This is a discussion about drugs to treat epilepsy. The big categories of how we treat epilepsy are with medicines, surgery, ketogenic diet, neurostimulation (such as the vagus nerve stimulation), biofeedback, and alternative therapies. They are all potential options, but by far the mainstay of treatment and the most used therapy is with anti-seizure medications. That will be the focus on what I talk about today.

How well do anti-seizure medicines work? In general, about two-thirds of people who take anti-seizure medicines have their seizures controlled – meaning they have no seizures or very rare breakthrough seizures under unusual circumstances. And then one-third take medicine, but their seizures are uncontrolled either because of continued seizures or inability to take medications due to side-effects. That’s still a pretty large group of people, considering that 1% of the world has epilepsy. One-third of 1% is a number larger than all brain tumors, larger than all multiple sclerosis, larger than all muscular dystrophy. Epilepsy is not yet a solved problem.

We have many anti-seizure drugs. Typically, you’ll hear them called AEDs – anti-epileptic drugs. But that’s a misnomer. None of these drugs cure epilepsy, so they’re not really anti-epilepsy drugs, they are seizure suppressant drugs. When you stop the medication, the epilepsy, which is the tendency to have recurrent seizures, remains. There is a movement to call these medicines ASDs, anti-seizure drugs, rather than anti-epileptic drugs.
This slide shows a timeline of anti-seizure medicines that have been brought to market since bromides were introduced in 1850. Bromides have a lot of side effects and we now use them infrequently. Phenobarbital, the first modern anti-seizure medicine, was introduced as a long acting sleeping pill in 1912. Then, Dilantin came in as the first scientifically developed medicine in 1938. For decades, Dilantin and phenobarbital – sometimes in combination – were the medicines most used to treat epilepsy. Now, we have many others. I won’t go through them in detail. In the 1990s, came in Felbatol, which is not much used since it is a fairly toxic drug. But Neurontin, Lamictal, Topamax, and Zonegram will be familiar to many of you. In the 2000s, Keppra, Trileptal, and Lyrica came into use. In the past few years – Onfi, Aiptom, Potiga, Vimpal, Fycompa, Banzel, and Sabril, have come into play. There’s a long list of drugs on the potential launching pad, which doesn’t mean that all of them will come to market. Most interesting to me is brivaracetam, brand name Briviact®. This is the daughter of Keppra; about 10 times as potent and it binds at the same receptor site on the nerve cell. It may have a lower incidence of psychiatric side effects, which is sometimes a problem with Keppra. Brivaracetam was just approved by the FDA.

In the US, we have 28 ASDs from which to choose.

| Carbamazepine (Tegretol, Carbatrol) | Levetiracetam (Keppra) |
| Clobazam (Onfi) | Lorazepam (Ativan) |
| Clonazepam (Klonopin) | Oxcarbazepine (Trileptal) |
| Clorazepate (Tranxene) | Perampanel (Fycompa) |
| Diazepam (Valium) | Phenobarbital (Luminal) |
| Etilcarbazepine (Aptiom) | Phenytoin (Dilantin) |
| Ethotoin (Peganone) | Pregabalin (Lyrica) |
| Ethosuximide (Zarontin) | Primidone (Mysoline) |
| Eizogabine (Potiga) | Rufinamide (Banzel) |
| Felbamate (Felbatol) | Tiagabine (Gabitril) |
| Gabapentin (Neurontin) | Topiramat (Topamax) |
| Lacosamide (Vimpat) | Valproic Acid (Depakote) |
| Lorazepam (Ativan) | Vigabatrin (Sabril) |
| Lamotrigine (Lamictal) | Zonisamide (Zonegran) |

In the US we have 28 anti-seizure drugs from which to choose. I’ve highlighted in red the medicines that are most commonly used. Every medicine has a generic name and at least one brand name. Carbamazepine (Tegretol), clobazam (Onfi), clonazepam (Klonopin), gabapentin (Neurontin), lacosamide (Vimpat), lamotrigine (Lamictal), levetiracetam (Keppra), lorazepam (Ativan), phenobarbital (Luminal), phenytoin (Dilantin), topiramate (Topamax), and valproic acid (Depakote). These are the main players, but sometimes we will use the other drugs on this list. Research studies show that your seizures will declare themselves fairly early as being responsive to medications or not. This means that we don’t have to go through all 28 of these drugs to know whether or not drugs are going to work. If you are not seizure-free on your first or second drug, unfortunately you’re probably in that one-third that is not going to be completely controlled by medications.

