Transcript Details
This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/new-and-emerging-therapies-for-complex-epileptic-syndromes/15345/

Released: 06/30/2023
Valid until: 06/30/2024
Time needed to complete: 45 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New and Emerging Therapies for Complex Epileptic Syndromes

Announcer Intro:

Welcome to CME on ReachMD. This activity entitled New and Emerging Therapies for Complex Epileptic Syndromes is jointly provided by Medical Education Resources, and Novus Medical Education, and is supported by an independent educational grant from Takeda Pharmaceutical Company. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Sullivan:

Hello, and welcome to this webcast entitled New and Emerging Therapies for Complex Epileptic Syndromes. I'm Joseph Sullivan, Professor of Neurology and Pediatrics at the University of California, San Francisco, and I'm joined today by my colleague, Dr. Elaine Wirrell. Uh, Elaine, would you like to introduce yourself?

Dr. Wirrell:

Sure, I'm Elaine Wirrell. I'm a Pediatric Epileptologist and Professor of Neurology at Mayo Clinic in Rochester, Minnesota.

Dr. Sullivan:

Thanks for joining us today. Uh, in this webcast, we're going to look at the new and emerging pharmacotherapies for treating patients with developmental and epileptic encephalopathies, such as Dravet and Lennox-Gastaut syndromes. Before we get started, let's quickly review our learning objectives.

Dr. Wirrell:

So upon conclusion of this educational activity, participants should be able to define the terminology and prevalence of infantile and childhood onset developmental and epileptic encephalopathy syndromes, to identify the current treatment strategies for managing patients with both Lennox-Gastaut and Dravet syndrome and some of the challenges that are associated with those, and to summarize the efficacy and safety profiles of newer pharmacotherapies for the management of patients with both Lennox-Gastaut and Dravet.

So when we talk about the developmental and epileptic encephalopathies, um, these are – are, um, early onset, very severe epilepsies, actually relatively common, the incidence is about 1 in 590 children prior to the age of 16. And these have very challenging seizures, very, uh, abnormal EEGs and very significant comorbidities, including intellectual disability, behavior, Autism, things like that. And most of these have both of what we call a developmental encephalopathy, which is the degree of encephalopathy that is due to the underlying cause, like a diffuse structural brain abnormality or a monogenic condition, as well as epileptic encephalopathy. And that's en - encephalopathy that's really, um, due to the very frequent seizures and epileptiform discharge.

And so we can see here on the graph, um, what we mean by these terms. So, um, you can see on the, uh, y-axis there's - there's development, and then age is on the x-axis. And we see a normal developing child in black, where, um, that child continues to gain new skills. And a child who has a developmental encephalopathy, we can see really from the get-go, that child's development is – is different, they gain skills at a lower pace. And if it's just a pure developmental encephalopathy, even when the seizure starts, which is

shown by the hatched line, that child continues to develop. Conversely, if a child has an epileptic encephalopathy alone, the child's development is normal until the epilepsy starts. But once that epilepsy starts and there's frequent seizures, we see a plateauing of development. And in reality, most of these children have a combination of the two. So they have both a developmental and an epileptic encephalopathy. So we see that their development is slow even before epilepsy begins. But once epilepsy begins, there's even a further plateauing of their development.

And when we look at the different, um, syndromes that we see in neonates and infants and in children associated with the DEEs, you can see here, um, the early infantile DEE that used to be called Ohtahara syndrome, or early myoclonic encephalopathy, it's now called early onset DEE. Epilepsy of infancy with migrating focal seizures, infantile epileptic spasms syndrome, which is probably the commonest one that we see in – in infants. And then the one we're going to focus on today is Dravet syndrome. And when we look at childhood, there's also a number of syndromes, epilepsy with myoclonic atonic seizures, often, um, initially, um, uh, mischaracterized as Lennox-Gastaut, and then there's Lennox-Gastaut syndrome, which we're going to focus. Um, DEE with slight wave activation in sleep, uh, febrile infection-related epilepsy syndrome, hemiconvulsion-hemiplegic-epilepsy syndrome pretty rare, Rasmussen, and then some of the progressive myoclonus epilepsies.

So Joe, do you want to tell us about, um, a little bit the evolution of Dravet syndrome over time?

Dr. Sullivan:

Yeah, absolutely. I mean, I really like this idea of a developmental and epileptic encephalopathy. Right? It's – uh, it's a broad category of disorders. But in this world of - of genetic testing, I think we're able to be, uh, much more precise, um, as you showed in that - in that - that last list.

