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Special Report: Management Considerations and Unmet Needs in LGS and Dravet Syndrome

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[CHAPTER 1]

Dr. Singhal:
Lennox-Gastaut syndrome and Dravet syndrome are 2 rare epileptic disorders with a pediatric age of onset. They are often refractory to therapy and have significant side effects due to polytherapy. Are you able to identify these syndromes in your patients? And are you familiar with the drugs in development that may impact the treatment landscape?

This is CME on ReachMD, and I'm Dr. Nilika Singhal. Here with me today are Dr. Elizabeth Thiele and Dr. Scott Perry.

Dr. Thiele:
Hi, and thanks very much for having me join this.

Dr. Perry:
Yeah, thanks a lot. Glad to be here.

Dr. Singhal:
Let's get started. Dr. Thiele, to set the stage for this chapterized course, can you please give us an overview of Lennox-Gastaut syndrome, or LGS, as well as Dravet syndrome?

Dr. Thiele:
Sure, I'd be happy to. And so I think, you know, we've thought a lot about these 2 particular syndromes over the past several years with all the clinical trials, and they are 2 very important pediatric epilepsy syndromes. I'll start with Dravet because it's honestly a little bit easier to diagnose. Dravet has a pretty typical onset. You know, pretty healthy baby, normal development, and then first 4 to 6 months of age in the setting of fever has a seizure, either tonic-clonic or hemiclonic. An EEG at that time is likely normal and MRI normal, and then the second year of life has an onset of different types of seizures and oftentimes a cognitive plateauing and often regression. It's been much easier for us with the availability of genetic testing to make an early genetic diagnosis of Dravet, and although there is kind of a spectrum of presentation, that's a prototypical story. The differential diagnosis would be other epilepsies with onset at that age, other etiologies, but again, the genetic testing is really, really helpful.

LGS is different, and I think most of us would say that it can take a while and can be difficult to diagnose a patient as having LGS. Distinct from Dravet, which is a genetic epilepsy and a pretty homogenous group, LGS can result from numerous etiologies, and the patient's journey can be very different. Some children will have infantile spasms and then evolve into Lennox-Gastaut, the pattern of seizures, the slow spike and wave on an EEG. And other patients may be perfectly healthy and normal and then sort of evolve in the

seizure types. And I think it's demonstrated how difficult this can be to diagnose by the ILAE [international league against epilepsy] recent kind of change in and age of onset of LGS up to the age of 18. Before LGS, it really is the history, the seizure types, and also the EEG features – both the slow spike and wave as well as the paroxysmal fast activity during sleep. I think even though there's not a genetic test for LGS, I think gene testing still plays a very important role because we know that several of our genetic epilepsies can present or evolve into a Lennox-Gastaut phenotype.

So for both of these disorders, EEG is important, genetic testing, I think, is becoming ever increasingly important in taking care of children with epilepsy. And I think the difficulty is really for our adult colleagues because the genetic testing wasn't available for Dravet, maybe not even recognized when they were young and started their epilepsy journey. I think there are plenty of adults that do have Dravet and do have LGS that have not had that specific diagnosis, and I think as a community, we're working on ways to find better ways and criteria to make that diagnosis, not only in pediatric population but also in the adult population.

Dr. Singhal:
Thank you so much, Dr. Thiele.

Dr. Perry, do you have anything else to add?

Dr. Perry:
That was outstanding, as we would expect from Dr. Thiele. I just want to emphasize that last point she made, that there are probably a lot of adults that have LGS or have Dravet syndrome that were not diagnosed. And it's recognizably more difficult in adults because you don't always have that whole history from their childhood, but I think it's something that providers need to keep in their mind when they're dealing with an adult with drug-resistant epilepsy who may have, you know, intellectual disabilities. These conditions may be present because the treatment may be impacted by understanding them.