We choose the best medicine by a combination of factors: it works for the seizure type, effective, few side effects, very few dangerous side effects, convenient, experience, inexpensive.

First we want to pick a drug that works for the type of seizures that you have. For example, you may have absence seizures, which used to be called petit mal seizures, with staring spells. Ethosuximide (Zarontin) works against absence seizures, but hardly against any of the other seizure types. You may have focal seizures with or without loss of awareness, or tonic-clonic seizures, which used to be called
grand mal seizures. Many of the drugs that work against those types of seizures. We want the drug to be effective, with few side effects and very few dangerous side effects – ones that can hurt you or be fatal. We want it to be convenient, for example, not a drug that you have to take four times a day. We want to have a lot of experience using the medicine. Ideally, we would like the medicine to be inexpensive. What drug meets all of these characteristics? The answer is none of them. We don’t yet have the perfect seizure medication, which is why we have 28 from which to choose. If we had the perfect medicine that worked for everything – few side effects, convenient, safe, inexpensive, then we wouldn’t have 28 drugs, but only that one.

Here is a list for which ASDs work for the different seizure types

- Partial (focal) and secondarily generalized seizures: most work, except for Zarontin.
- Absence (petit mal): Zarontin, Depakote, Lamictal, Topamax, Klonopin
- Atonic (drop), tonic (stiff), myoclonic (brief jerks): Depakote, Lamictal, Topamax, Zonegran, Banzel, Klonopin.

Next is the problems of side effects. The slide shows results from a mail survey of about 2000 people done in conjunction with the Epilepsy Foundation several years ago. Thinking and concentration problems collectively were the main side effects that people wanted to avoid in a drug.

Some people are bothered by weight changes. Drugs that can cause weight gain include Depakote, Tegretol, Trileptal, Neurontin, Lyrica, Fycompa. Drugs that commonly lead to weight loss are Topamax,
Zonegran and Felbatol. Other drugs weight neutral, but there are individual variations. These are statistical statements.

**Possible dangerous possible side effects**

- Stevens-Johnson (blistering) rash: Lamictal, Dilantin, Tegretol
- Kidney stones: Topamax, Zonegran, Diamox
- Depression, suicide: phenobarbital, Mysoline, Keppra
- Osteoporosis (fragile bones): Dilantin, phenobarbital, Tegretol, Depakote
- Metabolic syndrome (weight gain, high cholesterol): Depakote, Tegretol, Neurontin

Potentially dangerous side effects – things that we really don’t want to see happen with the drugs – include a really bad rash called Stevens-Johnson, where you have blistering or you have a rash on the mucous membrane. This is almost like having a burn from a rash. It is different from the more common itchy rash that’s annoying but less serious. The drugs that tend to cause the Stevens-Johnson rash are Lamictal, Dilantin, and Tegretol. Topamax, Zonegran, and Diamox can cause kidney stones in about 1%. Some of the drugs make people irritable and depressed, particularly phenobarbital, Mysoline, and Keppra. Some drugs cause osteoporosis: Dilantin, phenobarbital, Tegretol, and Depakote. Some cause metabolic syndrome, which is manifest as weight gain and elevated cholesterol levels: Depakote, Tegretol, and Neurontin.

Birth defects are another serious side effect that we worry about in women of child bearing years. Low risk drugs for this are Lamictal, Keppra, and Neurontin, even though they do still cause a slight increase from a baseline of 1-2% to 2-4% risk of birth defects when mothers are taking those drugs. Depakote and phenobarbital may be associated with up to a 10% risk drugs that may include as much as a 10% risk for birth defects – the technical term is “teratogenesis.” We use those in potential pregnancies only when it is clear that there is no alternative.