But something, um, we're going to go into a bit more detail today, uh, is, uh, Dravet syndrome. And this is a condition that I know is both – uh, is near and dear to both of us, um, in the sense that we have really - really come a long way, um, really first and foremost with making an early - an early diagnosis. And I think that, uh - that has really been driven, um, by two, um, big movements. One is the movement of genetic testing. Uh, obviously with the other is just I think improved awareness among, uh, clinicians and our colleagues, where no longer is Dravet syndrome considered one of these ultra rare esoteric, uh, diagnoses. And now it's very, uh, liberating to see when I go to conferences and things and we – and we talk to young residents, and it just seems like Dravet syndrome kind of rolls off the - off their tongue.

Um, but I still think there's a way to go. We still, um, you know, these children, as you showed in that slide, they start out, uh, neurologically normal, um, for the most part and – and come in with their first-time, uh, seizure, and often in the setting of fever, uh, and are still even today, I think, given a diagnosis, uh, of febrile seizure, though, um, I think there are some - some red flags, um, that exist in patients even at that time where someone should start to be thinking, 'I wonder if this is the first seizure that's presenting in someone, um, with Dravet syndrome. And while in - someone may not be able to give that, uh, diagnosis with the first seizure, if you have it on your radar screen and know what to anticipate what could be coming over time, I think that's where understanding the evolution will allow someone to – to arrive, um, uh, at that diagnosis.

And so, then they come in with their second, sometimes they – their third seizure, that seizure may not be associated with fever, it may be a focal seizure, where, uh, the first seizure was the left side of the body, the second time it was the right side of the body. Now, uh, in my opinion, these are where the – the – the bells and whistles would be going off, and someone should really be thinking, 'Okay, I think this might be a child presenting with Dravet syndrome,' and – and move on to genetic testing.

I want to stress, however, that genetic testing, while it's I think aiding, um, our ability to, uh, be more certain about that diagnosis, may be early in the evolution, there still are going to be some patients that – that come back and don't have a pathogenic variant in the SCN1A gene; however, if they fit this evolution, so with this presentation, evolving seizure types over time, one should not be afraid of – of making a diagnosis of Dravet, because I think, as we're going to show, uh, in this – this webinar, um, it's really important to have a precise diagnosis, not only so we can counsel families, um, but also so we can, um, figure out how to treat them in the most precise and effective way, uh, uh, possible.

And then I think it's important to – to note that, although this is a rare and – and catastrophic epilepsy syndrome, um, and these patients do have an increased risk of – of SUDEP, which is, uh, maybe even as high as 15%, uh, of children, um, uh, by their early 20s, the majority of these children do live and become young adults. And so I think our next, um, uh, real task is to try and identify all those young and middle-aged adults that are sitting in adult epilepsy practices, probably not with the Dravet syndrome diagnosis in hand, because, um, they often don't have the luxury of having the parent and caregiver give the story, um, that can, um, explain the evolution of the syndrome that makes us now suspect – uh, suspect that diagnosis.

And so I think, to any of the adult neurologists that are – are watching out there, uh, understanding this evolution and getting as much

information about that early childhood presentation could really, really help, uh, you arrive, uh, at a more accurate diagnosis of some of those patients that are sitting in our clinic.

So we also talked about - we're going to talk a little bit about Lennox-Gastaut syndrome, and in – in the last 5 years, largely driven by clinical trials, it almost seems like these are lumped into sort of the same, we're going to do a trial in Dravet syndrome, we're going to do a trial in Lennox-Gastaut syndrome. Yeah, I think we would agree they're very different syndromes. And I wonder if you could actually go over that a little bit?

Dr. Wirrell:

Sure. So I think where Dravet a syndrome, I think it's often reasonably easy to make an early diagnosis. The presentation is pretty clear with those prolonged often hemiconvulsive seizures, um, after vaccination, particularly or with – with fever. And then we also have, um, in most kids the ability to really find that SCN1A variant. Right? so we've got a – a nice genetic test.

I think it's more challenging to make an early accurate diagnosis of Lennox-Gastaut. So most of those kids, if you, um, look at how they initially present, present with different types of seizures. Right? There's a – a group, quite a number actually, that present with infantile spasms, or have some other early onset epilepsy, could be even, you know, focal or multifocal epilepsy. And then it really takes time for them to evolve. And, um, there was that nice study that Anne Berg did looking at her Connecticut cohort, and really found that it took probably close to 2 years on average for a child to develop all of the clinical criteria. So we could say very definitively, you know, yes, this is - this is Lennox-Gastaut syndrome. So I think, um, in Lennox-Gastaut, we really are looking very much at the clinical presentation, the clinical criteria, and recognize that those seizures evolve. So it's - it's really important to, when you're seeing those kids, you know, ask about how those seizures are changing, um, and recognize when they're changing.

