MD Ph. D program. She completed her child neurology residency training and a pediatric epilepsy fellowship at the University of Rochester Medical Center. Welcome, Dr. Hughes. Thank you so much for the invitation. Just a heads up in a warning, I tend to speak very quickly. And if I am going to quickly hopefully somebody will flag me down a little bit. But I want to first talk a little bit today about some of my favorite patients, which are adolescents. And of course, my favorite topic, which is epilepsy. I have no relevant disclosures to the the topic. Hopefully, at the end of the talk, you'll feel very comfortable with kind of thinking through the complex psychosocial milieu of living with a complex disorder like epilepsy, and how that can influence and be influenced by adolescents. And so many of the things that happened during that kind of transition to adulthood, will examine the evidence for interactions between epilepsy medications to treat seizures and sexual hormones, and discuss issues related to childbearing and patients with epilepsy though I often hope that my children, young adults and without epilepsy are not necessarily having kids early in life. Some of them certainly do. And we want to make sure that we know all of the information that needs to be available to them when that happens. So I want to talk just very briefly about my favorite organ, which is the brain it is awesome, it runs on electricity. It is an incredibly complicated interplay of all kinds of different processes that affect every single aspect of the rest of the body. For those who interact with things like EEG reports, you may see that there are such things as discharges on EEG reports, that's abnormal electrical activity that we don't expect to be there on the brain, the way that I tend to think of the brain as though it is a symphony, complex symphony playing a very complicated tune. And a discharge is basically as though there's a symbolist, kind of wandering into the middle of the, somewhere along the symphony and just kind of banging away at its own time in its own place and ignoring everything else. A seizure is when, for instance, in that analogy, the instruments surrounding where that abnormal discharge is occurring, start to pick up the rhythm and beat of that abnormal discharge. And it destroys or disrupts with it, the song they're playing at the time. So a seizure is when those discharges come close enough together to actually disrupt what the underlying brain activity is doing. And you can see that manifested on the person. And then epilepsy is the diagnosis, that really just means that someone has had at least two seizures in their life. And importantly, that's actually the pediatric definition, that someone has had at least two seizures in their life, and they have a reason to continue to have. And that's really all that that tells me about somebody that tells me that they have had at least a couple of seizures, they can have more, it doesn't tell me anything else about them or their outcomes, or they're like we've been doing well or poorly. Epilepsy is firmer, far more common than people think. So one in 10 people will have a seizure at some point in their life, because all you need to have a seizure is to have a brain, we're reasonably sure the majority of humanity has those. What I'm 26 People will have a diagnosis of epilepsy at some point in their existence. But when you think about the kind of statistics in general, about one in 100 people has active epilepsy in the

moment. And what's that discrepancy between that prevalence and incidence. And the difference is that many of our pediatric patients can outgrow their epilepsy, which is wonderful and awesome. But we don't necessarily automatically know that someone will outgrow their epilepsy when they've had their first few years and get their diagnosis of epilepsy affects many people across the world. At an estimated right now, about 75 million people around the world carry a diagnosis of epilepsy, with approximately 3.4 million of those living within the United States. And there are about 115,000 new cases of epilepsy diagnosed within the US each year with a bimodal distribution of the majority of those being pediatric and then survive late in their 50s 60s 70s and 80s. People can acquire epilepsy due to acquired brain injury, brain tumor strokes and such things. Where I come in as an epileptologist is that about 1/3 of patients will live with uncontrolled seizures because none of the available therapies work for them. And we sometimes call that medical intractable epilepsy. And it has many different names. So why does this occur? So that incredibly complex interplay of electricity and the brain can be surprisingly easily disrupted by millions and billions of things. Pretty much anything that can harm a brain and Lee Due to the development of epilepsy, whether that be disruptions and the terrible metabolism, disruptions in how the actual cells are functioning, trauma, strokes, vascular malformations, genetic conditions, autoimmunity, all of those things lead to injury and scar and injury and scar in the brain then leads to seizures. And then of course, we have many patients who have genetic predispositions where they have just a very different subtle firing of those individual neurons to seizure and kill them. So in general, though, neurologists and epileptologist debate and yell about this, when we talk about epilepsy with the rest of the world, I want you to mostly think about seizures as coming in to general flavors. So the first is focal seizures, and focal seizures start in one spot in the brain and spread and depending on where they start, and how they spread across the brain, you'll have different manifestations on the body. Kind of matching with that those little, the fact that each individual part of the brain has a different role to play. If a seizure starts, for instance, in the visual cortex, you may have visuals, visual changes, if it starts in sudden the motor cortex, you may see twitching and jerking. And so again, depending on how it starts and how it spreads different than the station's generalized seizures, we actually tend to think of an epilepsy starting deep within the brain primarily in the structure of the thalamus. And because the thalamus is so highly interconnected with the rest of the brain, it expressed is expressed across the EEG and on the brain all over at once. And those types of seizures tend to be associated with stopping and staring, full body convulsion, full body tonic stiffening, or whole body jerks, so myoclonus. And the reason that we try to kind of break it down into these two different concepts is that in general, different therapies tend to work better for them. So there are meds that really, really, really only work when something is a focus here. And those are some of the classic sodium channel blockers and a couple of medicines that were specifically created for that purpose. And then some of them are generalized seizure medications will really only work if it's a parameter driven of epilepsy. Thankfully, we have, at this moment about 33 Other anti seizure medications that are not too fussed whether this is a focal seizure or generalized seizure, though some will work slightly better for one or the other. And the reason that this, this separation is important is that if you have someone with focal seizures, and you try to give them generalized seizure medications, they're probably not going to get better. And importantly, if you have someone who actually has generalized epilepsy, but you're giving them focal seizure medicines, that have fair likelihood that they're actually going to get activity worse. And so those things are really important for us to continue to pay attention to