We come now to convenience; how easy it for you to take your medicines? A single daily dose is a lot easier to remember than 3 or 4 times per day. Dilantin, phenobarbital, Fycompa and extended release forms of many drugs can be taken once a day. Neurontin, Lyrica and Keppra do not have drug interactions, so they don’t throw blood levels of the other drugs out of the desired range. Dilantin and Keppra can be initiated quickly, but Lamictal and Topamax cannot because of side effects when started too fast. For those who are in a hospitalized situation, intravenous forms are available for Dilantin, phenobarbital, Depakote, Keppra, Vimpat, Ativan, Valium.

Last, but not least, is the cost of the medications. Some medicines are inexpensive – carbamazepine, phenytoin, phenobarbital, gabapentin, lamotrigine. These are all generic drugs – the exclusive patent has expired and there is competition. New drugs, not yet off patent, can be very expensive, sometimes over $1000 per month. You should let your doctor know if you are hit with a huge pharmacy bill because sometimes we make the assumption that your insurance is going to cover these drugs, when it doesn’t. Sometimes even the co-pay is not manageable.
Let me give you three instances of how doctors and how patients think about problems that occur on drugs and consider alternatives. These are hypothetical cases.

CASE 1:

Jane is 21 and has epilepsy with morning jerks, myoclonus of her arms and tonic-clonic seizures every few months. Her seizures are completely controlled by Depakote. That’s the good news. The bad news is that she has side effects of tremor, thinning hair, weight gain, upset digestion. She wants to have children and she’s worried about the higher birth defect risks associated with Depakote. What are her options? This is what I would consider if you came to see me in clinic with this kind of problem. We could switch to Lamictal, which doesn’t have those side effects. We would have to watch for rash. We might switch to Keppra, watching for moodiness, depression, irritability. We might switch to Topamax or Zonegran, but their main side effect is thinking or memory impairment and the 1% risk of kidney stones. Or we could switch to a benzodiazepine, such as Klonopin or Onfi, but then we would have to watch for sleepiness. That would be a discussion I would have in clinic. All options have positive and negative aspects, but different side effects will matter more or less to different people.

CASE 2:

Jack is 30. He has complex partial seizures, with déjà vu, a familiar feeling, loss of awareness, aimless wandering. These occur weekly. He takes Tegretol about 3 times a day. Side effects are not a problem, but he continues to have seizures. What are some options? We might change the Tegretol to twice a day because maybe Jack is forgetting that middle dose. A lot of people do. We might increase the Tegretol dose, watching that we don’t produce side effects. We might check blood levels to verify a therapeutic level in the blood. We might add another seizure medicine on top of the Tegretol. If that medicine works well, then we might taper the Tegretol and see if the new medicine can do the job in mono-therapy. Or we might decide to go in a completely different direction and try vagus nerve stimulation or epilepsy surgery if Jack is a suitable candidate for surgery. That will be a subject for another talk.

CASE 3:

George is 40 and has about 3 seizures a year with left face and arm twitching. Most seizures are in the morning. Sometimes, this progresses to a full-body tonic-clonic seizure with loss of awareness. He takes Dilantin, Keppra, and Topamax, producing many side effects: dizzy, unsteady, tired, poor memory. What are some options? We could move more of his medicine dose to the evening, so that the blood levels will be higher in the morning to prevent seizures at that time. It won’t matter if he’s tired in the evening because he will probably be asleep. We could check the serum drug levels to see if any medicines are below therapeutic – so they should be increased – or in the toxic range – so they should be decreased. We could streamline the medication schedule, for example, taper Topamax to make his memory better or eliminate Dilantin to improve balance. Sometimes streamlining to one drug makes seizures and side effects better than poly-pharmacy.