Um, the – the – I think the main seizure type that we see in – in Lennox-Gastaut were tonic seizures. Tonic seizures are, as you know, generalized stiffening of the body, um, and we are often see those at nighttime and they can be pretty subtle and sometimes families don't recognize them. And so it's not until you actually bring them in and do that overnight EEG, then you actually see those tonic seizures. And then in addition, they have, you know, many other seizure types as you know, um, atonic seizures, myoclonic seizures, atypical, absences, generalized tonic-clonic. Um, so lots of different - different types of seizures, and many of them also, you know, bouts of nonconvulsive status epilepticus, which are really problematic.

And then, um, you know, as we see these kids evolve, what we often see is the EEG is evolving more from a hypsarrhythmia or a very abnormal pattern into more of a slow spike-wave pattern. And then at nighttime, particularly with those - those tonic seizures, the generalized paroxysmal fast activity.

So it really is one of a much more slow evolution than, um – than Dravet syndrome. And because we don't have, you know, a clear gene to look for, a clear cause that we can look for, we know Lennox-Gastaut really is multiple different causes that – that can lead to that. It's a tougher diagnosis to make early on.

And I think it's also challenging is that people get older as well. So you know, in – in childhood, we often see those recurrent drop seizures and the slow spike-wave, as, um, you know, you get into your adolescent, your - or your young adult years, oftentimes, that slow swipe – spike – ah – the slow spike-wave pattern goes away. And, um, uh, we see, um, uh, other seizure types, predominantly focal seizures. And so sometimes it's actually less clear, that if you've not had that diagnosis early, that really what you have is Lennox-Gastaut syndrome.

Dr. Sullivan:

And to bring it back full circle, um, maybe you would agree that some patients with Dravet syndrome, as they become young adults, if they are just given this, you know, the old symptomatic generalized epilepsy of unknown cause they may just be slapped on a Lennox-Gastaut syndrome diagnosis, because our adult neurology colleagues feel more comfortable with that diagnosis, I think, than they do Dravet. And so it kind of becomes - it can get confusing, but hopefully – um, hopefully, it will show that that is important. Right? To be as precise as possible, uh, in – in trying to separate these out.

So as I mentioned, um, I think we both agree that having as precise a diagnosis as possible is - is important for so many reasons. But, um, in particular – um, so we can decide how to approach these individual patients in a more, um, rigorous and precise manner, that hopefully is going to translate into improved, um, quality of life, uh, for these patients and their families. And so we all know that we have 30, uh, more – or more, uh, anti-seizure medications, uh, and many of them, up until recently, um, didn't actually have formal approvals, not only in pediatrics, uh, but more specifically for some of these developmental and epileptic encephalopathies. And so I'm wondering if you could walk us through now, in current 2023, how do we choose, um, from this long list of medications to – to best serve these individual patients?

Dr. Wirrell:

Yeah. Well, that's a really good question. I think, you know, one of the – the really important things to do is to sort out your treatment goals. Right? We know that these children with the developmental and epileptic encephalopathies have very, very frequent seizures, drug-resistant seizures, and so the likelihood that you are going to achieve complete seizure freedom is very, very low. And I think we really have to sort out what's an appropriate treatment goal, what is an appropriate degree of seizure reduction, um, to really markedly improve quality of life?

And often what I do is, I mean, I think it's a – a discussion that you have together with the family, um, you're deciding on what are the most problematic seizure types. So for example, in – on Dravet syndrome, it's the prolonged hemiclonic seizures, the – the status epilepticus, that's very problematic. For the kids with Lennox-Gastaut, and often are those drops seizures, because that really is what's leading to injury. So you're really sort of focusing on – on what are the most problematic seizure types, um, and then sorting out what is a reasonable degree of reduction. Ideally, seizure freedom, but as you know, that's something that's really tough to do.

And I think, um, also very importantly, it's not just about the seizures. Right? It's the comorbidities that these patients have. So a lot of the – the, um, intellectual disability, the behavioral challenges, many of these kids have – fall on the Autism Spectrum. Um, many of these children have sleep disorders, sometimes they can have, um, you know, eating disorders or failure to thrive, um, attention difficulties, so it's really paying attention to those other comorbidities as well. And making sure that you've got your team on board. And – and it really is, as you know, that team that you need to take care of these kids.

And then I think, um, you know, sorting out, um, medication-wise, being cautious not to - to over treat, I think we certainly want to use the best and most effective therapies. Um, but I think we also want to be cognizant that we, um, you know, once we have a child on three medications, if we're talking about adding another medication, we got to start thinking about what one needs to go, so that we're avoiding sort of excessive polypharmacy, and that we're using medications together in – in a rational manner.