and make sure that we're always aware of. And then, as I mentioned, there's this idea that about a third of patients will have drug resistant epilepsy, which is something that is very important. And if you notice, somebody has tried to hold on to seizure medication, so at least two ineffective seizure medications, and they have failed to stay seizure free with those adequate trials, then it's really important that they get to see somebody like me epileptologist, to make sure that we can try to better match the therapy with the patient or to offer them potentially other options. So just a plug for epileptologist. And a plug for neurology is making sure that anyone can help a patient who is having a hard time with seizure control to hopefully get better seizure control by getting connected with someone who may be able to utilize other therapeutic options than just medications.

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So I have a pediatric neurologist and a pediatric epileptologist. So the question of why concentrate on kids with epilepsy is, of course, because they're the best ones. But there are a lot of really important topics and important ideas associated with this. Being a kid is tough being kid with a disease, that means that your brain is not always under your control is even tougher. And any kind of chronic disease where you have no sense you have a loss of sense of control is really difficult. teen years are a time of establishing autonomy, and many kids with epilepsy will lose their autonomy or fail to ever achieve it. And part of that is because seizures are unexpected. They're often not preceded by anything that lets anyone know that the seizure has been to occur. And so kids are often more supervised kids with epilepsy are more supervised than their peers, their safety, they don't get to bathe. Sometimes by themselves, they might, you know, we ask them not to lock the bathroom. People might be monitoring them when they sleep, their daily activities may need somebody with them to make sure that they're safe. There are limitations on driving, which is a huge right of American childhood and adolescence is the ability to be able to drive. But depending on which state you're in here in New York, you need to be one year seizure free. That is an unattainable goal for some of my kids. Some will be able to achieve it but the fact that they don't achieve it in the same way that other kids do, or at the same time that other kids do is often something that is troublesome for them. And then, despite the fact that we've done a lot of educational and training, do a lot of education with our families, many of our kids with epilepsy immediately assume that this diagnosis means that they will not be able to go to school, but they will not be able to go to college, they will not be able to have the job that they want to do, that they will not be able to do, the social activities that they want to do. And all of those things are things that we really need to work on families. And make sure that they understand what to do. Besides the fact that there are lots of factors of life that kind of include and enhance that difficulties that are associated with epilepsy, some of them are the social stigma of epilepsy, some I'll talk with you about the biology that occurs with changes in epilepsy and some of the others are the things that we've talked about. One of my colleagues, has recently taught me the phrase, epilepsy comes with the worst gift bag imaginable, which is a little bit dramatic. But it's also it's also true that there are many things that come along with a diagnosis of epilepsy that are fairly common things like ADHD, depression, anxiety, kids with epilepsy may have a higher rate of learning disability, disrupted sleep is pretty common, both from the risk of seizures and seizures tend to occur more associated with transitions into and out of sleep. And then also just the stress of being a kid who has epilepsy, we have anti seizure medications, and all of the interesting side effects that can be accompanied by those, and how

much these issues impact the patient will and their family are really going to be individual. And we need to individualize that management. course here at the University of Rochester, we're big proponents of the biopsychosocial model and its descendants. And that idea that epilepsy because it affects the brain and affects kind of how a person functions in life means that it's also going to affect their place in the world and their place, and how they feel about themselves. And all of those things are already so incredibly in meshed in the concept of adolescence, that the again, being a kid with epilepsy during your adolescence is particularly tough, particularly when you're having a maturation of your hypothalamic pituitary axis in a setting where you're having abnormal electrical activity that is sometimes going to affect that abnormal or that activity that access. So this is the limbic system loop that we often think about in epilepsy and in the middle of all of this. So while this is not necessarily something that psychiatry or adolescent medicine, medicine, adolescent medicine, think about a lot. All of the structures that are most commonly affected by epilepsy, the amygdala, the hippocampus, the thalamus, they all also feed into the hypothalamus, they also feed into all of the maturational processes and are affected by all the maturational processes of a rapidly developing brain. In part because of this, that grab bag and gift bag that goes along with epilepsy has sometimes been specifically associated with certain kinds of neuro psychiatric or neuro developmental consequences. So, patients who develop temporal lobe epilepsy have a higher, higher risk of autism and vice versa patients with Autism Spectrum phenotypes have a higher risk of temporal lobe epilepsy patients the treatment aisle myoclonic epilepsy have been sometimes described historically as having immature personalities or delayed delayed attribution of more mature phenotypes. There have been a variety of ways to say this, but and no one is quite sure if that is because of that super advisory activities that occur earlier in a kid's life so that they have a shift in how they see themselves that leads to this maturation or not, that research is actually still ongoing, versus whether or not this is a form of frontal lobe dysfunction. Children with Gervais syndrome, which is a severe epilepsy of childhood tend to have hyper activity and are more commonly associated with autistic features. Monica Stowe syndrome was historically associated with sluggish behavior though we know that that actually has a lot to do with the anti seizure medications used to treat that. And there are a variety of other neuro psychiatric outcomes primarily in HDX, and even in depression that are most commonly associated with any type of epilepsy over time. So when you put all of these things together, what are the implications for how kids grow and develop with epilepsy? There's this wonderful series of articles by Camfield at all and Riemann Ebert, who looked at every single one of the kind of biologic and physical aspects of developing with the diagnosis of epilepsy and how that gets you to that place where when you are in a position to make that transition to adulthood with epilepsy and going through adolescence, all of the things that can negatively affect your can negatively affect that process of transition and the success of eventual transition to becoming an adult living with epilepsy and being able to be in charge of and manage your own care. Some of these are I really like this slide because it kind of highlighted and showed all of the important things that we have to think about. So during times of adolescence, patients are thought to become more butter seeking or risky. But we also know that patients with epilepsy will have some difficulty with that limbic system frontal lobe maturation, and that this might be something that can give patients some trouble. We know that there's endocrinological development, specifically that HPA access that is actively developing smack dab in the middle of that limbic system. And then central to the development impure relationships may interfere. And there are lots of aspects of epilepsy that I'll talk about that can