We have discussed three examples about how doctors think about options in changing medications when there are problems with seizures or side effects.
Robin: A few questions came up during the presentation. If other people would like to answer or comment, send your input into the chat section.

Speaker 1: I myself have an anxiety disorder. My daughter and my ex-husband both have epilepsy with grand mal seizures. Many of the drugs I have been prescribed, for example Depakote or Klonopin, are the same that my daughter is on. These are used for anxiety disorders and bipolar disorders. How can the same drug work for anxiety, depression and epilepsy?

RF: Many of the epilepsy drugs work by causing the brain cells to fire more slowly. This can be helpful in conditions other than seizures that involve excessive firing in certain brain circuits. Lamictal (lamotrigine), for example, started as an epilepsy drug, but is more now being prescribed by psychiatrists for mood stabilization. Depakote is also a mood stabilizer. Neurontin (gabapentin) started as an epilepsy drug, but now is being prescribed for shooting pains where there is rapid firing of nerve cells in the peripheral nervous system. The benzodiazepines, such as clonazepam, Valium, Ativan are used for both seizures and anxiety. In your case, it makes sense that you take a drug for anxiety and mood issues and your family members take them for epilepsy.

Speaker 1: If I have had side effects on a drug should I let doctors know if they are planning to prescribe that drug for my child?

RF: If a genetically-related family member has a certain side effect from a medicine, then it’s worth letting the doctor know because there may be a tendency for another family member to have that side effect. I won’t go so far as to say whether or not you or she should be on that medicine. I’m going to work hard in these webinars not to give individual medical advice, but just to talk in general.

Speaker 2: My daughter is in eighth grade and she’s had her seizures since grade school, but they weren’t detected. She has a very difficult time focusing and she really needs one-on-one. The schools do not understand that her epilepsy probably has a lot to do with her learning disabilities. It has been such a struggle and a fight – so much so that we home-schooled her for 2 years. You teach her something and then she has a seizure and that information is lost. Now she’s going to high school and we don’t know how to educate the new school on how to help our daughter.

Robin: I’m going to introduce Speaker 3 – she’s a teacher.

Speaker 3: My son is 9 and he has complex partial seizure disorder from the frontal lobe. He’s tried nine medicines and we’ve never been able to get complete control. He’s currently on four meds a day. We were up to two seizures a day for about a week. We then started the ketogenic diet a week and a half ago and he has now gone without a seizure for 5 days for the first time in a year and a half. I’m a teacher and I work in special education. It’s really important that you get the IEP (Individualized Education Plan) – it has to be written in the IEP in order for it to be legally binding for the school to follow. It’s important that the issues she’s having academically that are directly correlated to her condition are noted in her IEP.

RF: Can you please explain what an IEP is?

Speaker 3: An IEP is an Individualized Education Plan. You must qualify with a special need according to the disabilities law in the Educational Act. You have to go through the testing process in order to qualify. Epilepsy is a qualifying medical condition even if there are no other symptoms effecting education. And
that falls under a medical condition that can affect education. Everyone with epilepsy can get an IEP whether or not they are having current symptoms. So I recommend every parent with a child with epilepsy get an IEP, so that the doors open if you need it in the future. If you request testing and writing. Legally within 50 days, the school has to have an IEP meeting with you to most effectively assist your child. For my family, I’m an unusually capable advocate because I’m also a special education teacher. I have the neurologist involved before every IEP meeting. I get detailed letters from her that I actually write with her over the phone. We compose the letters together stating all the issues, all of the side effects, all of the concerns, and realistic expectations of the child and then we have those put into the IEP document, so that they have to be legally binding. So I recommend having your neurologist involved in the process.

Robin: We have a question. What’s a good drug for occipital neuralgia? The pain is getting very severe.

Speaker 4: I’ve been having migraines for 30 years. I also have epilepsy and I’m on a few medications. I’ve recently have some nerve block injections that don’t seem to be helping. Any thoughts about drugs good for migraines or occipital neuralgia and seizures?