Dr. Sullivan:

Absolutely. Absolutely. Yeah, and we hear from our parents and caregivers, right, that, um, seizures are still, um, for the most of them, the number one priority to reduce, but a very close second, right, and third, all the things that you had mentioned, behavior, sleep. And I've often said, you know, even someone with one of these highly treatment-resistant epilepsies, who maybe even is, you know, having daily seizures, they're still spending the majority of their life not seizing, right? And it's all those other issues such as cognition, sleep, behavior, that really are having a negative impact, uh, on quality of life, and we need to be sensitive – uh, sensitive to those.

Um, but in the spirit of – of efficacy, right, um, I think it's – um, it's, uh, been really in – inspirational for – for me to finally have some data to back up some of the treatment decisions and choices that we're discussing with families, uh, in the clinic. And I hope to go through just, uh, a little bit of that, uh, um, right now, uh, in terms of the different randomized controlled trials that have performed in Dravet syndrome, uh, over the last 5 years. And, um, you know, what, um, really got things, um – got interest, I think, it sparked in Dravet syndrome, again, was, um, the trials with cannabidiol. Though before I go there, I think, um, it's long forgotten that there was a randomized controlled trial of a very good medication called stiripentol, um, that was, uh, studied in a small group of patients, oh, 20 years ago, and really had some pretty profound, uh, uh, results, um, with an overall reduction in seizures of about 70%, uh, and with about 25% of those patients actually being seizure free. Now, that clinical trial design was a little bit different than the other two trials that I'll go over here in a moment, they, um, only kind of generalized tonic-clonic seizures and clonic seizures, it was a shorter, uh, 8-week period. But it goes without saying that 70% reduction in seizures in this highly treatment-resistant group, um, wa – was pretty profound. And – and I will – I will note that that trial was done, um, in conjunction with all the other - all the children needed to also be on concomitant valproate and clobazam, and so therefore, that has influenced sort of the labeling, um, that we have here in the U.S. and also, um, in – in, uh, EMA.

Um, but getting more into the last, uh, few years, um, there have been, uh, two other trials that have been done, uh, in Dravet syndrome that have, um, uh, published, uh, data. And the first is – is cannabidiol. Um, these randomized controlled trials, um, are pretty much very similar in terms of their inclusion-exclusion criteria. Um, a 4-week baseline versus a 6-week baseline, being followed over 12 to 14 weeks, and the countable convulsive motor seizures are being counted and compared from their baseline, um, and – and compared to how they do, uh, in treatment.

Uh, and as we can see here, cannabidiol had a 43% reduction, uh, in seizures compared to 27, um, percent, uh, with placebo. Uh, and then fenfluramine, there were two different trials, um, that were actually done. So if we first look at the study that was done with fenfluramine without stiripentol, we can see the results were very similar to what was seen in the stiripentol trial, um, with an overall reduction in seizures of approximately 70%. And then fenfluramine had to be studied, uh, in another trial where concomitant stiripentol was given because of the drug interaction that we know exists there to make sure that we weren't overexposing, uh, patients to

fenfluramine levels. And as you can see, uh, the reduction in seizures here, uh, was also, um, quite good, with fif – 54%, uh, reduction in, um – uh, in overall seizures, that - correlating to a 50% respond rate, uh, in the same - in the same, uh, degree.

And so I'm wondering, you know, putting all that data together, how – how should a clinician - well, how do we put all this together? Like you said, it's a conversation with a family, but I'm curious, you know, how you - how you go through that – uh, uh, those data, uh, in order to influence your practice?

Dr. Wirrell:

Yeah. Right. So that's a very good question, you know, how do you actually approach these kids. And you've got, you know, a number of medications that have really been shown to be quite effective. Um, and so, um, we actually work together with, uh, an international group of child neurologists. You were involved as well.

And, um, uh, did, uh – surveyed the child neurologist, and we also actually brought families into this who had experience with using these medications in their kids, and – and kind of had a good understanding for their kids and also for other families of Dravet syndrome, how they worked. And we came out actually with this international consensus statement.

And so first line, um, uh, we thought was valproic acid. Now that's interesting, because that's a medication that's old, has, you know, never been trialed in a – a randomized placebo-controlled trial. But I think there is, um, uh, reasonable consensus that that is often a very effective medication for Dravet syndrome. And that's probably something that we should be looking at - at first line.

Um, the second-line agents, as you said that the two are ones the, uh, fenfluramine and the stiripentol, both of those would showed about, you know, a 70%, um, uh, reduction. Um, and so those are – are – they're in second line. Clobazam could also be used, um, particularly if you're using stiripentol, as you said, you need to use those together. And then third-line, um, pharmaceutical grade cannabidiol. Uh, fourth line topiramate and the ketogenic diet. And then others, um, uh, further down the road.

But it's also important what not to use, right? So in – in kids with Dravet syndrome, we know that the sodium channel blockers often significantly exacerbate seizures. And so we want to avoid things like oxcarbazepine, carbamazepine, lamotrigine, rufinamide, things like that. So those are medications that we really also want to avoid.