affect this as well. psychological development, we talked about the autonomy that is being developed at this age, and how this can be disrupted in patients with epilepsy. And then just rupture fun. epilepsy and anti seizure medications can also affect people's bone health, leading to increased risk of broken bones and other issues that we have to pay attention to. So in this very large set of things that we must be thinking about as pediatric neurologists and epileptologist. As we're taking care of these young adults, one of the things that I think I have had the least training on is actually sexual health. And while many of our patients are incredibly embarrassed about the idea of talking about it, it is fantastically important for us to address it because it is such an incredibly big part of people's lives. And it's one that we need to make sure that patients feel comfortable with as they are. They need to feel comfortable talking with every physician that is part of their lives about it. But it is incredibly important from an neurology thing to do as well. So one of the things that informed the my idea of needing to be able to talk about this with families is in a study in Norway, it was a survey that was done, just sent out to all kids in their national health system between the ages of 13 and 19 actually got 16,916 respondents in that age group. And 247 of them had epilepsy, which was actually a slightly higher than expected, or total number of people with epilepsy 1.4% of their sample size. Were kids with epilepsy. And they found that for this age group, kids with epilepsy were more likely to have reported having sexual intercourse usually fairly significantly higher percentage of kids 13 to 19. Had their initial for sexual intercourse, it was more likely to occur at a younger age, they were more likely to fail to use contraception, and they were more likely to have had a horse sex or negative sexual experience early on in life. And this was an unfortunate set of statistics but also matches what I think we see in the United States. So we don't have these statistics coming naturally, to be able to specifically connect with our patients. But this idea that our patients need sexual education needs some information is really important. There are many factors in this particular study that were felt to contribute to an earlier sexual debut and riskier behaviors in those patient populations as well. So many of them I've already talked about briefly that idea that our patients have ADHD and anxiety. Some of our patients have intellectual disability or learning disability are differences in their school performance.

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And then there are the psychosocial issues. So like self assess, stigma, social isolation, low self esteem associated with a diagnosis of epilepsy, all of which can contribute to people wanting to use sex or having no choice but to use sex as a modulator for their social standing, which is also not great either. And the United States study of the epilepsy birth control registry was based on a study of 1400 women are allowed 100 boarding for women excuse me with epilepsy ranging theoretically from ages 18 to 47, that they had many respondents under the age of 18 80% of patients with epilepsy, reported having at least one intended pregnancy and 65% of the total pregnancies noted in the registry. And the entire industry were unintended, which is higher than the background rate. And there were risk factors that were identified for younger age with a two fold higher risk of patients who are under the age of 18. Having an unintended pregnancy with those among those with epilepsy, which is something that's very important which also means that we're not having good conversations with our patients about managing those risk factors when they are having when they are having sex making sure that they want to have pregnancies or they are having unwanted pregnancies when they do. There's also a lot of complexity in dealing with young men with epilepsy and primarily all of it relates to libido or all of