Dr. Singhal:
Terrific. Thank you so much. So some of what I'm hearing, some of our key takeaways include, with Dravet syndrome, the age of onset, presenting in the first year of life in a previously typically developing baby; the typical seizure types, including hemiclonic, myoclonic, generalized tonic-clonic, and atypical absence seizures; the large percent of children that could have an underlying gene diagnosis with Dravet syndrome, so the importance of gene testing. And with LGS, how the group might be more heterogenous but still wanting to emphasize the importance of gene testing to uncover what could be the etiology that underlies LGS as well as the importance of our ancillary testing with slow spike and wave and paroxysmal fast activity seen on EEG. So those things can be important clues.

So to close, in the next chapter, we'll be discussing polypharmacy in LGS and Dravet syndrome. Stay tuned.

[CHAPTER 2]

Dr Singhal:
Welcome back. We were just talking about strategies for diagnosing Lennox-Gastaut syndrome and Dravet syndrome. Now let's focus on polypharmacy.

Dr. Perry, what can you tell us about the impact of polypharmacy on our patients with LGS and Dravet?

Dr. Perry:
Well, first of all, I think it's important to understand that polypharmacy is very common in these conditions, and frankly is often necessary because we have different seizure types, we have different etiologies that we're dealing with. And I think people need to remember that polypharmacy does not only apply to our antiseizure medicines, because a lot of these patients are going to be on other medicines for associated comorbidities, very often, like neurobehavioral comorbidities where the treatments are more likely to have a meaningful interaction with some of our antiseizure meds. You know, as a provider, I think we know that polypharmacy is going to increase our risk of adverse effects, which is important because it sometimes limits the ability to understand the efficacy of a drug. Because if we can't titrate it up enough because it's not tolerated, then we may be getting rid of a potentially very efficacious medication because of polypharmacy and adverse effects that maybe we could have limited.

So I think it's important that people, when they're thinking about adding a new therapy for these conditions, they first of all want to think about what they're trying to do. Like, we have a tendency to add drugs because we want to get seizure control, right? But there's a lot of other factors that we probably need to consider beyond that. So, you know, if it is seizure control, what are we trying to do? You trying to get seizure freedom? You trying to get seizure reduction? If you're trying to get seizure reduction, is it a certain type of seizure? Maybe it's the most severe for the patient. Maybe it's the seizure that is resulting in injuries. So what seizure are you targeting? And also think about where the patient is at the moment. At this moment when they're having seizures, is the most important thing to decrease the seizures more? Or is the most important thing to limit the polypharmacy in hopes of later adding the next drug?

What I mean there is, you know, maybe they've been having a lot of seizures for a while, and right now, what would be better for them is to be on less meds, take away things that haven't been very useful for them and get those out of the way. And once those medicines are out of the way, then you think about adding that next medicine to try to get that better seizure control. When you're thinking about those next medicines, again, you're thinking about what you want to achieve, and most importantly to me, I think, you're thinking about what is the underlying etiology? Are there certain medicines that might be better for that etiology? And what is the seizure type, in particular?

When you look at the drugs we have approved for these conditions, you'll see that the seizure types in the phase 3 clinical trials are often kind of clumped together, right? So they often look at drop seizures – drop seizures being anything that could basically result in a fall. So generalized tonic-clonic, tonic, atonic-type seizures all would be included in there. And then some of the other studies will look at groups that they will call major motor seizures or convulsive seizures, and again, those will be tonic-clonic, clonic-tonic seizures most typically. So when you look at that data, understand the efficacy you're looking at is usually the efficacy of a group of seizures. If you look at the supplementary data, you'll often find the outcomes for individual seizure types, and that's where you might see that some of these drugs are a little bit better for some seizure types than others when you break them out of that big group, so just important things to think about when you're looking at clinical trial data and thinking about what's the next medicine you want to use.

Dr. Singhal:
Thank you so much, Dr. Perry.

Dr. Thiele, do you have anything to add?