Dr. Sullivan:

Absolutely. This whole precision medicine approach, right, it's equally important to – to know what to go to, but specifically in Dravet syndrome, and maybe in to some extent, some medic – medicines in Lennox-Gastaut syndrome, those, uh – those, uh, to – to avoid.

So in the - in the spirit of – of Lennox-Gastaut syndrome, there was a similar, right – there was a similar, um, consensus statement that – that was, um, done, um, uh, by Helen Cross, um, that also tried to look at all the data, um, but also their real-world experience, right, to see how this translated into, um, sort of an algorithm, um, for lack of a better word, uh, or a framework I think is better, um, the – these things are not algorithmic, right? Every patient is going to be different. As you mentioned, you want to, um, be, uh, sensitive to the – the most disabling seizure type, and that certainly is going to be the case, uh, uh, with Lennox-Gastaut.

Dr. Wirrell:

I think importantly, in that, um, algorithm, as well, she talked about the importance of looking at things, the nonpharmaceutical options, um, VNS, um, ketogenic diet, really pretty early. And, uh, because we know these kids are going to be drug-resistant and sort of, you know, trying to avoid some of that polypharmacy as well.

Dr. Sullivan:

Absolutely, no, thank you for bringing that up. And – and callosotomy too. I mean, it seems so barbaric in so many ways. And I feel like it kind of has gone through sort of a pendulum swing where people stopped doing it, and then as we got new drugs, they came on. And then as you're running out of medication options, and these poor patients are still having multiple falls and injuries, uh, each day, um, callosotomy, while it seems like a big step, um, can be very, um, transformational in – in reducing those drop – those drop seizures.

So with, um, that consensus statement, um, in terms of the treatment algorithm for LGS, um, do you think that that is actually consistent with the data that has been shown in the randomized controlled trials in the LGS patient populations?

Dr. Wirrell:

Yeah, so I think when you look at the randomized controlled trials, there's been now quite a few medications that have been studied in that manner. Right? And, um, I think, you know, all of the approved ones, obviously, have been shown to be more efficacious than placebo. But I think none are highly, highly efficacious, right? And what we don't have is – is a – is super helpful therapy that's really

going to reduce seizures by 75% or 90% in a big chunk of patients with – with Lennox-Gastaut. Um, they're all I think, fairly similar. And so, um, when I'm choosing them, I'm really looking at, you know, um, uh, what are the potential side effects? Trying to choose those with lesser side effects. Um, there's some of the kids with Lennox-Gastaut can have very frequent seizures. And so while something like lamotrigine is a really effective medication, it can be very challenging to – especially if you're using it together with valproate to, you know, twiddle your thumbs for 3 months waiting for you to get therapeutic levels. Um, and so sometimes that's – that's problematic as well.

So I think, um, for a lot of them, um, really looking at what are the side effects? Looking at, um, how often do the medications need to be given? Some of these medications 3 to 4 times a day, and that can be challenging for families as well. Um, but really, you know, looking at that side effects and how they play with the other medications that you're u – you're using them with.

Dr. Sullivan:

Absolutely. And then these trials, right, I mean, they've got similar designs and everything. And this term drop seizures, I know, it's – it's criticized by some in terms of, right, because what is a drop seizure? It's, you know, there's very, uh, extensive detailed definitions for a clinical trial perspective. I think it's been, um, helpful from a clinical trial perspective, so we're at least, um, comparing, um, apples to apples. Right? That's not to say that there are other seizure types, such as a generalized tonic-clonic seizure, that certainly will result in a drop. And if we actually have data for some of these compounds that suggest that for patients who are having that as a prevailing seizure type, maybe there is a – a slightly differential efficacy that favors its use. I think that's something also to – to take into – to consideration.

So yeah, so we're taking into all these - these points, right, where efficacy and reducing seizures is important. But as we said, qual – this is all about quality of life, right? So it doesn't help these kids or their family and the caregiver burden if their seizures stop, but they're asleep all day, or they're eloping and running out of the house, and they almost increase the caregiver burden. So I'm wondering if you could go over how well are these medications tolerated? Not only in the trials, but do you also feel – but back to you, does that translate into real-world clinical practice?

Dr. Wirrell:

Yeah. So, um, so a great, great discussion. So I think, you know, first of all, um, stiripentol, um, I think the biggest side effect that we run into that is sedation. Now, some of that I think is – is, um, because we're not cautious enough about reducing comedication, particularly the – the clobazam. And we know that if we use together, um, stiripentol and clobazam, that's going to drive the clobazam and the norclobazam levels up. So we need to be cautious about that.