the research relates to libido and almost none of it relates to other things like fertility. or interaction with SEC their sex hormones and drugs. And so I'm going to give you the one small piece of information that I have about males and epilepsy, which is that males with epilepsy compared to the controls, report having decreased libido have increased risk for act of assumption and lower confidence in our sexual performance compared with healthy controls that don't have epilepsy. And there's been some research that has shown that patients with epilepsy have lower overall serum testosterone levels. So this was actually found on both men and women. Females with epilepsy compared to controls of decreased libido, fewer orgasms, increased risk for dyspareunia and decreased vaginal lubrication. And this was all self reported sexualized way. And additionally, there have been several studies that have shown for all patients that with more seizures, desire and enjoyment for sex significantly decreases. Import importantly, there are actually some anti seizure medication associations so that we know that medications that are particularly sedating, so Clobazam Quinn has a family other benzodiazepines tend to drive down with Ido fairly significantly. And then the medications that are considered to be inducing anti seizure medications, meaning that they up regulate the activity of the people with the system and the liver. Those tend to have a higher risk of decreased libido theoretically, because it will increase the likelihood that testosterone levels or testosterone is rapidly metabolized by the liver and reducing total levels. So medications that just carbamazepine, phenytoin phenobarbital are pretty famous for this. Theoretically, pregabalin two apparently are primarily acting through sedating properties that make this difficult, that make libido and sexual dysfunction more libido lower and sexual dysfunction more likely. So for patients, almost all of the research that has been done has been done traditionally on women with epilepsy, high estrogenic environment, essentially in epilepsy. And one of the reasons why is that estrogen has been found to be essentially proconvulsant in many, many patients. We actually know some of the biology behind that it can reduce the inhibition of the GABA a receptor and GABA is essentially putting the brakes on the brain and helping stop seizures on to get started. It also alters the mRNA for Gad, and inhibits GABA synthesis. So again, we're reducing GABA, which are the brakes for the brain that helped us stop seizures from occurring and just for extra fun and enhances some of our anti seizure medication clearance. Interestingly, progesterone may be anticonvulsant. But it's not as beautifully anticonvulsant in the sense that I can give you progesterone to completely prevent you from having seizures, but we do know that it antagonizing some of that activity that actually has a main increased GABAergic signaling. It can also attenuate glutamate and glutamate, we kind of feel to be the gas of a seizure that kind of keeps a seizure going. And so we can reduce the glutamate signaling by exporting more progesterone. And again, it alters gad mRNA and increases GABA synthesis. And so of course, we know that patients who are phenotypically female or who are so women of childbearing age who are experiencing their menstrual cycle will go through cycles of having higher estrogen and progesterone at different points of that menstruation phase or menstruation cycle. And so certain patients will actually experience something called catamenial epilepsy so they can experience seizure exacerbations that are timed within their menstrual cycle. Interestingly, it can actually vary for individuals. The majority of patients that this is described, will experience it most commonly in the three to four days prior to onset of menstruation when theoretically there is a higher burst of estrogen compared to progesterone. But there are individual people who will experience it in the luteal, there are individuals who expressed experiences at the end of their menstrual phase. And the precise

reason for this is unclear, but it's found by people keeping a careful seizure diaries matched with information about their menstrual cycle, that we're able to identify this. The reason that it's important is sometimes that means we actually may need to vary medication administration during those times when patients are most susceptible to having increased seizure activity. Or sometimes we may actually choose to use hormonal modulation and just prevent menstrual cycle internally, particularly in patients with developmental disabilities or for whom the cycles are may be disruptive for other reasons as well. So interestingly, when we start looking at all of our patients with epilepsy who menstruate, we find that menstrual disorders and irregularity administration also turn out to be really common among these patients. And part of it as I said, The hypothalamic pituitary axis is sitting smack dab in the middle of this very disrupted electrical activity of either the temporal lobes the amygdala, the canvas, or from that thalamic current bulimic signaling pathway which is also sitting right next to the hypothalamus as well. So menstrual disorders have been described as being more common in both temporal lobe epilepsy as opposed to primary generalized epilepsy, but have been found to occur in patients in general with epilepsy at a much higher rate compared with healthy controls. And that can be range from complete amenorrhea to oligo amenorrhea. to higher likelihood irregular cycles are irregular bleeding pathways, and some of our patients have Frank hypothalamic amenorrhea. And that can lead to increasing complexity and trying to figure out for instance, if someone is experiencing catamenial epilepsy when they have incredibly irregular periods in the first place. In addition, patients can have an increased risk of polycystic ovarian syndrome PCOS associated with their epilepsy. And again, because of those disruptions of the hypothalamic pituitary axis, though it can actually be a higher incidence in some patients with specific anti seizure medication exposures without proc acid, or Depakote being one of those highest expressed ones are associated with developing PCOS. We know that PCOS can be more associated with higher androgens and normal estrogen expression. The theory behind why the Depakote is associated with this market frequently or valproic acid is a combination of alterations in fatty acid metabolism that comes because valproic acid is itself with fatty acid and can disrupt the metabolism of other fatty acids. But also because valproic acid more than any other anti seizure medication tends to be associated with very rapid rapid onset and high mounts of weight gain in a very rapid way that allows patients to develop metabolic syndrome concurrent with it. So polycystic ovarian syndrome can also be associated hypothalamic amenorrhea, functional hyperprolactinemia. And of course, that underlying metabolic syndrome puts patients at higher risk for diabetes. Cardiovascular disease is a major concern, all of which are reasons why we very often try to avoid using valproic acid and many young women with epilepsy specifically to try to avoid this risk. On the whole, there have not been associations with young men with epilepsy having significant hormonal disruption in the setting of Depakote. But again, interestingly, that research is less well defined in men with epilepsy compared to women. We also know that oral contraceptives that we might utilize for treatment of these menstrual disorders for treatment of catamenial epilepsy, themselves can negatively affect seizure control, particularly use of estrogenic containing epilepsy, or excuse me, estrogenic containing oral contraceptives, a wonderful study that was done by Herzog at all in 2017, which looked at that birth control registry,