Dr. Thiele:
Yeah, I think Dr. Perry did an excellent job kind of giving the overview, and I think it's fact that most patients with a DS and LGS do end up on polytherapy, not only with our antiseizure medications but also with dietary therapy, our neuromodulation, et cetera. So often these patients get various approaches to treatment, and I do think it's very important. You know, I think it's frustrating for the patients and families and, honestly, frustrating for us that one size doesn't fit all when it comes to managing these disorders and seizures in these disorders. And as we talk with our families, there's the science and the clinical trials, and there's the art of really applying what we've learned in the trials to each patient on an individual basis.

I think as Dr. Perry mentioned, we have to be mindful of the drug-drug interactions and tolerability issues, but we also need to think about possible benefits of polytherapy and possible synergism or additive benefit to a patient from using medications or treatments with different mechanisms of action, different approaches. And I also agree with what Dr. Perry said, that for each patient, it's really a discussion of what is the goal. What are the patient's seizure types? What is the goal versus seizure control versus other comorbidities versus tolerability? So it's a complex paradigm with each of these patients that we approach in optimizing their management.

Dr. Singhal:
Thank you so much. Some key takeaways that I'm hearing are how there are recommended treatments for both Dravet syndrome and LGS, but the treatment of any individual patient is nuanced, and taken into consideration importantly are the patient's quality of life and what the patient and their family value in terms of which seizures to try to suppress versus the impact of medication side effects. And I'm also hearing that for these conditions polytherapy, polypharmacy is just so common since the seizures are so drug resistant.

So next, in Chapter 3, we'll be discussing investigational drugs for LGS and Dravet syndrome. Stay tuned.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Nilika Singhal, and here with me today are Drs. Elizabeth Thiele and Dr. Scott Perry. We are discussing management considerations and unmet needs in LGS and Dravet syndrome.

[CHAPTER 3]

Dr. Singhal:
Welcome back. We just discussed polypharmacy in the treatment of Lennox-Gastaut syndrome and Dravet syndrome. Now, let's move on to some investigational therapies. I'll get us started by discussing some drugs in development for LGS and Dravet syndrome.

To get us started, I'd like to talk about the use of soticlestat in the treatment of Lennox-Gastaut syndrome. Currently, in a phase 3 trial, this study is a placebo-controlled, randomized clinical trial using soticlestat as an add-on treatment for children, teenagers, and adults with LGS. Now, this medication is interesting in that it works differently than other currently available antiseizure medications by impacting cholesterol metabolism in the brain. The drug being tested is called soticlestat, and the trial will assess for efficacy, safety, and tolerability in pediatric and adult participants. So the outcome measures for this clinical trial will be following the placebo-matched titration phase and maintenance phase. The dose will be down tapered, and participants can decide to discontinue the treatment or could be eligible for open-label extension. And the idea is that to look at changes from baseline in major motor drop seizure frequency for 28 days during the full treatment period. Also being assessed will be the impact of quality of life. So we're hopeful that this opens up

another therapeutic avenue for patients with LGS and Dravet syndrome.

Now another study in clinical trial currently is looking at the safety and efficacy of carisbamate as an adjunctive treatment for seizures associated with LGS in children and adults. This is also in a phase 3 trial. The objectives will be to look at reducing the number of drop seizures, including tonic, atonic, and tonic-clonic, compared to placebo in pediatric and adult subjects. This trial is eligible for children over the age of 4 diagnosed with Lennox-Gastaut syndrome. And similarly, the secondary objectives also include to assess the subject's quality of life and evaluate the safety/tolerability of carisbamate in the LGS and Dravet populations.

Another trial to mention is looking at lorcaserin for the treatment of Dravet syndrome and LGS. And similar to the first 2 that we discussed, this will be used as an adjunct add-on treatment for patients with LGS and Dravet syndrome and looking at the impact compared to baseline of major motor seizures. So of these trials, we're hopeful that we have more medication treatment options for these epilepsy syndromes, which are otherwise resistant to traditional antiseizure medications.