The other thing was stiripentol is, um, I think, you know, when - when you look at the recommended dose, that's a good dose for a young child, but I think if you try and – and, uh, you know, put an adolescent on 50 mg/kg per day, they're going to fall asleep. I think that's too big of a dose. So, you know, I think for – for many of these medications, you know, start low, go slow. And, um – and – and don't try and sort of hit that target dose right away.

Um, so stiripentol can also, as – as can all of the medications we use for Dravet, pretty much reduce appetite. And that can be challenging as well, because as you know, kids with Dravet syndrome tend to, you know, kind of grow a lot on their own little growth curve, they tend to grow slower than the other kids, they're often quite thin. And so that's a – a challenge as we're using these medications, because all of these medications, suppressing appetite also translates to poor growth.

Uh, when we look at fenfluramine, again, um, you know, that initially was marketed as a - as an anorexic agent. So not surprisingly, it can cause some decreased appetite. But again, I think if we watch these kids, it's – it – that's a side effect in my experience, that tends to go away. So using at a – at a lower dose, watching the appetite, but oftentimes, that does tend to go away.

Um, there is potential concern, as you know, with fenfluramine for, um, a cardiac valvulopathy and pulmonary hypertension. I think, thankfully, in the clinical trials and in – in, um, the data, so far, since it's been licensed, that seems like a really, really rare side effect. But obviously, it is an important, um, concern to discuss with families and - and all of these kids are going to need echocardiograms every - every 6 months.

And then cannabidiol, um, I think the biggest side effect that - that I see with that are sort of GI issues.

Dr. Sullivan:

Yeah.

Dr. Wirrell:

Um, some nausea, and particularly loose stools. Again, that seems to be a lower risk if you're starting out at a lower dose, um, and you're just moving up really slowly. And then some of these kids can also have, um, some – some, uh, decreased appetite, sedation. And, um, when used together with valproate, you can also see an increase in transaminases. Um, usually that's a reversible thing. And I've never, uh, seen in my practice or, uh, read about a child, um, uh, developing liver failure with that. So I think just recognizing it's there, um, and recognizing you need to watch the transaminases.

I think overall, for many of these – um, these patients, these are overall pretty well-tolerated agents. And does the fact that these medications act in different ways, is that – does that play a role in which ones you – you choose? Do you try and choose those with, you know, different mechanisms of action?

Dr. Sullivan:

Yeah, absolutely. And I think this is where, um – I never knew I was going to have to, uh, understand so much pharmacology. Uh, but it's been helpful, right? I mean to – so, um, we try to use this term rational polypharmacy, right, to the extent that we understand at least the primary mechanisms by which each of these medications, uh, work. And certainly, if we have someone who is on a serotonin agent, um, we may not want to add another serotonin agent, maybe because that's not going to give us any more efficacy, maybe it'll increase the actual serotonergic side effect profile. So we want to reach for something that maybe is nonserotonergic. And so, this whole idea of rational polypharmacy and choosing differential mechanisms of action, I think, does - tries to accomplish two things, one, to improve efficacy with these non-overlapping mechanisms, and two, to minimize, uh, the adverse event profiles. Because if you just start pounding the same receptor, right, uh, it just stands to reason that maybe the adverse events are going to be - going to be higher, and then that's not going to translate into – to good tolerability. And so I think that's why, even though we've made so much progress and have new medications with novel mechanisms, we need more, right? Um, we – we need more mech – we need more medicines with – with novel mechanisms. And ideally, maybe even getting to more of a really precision medicine approach, um, specifically with – with conditions like Dravet syndrome, um, where maybe we can actually target the actual, uh, underlying genetic cause, uh, itself.

Dr. Wirrell:

That's a great segue going into our – our next, uh, uh, part.

Dr. Sullivan:

Chapter 3.

Dr. Wirrell:

Chapter 3.

Dr. Sullivan:

Yes.

Dr. Wirrell:

So the third and final chapter is on novel treatments and their role in the evolving polytherapy paradigm. And so looking ahead, where are we going? I think one of the really exciting, um, things that I've seen in the last few years is the focus on disease-modifying therapies. Um, and I think, you know, now that we really have a much better understanding of many of the genetic causes of early life epilepsies, um, I really see this as a – as an area that is – is going to become much more, um, widespread.

Dr. Sullivan:

Yeah.

Dr. Wirrell:

And that's super exciting.

Dr. Sullivan:

It's wild. Yeah.

Dr. Wirrell:

So these disease-modifying therapies, um, you know, really are targeting, uh, what is the - the channelopathy or what is the – the pathogenesis that's leading to the seizures, but also leading to this significant comorbidities? And at least my hope, and I'm sure yours

as well, is if we can identify these kids early, and we have these disease-modifying therapies and we can start those therapies really early, boy, I think we can probably really, um, change the – the long-term outcome for these kids, reducing seizures, maybe even making them seizure free. Really significantly attenuating those comorbidities or even preventing some of those comorbidities.