RF: It’s a medical question, so I’ll answer briefly and others can chime in. The seizure medications that are used for nerve pains are Neurontin, which is gabapentin, Lyrica, which is pregabalin, Tegretol, which is carbamazepine, and the Tegretol-like drugs, Trileptal and Aptiom. These medicines may be effective in shooting nerve pains, but they don’t always work. There are a few others that you would have to hear about from your doctor. In addition to injections, there are also local nerve stimulators.

Speaker 4: Is that often the case with people who have epilepsy?

RF: Epilepsy can be associated with migraine headaches, especially after seizures. Occipital neuralgia is less common and an association with epilepsy is not clear.

Robin: Speaker 5, you wanted to talk about surgery and the effects of it. Apparently, it did not have much of an effect. She wants to know how often epilepsy surgery is unsuccesful.

RF: I promise you a whole session on epilepsy surgery in the future. The odds of success depend on the type of operation you have. Success rates vary with a partial temporal lobectomy or a focal removal of a seizure region around an abnormal blood vessel or brain scar. For the most common operation, which is partial temporal lobectomy for complex partial seizures, the cure rate is about 50-65%. The benefit rate is about 75%, meaning that people may not be totally cured, but seizures are much better.

Robin: Several people have been having an ongoing conversation about CBD.

RF: I didn’t talk about any experimental drugs or any drugs in development. Cannabidiol (CBD) is one of those. CBD is a component of marijuana, but one that doesn’t get you high. It’s from the hemp part of the plant. The GW Pharmaceuticals Epidiolex trial, run by Dr. Orrin Devinsky in NY just gave its preliminary results from a double-blind study. CBD was given in a dose of 20 mg/kg/day. The results were 39% average improvement in seizures, which is statistically better than placebo response at 13% improvement. CBD was well-tolerated and safe. The most common side effects were sleepiness, nausea, vomiting, diarrhea and decreased appetite. The optimistic view is that CBD is a useful drug and it may have a chance of coming to market, though that may be difficult with the legal issues associated with bringing a marijuana ingredient to market. The pessimistic view is that an average 39% improvement is
similar to what you get with any of the new epilepsy drugs and far from a miracle. CBD may be better for certain rare genetic forms of epilepsy, such as Dravet’s syndrome, which was what the young girl who started this on the CNN special had.

Speaker 1: I’ve been checking into the CBD possibilities for my daughter as well. She’s 33 now. She started having seizures when she was 16. They’ve never been controlled. And she does use medical marijuana, although the CBD type is hard to find. You can purchase them at a dispensary or online if you have a prescription already. And you can grow your own if it’s hard. It is expensive at the dispensary if it’s pure CBD. It costs more than any of the other types. Because it’s still controversial, the best way to go might be to grow your own plant or two and try it. Right now there aren’t any “neurologists” that are going to prescribe it for you, unless I’m mistaken. Not in California anyway.

RF: That’s probably true. I’m not prescribing it until it’s legal, which I hope with the upcoming 2016 initiative will be by the end of next year. A lot of people contact the website http://cwbotanicals.com/all-charlottes-web-products – in Colorado.

Robin: A question asks if genetic testing is useful to select the best anti-epilepsy drug. She mentions that gene site is used in the selection of some antidepressant, pain and hyperactivity medications.

Speaker 7: Is genetic testing to see what medications are maybe the best match in the works? My daughter was suicidal on Keppra, and it would have been useful to predict this in advance.

RF: We wish we could do this better in the epilepsy world. It’s a huge area of research and interest, called “personalized medicine,” or “precision medicine.” One size doesn’t fit all. We have a few hints in possible personalized epilepsy therapy. For example, we mentioned CBD to be useful in Dravet’s Syndrome. There’s a genetic test for Dravet, so that might point to CBD. You can do genetic tests to predict certain side effects of medications. There’s a genetic test to see whether you’re likely to get Stevens-Johnsons syndrome from carbamazepine or from phenytoin. And there’s a genetic test called MDR – multiple drug resistance gene – that tells you whether you have a gene to clear drugs very quickly out of your system and so ordinary seizure medicines probably will not be very effective. These are tantalizing hints. We hope to have much more to say about genes allowing personalized medicine for epilepsy treatment in the future.