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in patients with epilepsy, found that 28% of patients with epilepsy reported a change in their seizures when utilizing hormonal contraception. And in fact, the likelihood of somebody having seizures when they were just put on high estrogen or estrogen primarily containing oral contraceptive medications is 4.5 times higher than those who are not receiving hormonal contraceptive or those who are using non hormonal contraceptive types. So it's really important to know that you can actually cause more seizures in someone if we choose the wrong types of OCPs for them. And that's something that we try to make sure that our patients are aware of because it's education that is still ongoing within the OB GYN community, and among PCPs, and people who may be prescribing oral contraceptives, we want to make sure that people are choosing the right stuff. Importantly, oral forms of contraception have higher and greater rates of failure than non oral forms among our patients with epilepsy as well. And some of that is thought to be interactions between anti seizure medications and the hormonal birth control but then also the fact that hormonal birth control has seizure. Seizure frequency, indicate the implications, which means that patients are less likely to more regularly take their hormonal birth control if it's going to cause them more seizures. So, in particular, hormonal contraception that was combined with enzyme inducing or people 50 inducing anti seizure medicines have a much higher failure rate than hormonal contraception combined with no anti seizure medicines or with other anti seizure medicine categories. So on the whole when we can like try to encourage our patients to have a barrier based, or IUD based contraception, or hormonal contraception that primarily utilizes progesterone or estrogen, and to make sure that we are always working together with whoever is the prescriber of the contraception to make sure that it matches well with the patient. So just a quick reminder, which OCPD isn't anti seizure medications kind of interact, the ones that are considered to be inducers or carbamazepine felbamate oxcarbazepine Fein and Barbara top and a Cohen primidone, which is a breaking breakdown product with phenol barbital. All of these are known to definitively reduce the effectiveness of oral contraceptives. And that's what progesterone and estrogenic compounds. The ones that we consider to not alter contraceptions themselves may have some complications, so benzodiazepines and Gabapentin and then pregabalin, we know that this can alter your patients libido and other things associated with their sexual health. But medicines such as the motor gene and Mother TRUST Him do not alter oral contraceptions contraceptive efficacy. Interestingly, valproic acid is considered to not alter oral contraceptive efficacy. But as a practical matter, I've actually seen it, at least in some patients appear to have that effect. So it is something that we tend to avoid. And we have other reasons like I mentioned the PCOS risk to try to avoid it. Interestingly, oral contraceptives, particularly those that are estrogen containing may decrease the plasma concentrations of Lamotrigine oxcarbazepine, and to some extent, or pyramid as well. And those things need to be modulated so that we need to know as neurologists when someone outstrips an oral contraceptive agent or hormonal contraceptive agents so that we can monitor anti seizure medication levels and to make sure that they're appropriate for our patients. When patients do become pregnant, we know that there is when patients want to become pregnant, we know that there is an increased risk that patients may experience fertility issues. So the fertility rate of patients with epilepsy when compared to that of their siblings without epilepsy is actually 40% of what's considered to be in healthy control within their own family. And we know that there are significant risk factors for that among our patients, including increased risk prevented and average for menstrual cycles as part of that. menstrual disorders, higher risk of menstrual disorders overall, when we talked about the decreased libido,

psychosocial ER patients also have a reduced marriage and partner rates. And patients when they do become pregnant have a higher risk of miscarriage. We know that some of that comes from anti seizure medication from fetal survival. But we also know that having seizures when you are pregnant, increases the risk of fetal demise as well because of altered blood flow. stress hormone can have all kinds of things that can occur within that pregnancy. So when someone becomes pregnant, whether it is whether it is on purpose or surprise, we know that very rapidly and very early in pregnancy, a whole bunch of things can occur, that it can affect a seizure frequency and intensity. So one of the things that can happen is that patients will have decreased compliance, adherence and tolerance of their anti seizure medication. So if you have hyperemesis gravidarum, the late, you're going to be able to keep your entire morning anti seizure medications down really drops pretty rapidly. The increased plasma volume and alterations and protein binding that occur happen very early in pregnancy, and people may have astonishing ly different anti seizure medication levels, even before they really start to significantly recognize that they are pregnant. There are some reported ideas that they're altered intestinal absorption. That occurs, it shifts in intestinal absorption that might be microbiome shifts related it might actually be differences that are occurring in what the intestine is actually absorbing of anti seizure medications. And we know that the kidney very rapidly increases drug clearance as does a shift in the people 50 system. And so again, patients can have fantastically different levels of their anti seizure medications, even in those very early periods of pregnancy, before we start to see some of the other body shifts and changes that occur occur as someone who is pregnant and creating a child with them. So one of the important things, lots of people talk about the anti seizure medications and the risks associated with them to after antigenicity. It is important to know that more than 90% of pregnancies in patients with epilepsy are absolutely and completely and utterly normal. And that's a really important thing to lead with. When we have a patient who is pregnant because we've seen a lot of panic and worry that accompanies that in our patients. It is important to know that technically all anti seizure medicines have Tourette agentic risks and there is absolutely a registry for every pet tendency that occurs when patients are on anti seizure medications, to try to make sure that we are tracking those risks and understanding them and making sure that you can give all of our patients very good advice. So if you have a patient that is on an anti seizure, medication and they become pregnant, there is a national registry that we highly encourage everyone to have their patient register with so that we can monitor those over time. On the whole compared to a two to three risks. Two to 3% risk for congenital malformations, our patients have on average, about a two times higher risk of a congenital malformation about four to 6%. With compared to the national average, as I said, the more medicines a person is on the higher that risk is, the more seizures they have, the higher that risk is as well. And that is an important concept to think about too, so that the overall risk of a patient for being on an anti seizure medication still remains lower than the risk of having uncontrolled seizures during pregnancy. And both of those things need to be discussed with our patients when they do become pregnant. So the as I said, there is a national anti seizure medication pregnancy registry. This particular pregnancy registry is called the AED, anti epileptic drugs, pregnancy registry, but for a variety of reasons. We're shifting to anti seizure medicine as our primary discussion of these patients and what they're taking. So it's an active malformation survey program out of Brigham and Women's and they have a control group that is there and for certain medications we found is kind of a 7.3 fold increased risk of major malformations compared with the background. There are some