Dr. Sullivan:

Absolutely.

Dr. Wirrell:

And so there's some really exciting stuff in clinical trials, um, the antisense oligonucleotide, um, that's really targeting now Dravet syndrome, and that's, as you know, in clinical trials. Um, there is some gene therapies, um, really, again, targeting Dravet syndrome that are likely going to be coming into clinical trials over the next year or 2. So really excited about those. And – and as I said, we – we now have the technology, right? We know how to do this antisense oligonucleotides. We know how to get, you know, genes into people. Um, so we have all of these genes, I think it's – it's going to be a much easier step to apply those more broadly.

Dr. Sullivan:

Yeah. Absolutely. Yeah, I'm trying to be a cautious optimist here. I mean, these - some of these technologies, you know, I didn't even know – know anything about, right. And I think I've put my foot in my mouth 5 years ago or so, families have asked me do I think gene therapy, you know, is going to be in – in – in my career or my lifetime. And I was pretty pessimistic about it. Because I was thinking it more in this classical sense, I think that people are aware of like CRISPR and gene editing and all the complexities that are involved in a central nervous system disorder and a gene like SCN1A, with it being so large, but now all of these other, you know, uh, approaches to try and, you know, upregulate, um, that messenger RNA production and therefore into the functioning sodium channel, is – is super, super exciting.

Um, and I say cautious optimist, because I think everyone is proceeding like, yes, we want cure. And you know, what's cure mean? Never have a seizure and get someone back on their developmental trajectory. Maybe, you know, with time, and as we refine these - these approaches, we will get there. But I think there's still going to be a need for what we would consider like conventional anti-seizure or symptom - symptom management. Um, and so in that spirit of – of we need more medicines with more mechanisms, I'm wondering if you could maybe go over some of those ones that are sort of at varied stages, uh, in – in the pipeline.

Dr. Wirrell:

Yeah. So I think – and I think you're right. I think we are going to need some, and I think, you know, novel mechanisms different than what we have already, um, is – is going to be still very, very useful for many of our patients. So maybe we'll, uh, we'll go ahead and – and talk a little bit about, um, soticlestat. It has been in – in clinical trials, both for, uh, Dravet syndrome, as well as for Lennox-Gastaut syndrome. Um, and here's the data for Dravet syndrome. So in the, uh, clinical trial, there was a reduction in seizures from baseline, um, 36.5%, compared to an increase actually 10%, um, in the – in the control group. And so that was really exciting. And that was, uh, statistically significant.

Um, this has also been looked at for – for Lennox-Gastaut, and maybe we'll move on to the next slide here. Um, and here, that – the numbers were a little bit less robust, um, but overall, about a – an 8 – 19 to 20% reduction, um, in the treatment group versus about a – a 2 to 5%, um, in the – in the placebo group. This was not quite statistically significant. But I think also, you know, potentially very important, um, uh, for these patients. And overall, I think, you know, these were medications that were – this was a medication that was pretty well tolerated as well. So no concerning, uh, uh, severe side effects. And they – they've just released their data, um, last week at American Academy, um, uh, looking at patients who were in their open-label extension study, and after 2 years in the open-label extension study, um, there was an – an overall reduction in seizures, 54% in the Dravet group, and about 28% in the Lennox-Gastaut group, and they did not find any new side effects. So I think this is going to be a really promising new therapy as well.

Dr. Sullivan:

Yeah, absolutely. And if you look at that Drav – those Dravet numbers and put them in the context of the data we already reviewed, right, it falls in there. It's like cannabidiol is, you know, it's maybe not as good to stiripentol and fenfluramine, but, you know, as good if not a little bit better placebo-adjusted numbers for - for cannabidiol. And then, um, the fact that it's actually having that durable - durable efficacy. So I think we'll - we're all excited to see the – the data readout from the phase 3 trials in – in – in both of – uh, both of these, uh, con – conditions.

And then I guess riding, you know – riding the serotonin sort of, uh, uh, success, uh, of fenfluramine, um, and why is – is the serotonin pathway, I think there's a lot of interest, uh, now – now in this pathway with at least three compounds, um, in various stages, uh, of