And excitingly, in addition to oral medications there are also ongoing trials looking at neuromodulation, including one that's enrolling patients with LGS and Dravet syndrome to look at responsive neurostimulation for feasibility in these conditions. So this preliminary trial of responsive neurostimulation, or RNS, will be to generate safety and effectiveness data for using RNS in thalamocortical networks as an adjunct therapy to reduce the number of generalized seizures in individuals ages 12 and up with LGS or Dravet syndrome who are refractory to antiseizure medications. And this study will be a 2-stage, single-blind, feasibility crossover study to provide early safety and effectiveness for using RNS for the treatment of generalized seizures in this condition.

In addition to this, in the realm of, quote/unquote, gene therapy are 2 interesting trials to know of. Now one is looking at antisense oligonucleotides in the treatment of Dravet syndrome with an SCN1A mutation. And the thought process is that this is not impacting at the cellular level the DNA in an affected person with Dravet syndrome, but rather using an antisense oligonucleotide will hopefully augment protein expression and so increase the number, the formation of sodium channel that's functioning in patients with Dravet syndrome and is given via an intrathecal route of administration. So this trial is ongoing and enrolling patients with Dravet syndrome. And excitingly, similarly in this other realm of treatment options, is a trial called Encoded. And the study compound here is ETX101, which is a one-time dose that could potentially be disease modifying in upregulating the gene involved in SCN1A-positive Dravet patients. So the idea is that a one-time administration of ETX101 would upregulate the otherwise insufficient sodium channels in Dravet syndrome, hopefully addressing the root cause for this condition.

So I'm going to pause here and invite my colleague, Dr. Thiele, if you have anything else to add.

Dr. Thiele:
No. I think just to say that even with the recently approved medications, which are a big and very valuable addition to our treatment armamentarium, I think there continues to be a significant unmet need in both Dravet and LGS for effective, safe, and well-tolerated therapies. And I'm pretty wicked excited about all these medications in development. The phase 2 data for soticlestat looks really good for efficacy as well as tolerability both, particularly in Dravet but also in LGS. Also very interested in others because, again, these are medications with different mechanisms of action from some of our traditional ones, and I'm hopeful that all of these will be available to improve seizure control in our patients.

Dr. Singhal:
And, Dr. Perry, anything to add?

Dr. Perry:
Yeah, for sure. On that last treatment you know, I'm from Texas, so I don't know if we're allowed to get wicked excited like Dr. Thiele is up in Boston, but I'm wicked excited about this opportunity. And the reason is because we've spent years, like, treating the symptom of seizure, but now we're talking about treatments that are actually getting at the etiology, actually trying to change how the abnormal gene that causes Dravet syndrome, how it works, how can we upregulate the good copy to overcome that loss and actually, you know, maybe treat something more than just the seizures. So it's super exciting. Super exciting.

Dr. Singhal:
Thank you so much. So some of our key takeaways include a variety of clinical trials underway looking at oral adjunctive treatments, antiseizure treatments even with novel mechanisms for Dravet and LGS and new trials looking at neuromodulation in this patient population to see if responsive neuromodulation will be safe and effective for generalized seizures. And excitingly, looking at these treatments to upregulate transcription of a mutated gene, so hopefully actually addressing the underlying root cause of Dravet syndrome.

Now, in Chapter 4, we're going to explore surveillance and safety monitoring. Stay tuned.

Dr. Singhal:
Welcome back. We just talked about investigational drugs for LGS and Dravet syndrome, and now we're going to close with a discussion on surveillance and safety monitoring.

So, Dr. Perry, what are some concerns for patients and caregivers regarding surveillance and safety monitoring of therapies?

Dr. Perry:
Well, I mean, you know, as you know, with most medications, there may be some recommended things that we want to look out for and then some things that are required. Some of our new treatments, specifically for LGS and Dravet syndrome, do have FDA requirements for monitoring. Most notably, fenfluramine does require that echocardiograms be done every 6 months, and that's because there is potential risk for cardiac valvulopathy and pulmonary hypertension. There are other medications that we commonly use where monitoring is definitely suggested. For instance, liver function testing may be more commonly done with people on Felbatol, valproate, cannabidiol. You may get blood count CBCs for Felbatol, valproate as well.