complications. So age education, smoking, alcohol and seizure rates are found to be similar in the VPA, not EPA group and it is specifically valproic acid that creates a significantly increased risk of major malformations and there are a variety of ways that we think valproic acid does this. So it is a very complicated anti seizure medication and it is a fatty acid that can disrupt fatty acid metabolism of other things in the body, including sex hormone, as well as other other types of hormones in the endocrine pathway. Additionally, it is histone deacetylase inhibitor which actually alters gene expression. Some of which ways are understood and some which are not, is both an inducer and inhibitor of people 50 systems which causes fun downstream complications of a variety of metabolic pathways. And then it also can decrease carnitine and vitamin D levels are all of which can contribute to, particularly in patients meat, which may already have some nutritional deficiencies to having enhanced nutritional deficiencies, all of which can increase the risk of major malformation. It also disrupts boys metabolism, increasing the risk for Spinal Bifida cystic dysplasia of the kidneys, microcephaly and other brain issues primarily associated with that specific decrease in folic acid levels.

38:15

So even more patients have completely happy healthy pregnancies. Even at the end of those pregnancies, particularly for patients on enzyme inducing anti seizure medications. And Depakote. There is a higher risk of both in utero bleeding and immediate periodic Peri partum, or postpartum bleeding that can occur both for the mother and for the incident. Specifically, because of deficiencies in K, Vitamin K dependent clotting factors that occur with those alterations in the P 460. System in the liver. And patients can have increased PT and PTT. And those are things that are again, ob colleagues and family medicine colleagues, when they're delivering these patients need to know. So we can help to make sure that we're monitoring for those things in patients that have been exposed to those and helped to make sure that we recognize those early and treat them when they burn. For that other peripartum, and postpartum considerations, lots of patients have been told erroneously that they should not just be their press feed, to produce milk for their baby. And one of the things that really stinks about that, as we know that there's so many great and important cofactors and immune things that we can give to our babies through breast milk. But one of the things that we are giving them to is anti seizure medications in our patients who are on anti seizure medications. One of the things that's really important is the baby who is being exposed to anti seizure medicines through their mom, or their parents, human milk has also been growing up in those things. And so there's not a huge increased risk to having them continue to be exposed to them through the very small portions that they would have through human breast milk. But we do know that At some medications, particularly barbiturates and benzodiazepines can actually be slightly concentrated relatively in the middle, and may contribute to things like sedation and for sucking jitteriness. But when breastfeeding is discontinued, patients who were infants who have been exposed to these anti seizure medications continuously through depression, can even suffer withdrawal symptoms, most commonly, Jennifer Richardson, benzodiazepine, far less some of the other anti seizure medications, on the whole benefits of breastfeeding and exposure to their parents not as significantly likely to outweigh the rest of the charter to the anti seizure medicines. So we think that that's actually really important. Some of the really great work that was done across the country has actually identified exactly what how much medication we actually think is going to end up in the baby through breast milk. And of course, if anyone ever has any questions here,

you have our we have a wonderful resource center, lactation resource center that has a ton of information about medications and how they translate into exposures through through breast milk, which is really awesome. So I've just talked with you about pregnancy and kind of that process. But what if our patient doesn't want to be pregnant? One of the things is actually, surprisingly little information about is interactions with medical abortion information and the seizure medications. This year, specifically to the American epilepsy society. Just in December, there was a wonderful presentation about her and Davis and OB GYN who works very closely with her epilepsy division. Who said, basically said she, there is no published data, but here's my experience. And so her experience will show that methyl crystal, which is metabolized by the P 450 system can have its effective levels lowered, and it's particularly those enzyme inducing AEDs things like program is a pain oxcarbazepine just as a reminder, phenobarbital phenytoin, possibly valproic acid, but that the utilized doses are high enough that it has not not had an issue overcoming the effect of those induction on the paperclip D system and the typical doses of medical Castanea and should be effective and all patients with epilepsy. misoprostol is not metabolized by the P 450s. and should not be affected by ASM and vice versa. Those two medications should not affect anyone's anti seizure medications. Procedural abortion can also be incredibly safe. But if there's ever a concern, patients and or the providers or should just contact their neurologist, and the neurology team can help her prepare a patient and reassure everybody because seizure control is unaffected as likely to be unaffected by the procedure itself. And seizures can be managed using the patient's typical rescue plan. And the most common sedation that's utilized during procedural abortion is usually mid Aslan, which is incredibly productive. And so the biggest thing is making sure that patients take their anti seizure medications as they normally would, even if they're otherwise NPO. And making sure that everyone knows what to do in case of a seizure, because that's actually just a safer way for all of our patients to experience any kind of care. Another important concept within our patients is to care for trans patients with epilepsy and another part of epilepsy research where there's still only a small amount of emerging data. So there's one really great paper by Johnson, Kaplan. That examined kind of what is known about transgender care in epilepsy at this point, and there are no large scale epidemiologic studies, really only some case, case descriptions, more than anything else. So there are approximately at the time that this was originally published in 2017. There's a presumption that we're about 15 million people with epilepsy worldwide. Now we know it's about 70 to 75 million of the prevalence of transgender population. And so they did some math and figured out that we're aiming for somewhere between the basically there are a lot of patients who need to have this information available to them and we don't get we know that enzyme inducing anti seizure medications may interact with hormones used for gender affirming treatment. We know that for all patients, estrogen has proconvulsant properties, or can have proconvulsant properties. And so when trans women begin with epilepsy begin treatment with estrogen, they may experience an exacerbation of seizure activity, and that's not an indication to stop gender affirming care, it's an indication to check medication levels and adjust them appropriately. Anti seizure medication adjustment and then endogenous progesterone is known has anti convulsive properties. But interestingly, this is synthetic majority progesterone that we most commonly use for gender affirming treatment, isn't metabolized into the allopregnanolone does not offer the same protection. And so again, trans women may need to have additional support of their anti seizure medications to essentially counteract the effects that their gender affirming care is providing for them.