Speaker 8: What is the genetic test for the Stevens-Johnsons Syndrome? Because a medication that we’re looking to try for my daughter is Lamictal, but I hear there is a risk with that.

RF: It’s a blood test for the histocompatibility antigen called HLA B*1502. The test is of particular use for people of Asian descent taking carbamazepine (Tegretol), since the gene is most prevalent in Asians. Lamictal can cause a rash or even Steven’s-Johnson but it is not predicted for Lamictal by HLA B*1502.

Speaker 9: A lot of people have been asking about VNS. I’ve had it for about 2 years. My seizures were getting so bad and I was out of it for quite some time. People have been asking if I drove and I don’t drive. I’m still not completely seizure-free. When I do have seizures I am able to get back up; whereas, before I would be on the floor, paramedics would come... Now it’s like the VNS has really changed my seizures. IT has helped tremendously, but it took some time. I’m hoping to get off some of my meds some.
Robin: I think what I’m hearing is you were uncertain about it in the beginning, but now you feel like gradually it is making an improvement.

Speaker 9: The VNS has not helped my daughter and she has had the device for 7 years. I read online that some people have good luck with it and some people done.

Robin: I’d like to go to one last question. Are there any genetic tests to see if you have genes that are known to cause epilepsy?

RF: I see Dr. Susanna Cornes on the call. UCSF is one of the world centers for epilepsy and genes.

SC: Some of you may know, Dan Lowenstein is now Vice Chancellor and Provost of our Epilepsy Division, who has been very interested in the development of precision medicine for the development of epilepsy and genetic testing. I think over the course of our lifetimes we will be making a lot of progress in this area. Right now we have an ongoing study that one of the big epilepsy study groups is promoting and funding and that will enroll folks that are having whole exome testing in order to then enable them to be entered into a database, so that as we learn more about genetic testing over the course of the upcoming decades, we’ll have this database to refer back to and screen in order to identify more and more genes over time. Right now the role for genetic testing is minimal in folks that are developmentally normal and functioning. Unless there is a strong family history, we don’t often go on fishing expedition for high-risk genes. For individuals that have epileptic encephalopathy (confusion), it can be useful and there’s a pretty high hit rate for genes. It might be worth speaking with your doctor to see if it would be useful for you potentially, but it’s more of a future question. Also, I think cost for testing is prohibitive for a lot of people. As insurance companies get more on board as we develop the role for genetic testing for the treatment decisions for our patients and to get people on board to pay for testing, it will probably develop as more of an outlet for our patients. Right now it’s pretty prohibitive for our patients with MediCal and private insurance that does not cover genetic testing.

Speaker 9: I’m not so much worried about cost. I only have one daughter. Telling you that your children will have a 50/50 chance of having epilepsy it not itself helpful. There must be some way to tell if you’re going to pass it on.

SC: Autosomal inheritance patterns are very rare in epilepsy. You have a 50% chance. That would be surprising. It wouldn’t be appropriate for me to comment directly not having more information. If you feel like you have additional questions, it would be worth it to bring up to your doctor. It would be difficult to answer your question without a positive test of some kind.

Robin: Thank you all for fantastic participation and discussion. We’re going to wrap it up now.

RF: I’m very pleased that you all showed up. We’re going to do this once a month. It will always be Saturday at 11:00 am, usually the second Saturday of the month. The upcoming schedule and links are:

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We’ll welcome all of you back for future programs. Please spread the word for those in Northern California with epilepsy or with a family member with epilepsy. Many can’t drive and this virtual meeting is one way to reach out, provide information, and bring people together to share experiences with each other. We can have up to 100 on each call and we can always do more than one broadcast if there is demand. You are in the charter group of a new way to provide education. Robin, the Epilepsy Foundation of Northern California and I appreciate your participation in this first round.