So, you know, there's going to be some laboratory and maybe some ancillary testing that needs to be done with some of these medications, and that's something to take into consideration when you're thinking about the treatment that you're going to use and, you know, is it going to be difficult for them to get those tests? Is that going to be a burden for them to get those tests? Et cetera.

In addition, I think it's worth thinking about the drug-drug interactions. Of course, we talked about polypharmacy in an earlier chapter, and there are some notable options that I think people need to be aware of, again, especially with some of our newer therapies. Some of those to think about would be fenfluramine and stiripentol. When using those medications together for Dravet syndrome or if you were using it for LGS, you need a lower dose of fenfluramine in the setting of stiripentol. Stiripentol also has some interactions with clobazam and valproate, so often those drugs are going to need to be reduced when you start stiripentol in an effort to avoid some of the adverse effects, most notably somnolence and ataxia that would come with those combinations. Cannabidiol as Epidiolex has some risk for elevated liver enzymes, especially in the setting of valproate use and also can have some interaction with clobazam. This is an important interaction to know about because what happens is the active metabolite of clobazam, desmethylclobazam, elevates, and then over a couple of weeks of starting that combination therapy, you may start to see increased somnolence and ataxia in these instances. I point out that it's desmethylclobazam because if you were to be drawing labs to try to prove that that indeed was the problem, you want to make sure that the lab you're ordering is not a clobazam level per se, but it also had desmethylclobazam, which is the part that is going to elevate.

And so those are some of the drugs we commonly use, some of the interactions we may encounter, and just things that people need to be aware of when they're using these treatments.

Dr. Singhal:
Thank you so much, Dr. Perry.

Dr. Thiele, do you have anything to add?

Dr. Thiele:
I, again, I think Dr. Perry gave a very comprehensive overview. I mean, I think as pediatric neurologists and taking care of children with epilepsy and often refractory epilepsy, have been expert in kind of managing drug-drug interactions most of our careers. And I think the newer medications, I think we have to be even more thoughtful, as Dr. Perry said, with fenfluramine and Epidiolex and their drug-drug interactions. And as I often say now, I think in my next life I'll be a hepatologist, because prior to these 2 new medications and having to think about drug-drug interactions, it's really amazing how variable people's metabolism of these medications are, making following levels and thinking about safety, tolerability really important as it always has been for us.

I think we also all learned during the pandemic that kind of the type of therapeutic monitoring – safety monitoring does matter in choosing medications and how we manage our patients. During the pandemic, for obvious reasons, it was difficult to get labs. Families didn't want to go get labs, but even in everyday life prior to and after the pandemic, thinking about the burden on the caregivers, the patients, and the families with kind of the amount of safety monitoring that needs to be done. So I think when I think about this, I like to think about can I come up with a medication regimen that would allow me to follow the patient as easily, less stress for the patient and family, as possible but enable me to not only optimize efficacy but ensure safety and tolerability of the treatments.

Dr. Singhal:
Thank you so much. This has certainly been a fascinating conversation. To summarize, using polypharmacy is so expected with both Dravet syndrome and LGS, unfortunately, given the drug-resistant nature of these epilepsy syndromes and the need for multiple medications to try to treat our patients' seizures, but it comes at a cost. And there are significant drug-drug interactions to know about as well as monitoring for safety and tolerability that can take a toll on the patient, on their family, and on the healthcare system in general.

And I've learned a lot about upcoming, exciting new treatment options for children and adults living with Dravet and LGS, further underscoring the importance of a precise underlying diagnosis for anybody living with epilepsy regardless of age to hopefully open up some treatment options for them with new emerging treatments on the horizon.

And unfortunately, that's all the time that we have today, so I want to thank our audience for listening in, and I want to thank both Dr. Thiele and Dr. Perry for joining me and sharing all of their valuable insights. It was great speaking with you today.

Dr. Perry:
Thanks so much for having me. It was great talking about this subject today.

Dr. Thiele:
Yeah, I'd also like to say thanks. I think we're all pretty excited about the advances we have in treatment options for these patients and I am pretty wicked excited, so thank you.

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