45:04
We know that enzyme inducing anti seizure medications can increase the level of sex binding globulin and sex hormone binding globulin in the blood and can decrease active free testosterone, which may lead to decreased libido erectile dysfunction, and we know that total serum testosterone levels may be altered. And so importantly, it's important to make sure that patients are aware of this and that we're modulating based off of symptoms and based off seizure frequency. With cessation administration transmitted by ketamine, exacerbations of seizure frequency can experience some improvement in seizure control. So that that's positive, and to Sasha and Andrea, surprisingly, primarily anticonvulsant effect, which is a little bit less studied. Because theoretically, it is metabolized into estrogen, the effects are more mixed. And then there is less well known about other disaster metabolites, but some are believed to potentially be mildly convulsive. So in the last few minutes, I want to talk about the idea of how do we help our patients transition from adult or pediatric forms of epilepsy care into pediatric. She's in pediatric forms of epilepsy care into adult forms of epilepsy care, we want to make sure that this is a structured process that kind of addresses all of the things that are important to the team and to their family as they're making that transition into adulthood. And we know that there are lots of differences between the pediatric versus adult model of care. So patients tend to be passive in the pediatric version, they lack autonomy, they have minimal direct burden of care for most of their patients, they have established long standing relationships with our providers, and all of those things shifted, they move to adult and the adult world and they become the active participant in communication. They theoretically have autonomy to the best of their ability, they're the primary burden of self care, and how do they make those transitions without us helping to teach them. So one of the things that we were really proud of here at Johar is that we've actually worked with our local epilepsy Association Alliance affiliate, excuse me, empowering people's independence, to create programs, such as our teen weekend where we actually teach all of these things, including this sex education information and talk to our patients, to help to get them ready for eventually becoming an adult living with epilepsy. And we also give some a small version of this education to our camp here and camp post kids, as they grew up through their summer camp experience, through EPI, which we're very proud of. We also have a really great program, which is the medical student transition educator program created by Dr. Mary Beth Jones, and led by Dr. Emily Walsh, where we have medical students who have been trained how to teach patients how to make that transition to the adult care model. They actually do zoom meetings with the patients and practice with them, slowly taking more ownership of their the care model, and they're on health care, which has been really awesome experience. And we're very excited about that. And some of the stuff that gets asked a lot about of our transition educators are some of these things about ministration and sex ed, and what happens when you have a family and all of those things. So we try to make sure that everybody gets taught those things. And so again, thank you so much. Happy New Year, a little bit late. And thank you so much for the opportunity to to have this discussion. Please let me know if there are any questions.

48:33
Thanks so much. That was that was really a terrific presentation and highlights how complicated really care can be I think we're quite fortunate to have access to such specialty care. And

hopefully, that's that's sort of generally available, it seems like it would be hard to manage, especially the transition without that kind of access, because pretty complicated pharmacology. There is. There is a question in the q&a of can a person have lasting side effects, personality changes, or alterations in their brain after a seizure?

49:18
So, the answer traditionally is no. Most patients do not except in the situation in which that is so in very prolonged seizures, in seizures that have interrupted blood flow to the brain in some way. So most commonly in Status Epilepticus, or prolonged individual or acute repetitive seizure. That is when we have seen those changes to the majority of patients with epilepsy. seizures, individual seizures don't cause harm. In the sense they don't cause a lasting harm. The biggest thing that they do is they teach the brain how to have a better seizure the next time and that's something that we would like to avoid, but it is pretty unusual for an individual seizure to have Long lasting long permanent differences for a patient. But thinking about it, each individual seizure or seizures in particular situations can be incredibly psycho socially devastating to people as well, right? Is getting a diagnosis of epilepsy changes a person's whole life. And so sometimes when we do see psychosocial changes, or we see behavioral changes in someone, we're actually needing to address a trauma response. And make sure that they know that their brain isn't melting and that they can live with this and that this is a chronic disease that they can live well and healthily with. Because when people don't believe that we actually do see significant enhancement of anxiety, depression and worsening outcomes.