clinical development. Uh, one that I'd like to talk about, um, is actually, uh, clemizole, which is really interesting story that I don't have a ton of time to – to – to go into, but I know it well because it was, uh, discovered by one of my colleagues actually, uh, at UCSF and his zebrafish, uh, model where he basically, uh, did a blinded, uh, screen of many FDA approved compounds to see which of them actually were anti-seizure in this SCN1A zebrafish model. And lo and behold, it was done in a blinded manner – and lo and behold, a number of compounds came out, um, but one of them, um, was clemizole, which was initially a little bit of a – a why clemizole? It was a - it was an antihistamine back in the 50s and 60s, it was taken off the market because other antihistamines became - became available. And usually we don't think of antihistamines as being - sometimes we even think they're somewhat contraindicated in our epilepsy patients, right? So why would this work in a - in a zebrafish model? And then lo and behold, when some further work was done, it turns out the – the major, um, secondary mechanisms and receptors that it binds to, is actually the – the – the serotonin, uh, pathway. And so that's actually, um, in, uh, a phase 2 trial, uh, right now in patients with Dravet syndrome to - to ideally see, I think the theme with a lot of these serotonin agents, um, because of the concern for cardiac valvulopathy that you mentioned, uh, with fenfluramine, because the – the dose is limited in those patients because of the concern of that - that valvulopathy, is could these other serotonin agents actually, um, give us more, uh, data as to which receptors are – are most important, um, in terms of being anti-seizure? Uh, and would we actually be able to avoid some of the potential valvulopathy because of those serotonin receptor subtypes, but still have improved efficacy and tolerability if we're focusing on other serotonin – ser – receptives – serotonin receptor subtypes. And so I think this is going to be really exciting next 12 to 18 months, as, uh, a lot of these trials, I think should, um, actually, um, have data, uh, to present.

Uh, another medication is – is lorcaserin, um, which also, uh, it was a weight loss, uh, medication, um, but a little bit more specific for the 5-HT2C, uh, uh, receptor which is not supposed to have the same – incur the same cardiac - that valvulopathy, um, risk, and there's been some long-term, um, studies, uh, when it was used in the weight loss population tens of thousands, I think up to 50,000 patients, uh, where that risk of valvulopathy was – was exceedingly low. And we do have preliminary data, um, uh, that supports this as a use – supports its use as an anti-seizure medicine, not only in Dravet syndrome, but in some of the other, um, developmental and epileptic encephalopathies that we've already, uh, uh, discussed. Um, and in this one, uh, sort of basket study, uh, of various different, um, epilepsy types, um, where Dravet syndrome represented the majority, there was an overall reduction in seizures of almost, uh, uh, 50%. So something that is, um, uh, not to be shied away from. And so certainly open label, uh, we need better control data, but that – that study is – is underway, uh, uh, as well.

And then the last, uh, one is - is a medication that currently is being developed by Longboard and – and has this abbreviation LP35, uh, 2, um, is – is what's called the superagonist. So look at it as – as lorcaserin, um, but even more potent, um, for the 5-HT2C receptor with very, very small, almost little to no off-target effects on some of the other, uh, serotonin agents. And this is actually being studied, again, in a basket trial, focusing on Dravet, because we're trying to pick up on what we already know from the success of fenfluramine. But is there really a underlying pathophysiology to an SCN1A patient that would make a serotonin agent only work in that patient population? I don't think we know. I mean, we saw the differential responses in the fenfluramine Dravet and LGS trials, but still effective in LGS, right? So I think, um – I think casting a wider net as much as we, uh, uh, um, are very interested in Dravet syndrome and Lennox-Gastaut syndrome, there are a lot of other patients out there that don't have those syndromes, right, that still have a huge unmet need for - for novel therapies, uh, to be brought to the – brought to the clinic.

Dr. Wirrell:

So let's take a second and review some of the practice pearls from this presentation. So I think we know that there are more treatment options for Dravet and Lennox-Gastaut, and thankfully more coming - coming down the, uh, you know, the corridor. Um, when we look at – at treatment for these kids, I think, um, you know, despite our – our best efforts, most of our kids are on - on polypharmacy. And so we really need to think about how we use that rationally. We want to choose medications with, you know, different mechanisms of action, we want to choose medications that are not going to sort of exacerbate side effects from one another. So I think, uh, be cautious how to do that. Um, seizure freedom is the hope but - but I think still it's probably not realistic for most of our kids with developmental and epileptic encephalopathies. And really important is balancing that quality of life and – and addressing some of those comorbidities.

Dr. Sullivan:

Absolutely. Absolutely. So Elaine, it's been a pleasure as always. Thank you for joining me today, uh, in this – in this discussion. Uh, I hope that what we've presented to – to you all, um, is going to be helpful, uh, in your clinical practice. And I want to thank you, um, for – for watching and for partnering with us and trying to improve the overall care, um, that we can, uh, give these patients. Thank you.

Announcer Close:

You have been listening to CME on ReachMD. This activity is jointly provided by Medical Education Resources, and Novus Medical Education, and is supported by an independent educational grant from Takeda Pharmaceutical Company. To receive your free CME credit or to download this activity, go to reachmd.com/cme. Thank you for listening.