50:44
So, very similar to the approach we take with a new diagnosis of HIV, which carries so much stigma and lifelong impact. Daniela, you want to say your question, if

50:57
you didn't want to call people of childbearing potential who haven't seizure disorder, do you have sort of a go to medication for for them an anti seizure medication? So whenever I

51:14
think, favorite indicator, basically there are two answers to this. So for the majority people the first anti seizure medication that most of humanity now seasons and medication home limiter is Tamar Capra. The reason that that one gets chosen over all others, it doesn't care too much, whether it's focal or generalized seizures. It's mostly pretty standardized dosing, and there's not a whole lot of monitoring associated with it. The blood levels are not as important as efficacy and side effects and the side effects overall are pretty low. So when patients all comers are first diagnosed with epilepsy, most patients start out with Keppra. When we have patients particularly of childbearing potential, who have focal seizures, where we know they're definitely focal seizures, they now have generalized seizures that we know they're very generalized seizures, but they're actually relatively spread out seizures, they're more likely to get started on Lamotrigine. Lamotrigine is the medication that has been found to have the lowest Terada, just Terada genericity. And we know the most about its metabolism. But when someone becomes pregnant, it is also one of those that is the most highly affected by pregnancy. And patients at the end of their pregnancy may end up on as much as six times as much medication at the end

of their pregnancy as they're on at the beginning of their pregnancy or prior to pregnancy. And as soon as that baby is delivered, within about three days, their metabolism flips back to where it was pre pregnancy, and everybody needs to be on top of very rapidly adjusting those anti seizure medications. So very rapidly adjusting them during the pregnancy itself and after the pregnancy so that people are not sick and miserable in either direction. So is having pregnant patients with epilepsy is an exciting adventure and lots of lab draws for everybody involved, and requires kind of lots of communication and lots of interaction to make sure that we're safe.

53:20
I do have one more question. You had mentioned, you know, some of the transition the navigator program that you have, but are there resources for adolescents or young people who are not in your programs, that maybe they can talk to their partners about epilepsy, just kind of sharing some information with others around them, who might be able to help them if they have a seizure or just kind of sharing, you know what it is and this.

53:52
So, the research is that I actually share with my own patients, our epilepsy.com, which is a creation of the Epilepsy Foundation of America and epilepsy therapy project. It actually is a really great just general clearing house and there is a learn function on the epilepsy.com website. And in there's a section called epilepsy one on one and while there isn't necessarily a specific component for here's what to share with your partner. There actually is just here's information about epilepsy and how epilepsy works and how it affects someone. There is also a very great resource called Young epilepsy, which is a group in the UK. And it's actually for teens by teams with epilepsy. And there's some good discussion there about how to address or how to interact with your partner about your epilepsy and how to help them to understand what's happening when someone has a seizure. And those two resources and also just making sure that we teach our patients about themselves. In my experience The better that I can teach my patients to know themselves and to be comfortable talking about their own epilepsy, the better their relationships are going to go to the point that I feel incredibly successful when my patient brings their significant other with them to clinic, so that they can ask questions and that and as long as we have permission, I'm always happy to do that.

55:25
A couple more minutes, and I had two more questions if nothing else comes in. One is in the early early slides about sort of all the factors that can contribute to the development of epilepsy and genetics was one of those. So if you have a patient who is undergoing a gender transition with clearly if they have a history of epilepsy, epilepsy, it sounds like that would involve a referral to it to a specialist about epilepsy to help manage the, the hormones. But if you had a family history of seizure disorder, would that be enough? Like, like, what how prominent is the genetic component? I guess.

56:11
So the genetics and policy are actually incredibly complicated. And almost all of the known genetic syndromes have very variable penetrance. So even when we absolutely know that someone within a family carries exactly the same genetic difference, there is no guarantee that

they are going to experience a seizure. And so there's no prophylaxis that needs to be made for someone who has never experienced a seizure before just to throw increasing complexity into that there are people who will have an incredibly abnormal EEG, when they are just screened for EEG for some other reason, but also may never have a seizure. Because you can have an abnormal EEG and still not have to use. And so it really is, if someone has, for instance, they've never had a seizure before. And they get started on an estrogenic compound, because they're going to make that transition. And now seizures are occurring, they most likely are someone who had a predisposition to epilepsy that now that pro, you know, something that lowers the anti seizure threshold, or the seizure threshold is now unmasking. We're not going to tell them that they need to stop taking their gender affirming hormone, we're going to tell them now you need to go on an anti seizure medicine because this has been unmasked.

57:29
And then one last question I was, I was sort of surprised when you ran through kind of the risks of the gift bag that you refer to. And they're all things that we see with other conditions as well, that are often associated with substance use or alcohol use as a sort of self medication or associated condition that can correlate with rising rates of STIs, for instance, and I'm I was surprised that that was an on there is that is that also in association.

58:02
So raising rates of STI

58:06
and substance use or alcohol use.

58:10
Yes, so substance abuse is higher, not well studied in the pediatric epilepsy population. So pediatric epilepsy that has been treated by neurology epilepsy ology, those kids actually have a lower risk because we're continuously telling them don't miss mix stuff with your anti seizure medicine. And they have a very high likelihood of having higher supervision rates. But there is data on the adult side that patients adult onset epilepsy patients or patients that are now late in their transition to the adult side of neurology, they do have a higher risk of substance abuse and alcohol abuse. And so I'd like to believe that you know, really good support and making sure that we're treating their ADHD and making sure that we're treating their psychosocial distress, that those things help to lower our patient's risk as they transition to adulthood. But we don't yet have the data to help us support that idea.

59:08
All right, well, it looks like we're

59:11
just exactly at time. So thank you so much for a really, really informative presentation.

[End Transcript]