Beyond Seizures: Addressing Neurodevelopment, Quality of Life and Emerging Therapies in Dravet Syndrome Patients

Editor's Note: This is a transcript of an online course released in April 2026. It has been edited for clarity. To obtain credit for participation, CLICK HERE.

UNDERSTANDING DRAVET SYNDROME

Our first module is on understanding Dravet syndrome. It is more than just seizures. Dravet syndrome is a developmental and epileptic encephalopathy. What that means is that there are 2 components that are leading to the developmental impairment. First of all, the sodium channelopathy that virtually all of these patients have and, even without seizures, that would lead to some degree of developmental impairment. But superimposed on that are the frequent, prolonged and difficult seizures. And that adds further impairment to that already seen with the sodium channelopathy.

Dravet syndrome begins in normal infants between a range of 1 and 20 months, but the vast majority of infants start having their first seizure somewhere around midway through their first year of life, with a mean age of 5 to 6 months. The initial presentation is with seizures, and there are a couple of clues to those seizures that would make us suggest this might be Dravet syndrome. First of all, seizures are often prolonged. Many patients with Dravet syndrome present with a seizure longer than 5 minutes, and about a third present with status epilepticus lasting more than 30 minutes. The seizures are also often triggered typically by low-grade fever or following vaccines and, again, about a third of patients with Dravet syndrome will have their first seizure following a vaccination. Other common triggers would include excitement and hot baths.

The seizures often present with convulsive activity and those can either be bilateral tonic-clonic or even more classic as a hemiclonic or hemiconvulsive seizure. The initial brain MRI is normal, although with time—and usually over a number of years—patients can develop usually milder degrees of cortical atrophy, and some will also develop hippocampal sclerosis.

In addition to seizures, patients with Dravet syndrome ultimately will develop variable degrees of intellectual disability, often with plateauing but not necessarily regression development. They also develop behavior problems, such as autistic features.

Looking at development, when children initially present with their first seizure, their development is normal and this often can delay the diagnosis of Dravet syndrome because many people are looking for a child with developmental impairment. That's not the case at initial presentation. This is data from a large group of patients in Australia, and it looks at when developmental impairment was first recognized. In the majority of cases, developmental impairment is first recognized between the ages of 18 and 24 months, although occasionally some patients can appear to be developmentally normal until early preschool years.

This is data from the Natural History Butterfly Study. This was a study that looked at children and adolescents between the ages of 2 and 18 years and these children were treated just with our usual antiseizure medications. This was not part of an interventional drug trial. And these children were assessed with the Vineland Adaptive Behavior Scale as well as the Bayley Scales of Infant Development. What was found is that children with Dravet syndrome are showing generally slow gains, but it's much slower gain than you would expect from a neurotypical child. And the gap between the child with Dravet syndrome and neurotypical children widened with age, and essentially all children with Dravet syndrome will ultimately develop a variable degree of intellectual disability which can be really anywhere from borderline to severe.

Other comorbidities that can occur are gait abnormalities and young infants or young children with Dravet syndrome often are a little slower in their walking. Sometimes we see ataxia that can be related to medications, things like clobazam sometimes can exacerbate the ataxia, but ataxia is a very common finding in young children. In addition, as they get into their older childhood years, and certainly adolescence and adulthood, many patients with Dravet syndrome—and nearly all of them, have a variable degree of this at that age—develop this crouched gait where there's flexion at the hip and flexion at the knees. And that can be a clue, particularly for our adult neurology colleagues, as these patients are walking into the clinic, and recognizing that, and thinking that might be Dravet syndrome.

In addition, persons with Dravet syndrome have challenges with growth and feeding. Feeding problems often lead to a reduced height and weight growth trend and we think that probably patients with Dravet syndrome have their own growth trend. In addition, many of our medications that we

use to treat Dravet syndrome also have anorexia as a potential side effect. That includes things like fenfluramine, stiripentol, cannabidiol (CBD), valproic acid and so sometimes the weight challenges and the eating challenges can be medication-related as well.

Other comorbidities that are commonly reported are some behavior issues. Looking at parental reports, inattention and hyperactivity are very common, probably two-thirds of patients. Children with Dravet syndrome often perseverate on topics and that's seen in about half of children. And then oppositional behavior in about 35%. As I mentioned, up to about 50% of these children are diagnosed as comorbid autism.

In addition, there are high rates of sleep problems. Many of these children cosleep with the families because of concerns of sudden unexpected death in epilepsy (SUDEP) and that might potentially exacerbate sleep problems. But when they asked parents how their child sleeps, nearly 40% indicated their child had difficulty initiating and maintaining sleep, had difficulties with sleep with transitions, that was seen about a third, and about a third also had sleep breathing disorders. That's an area that I think we really need to be paying attention to on our routine follow-up visits with Dravet children.

Looking at the pathophysiology, more than 90% of patients with Dravet syndrome are found to have a pathogenic loss of function variant in the SCN1A gene. The SCN1A gene encodes the alpha subunit of the voltage-gated sodium channel NaV1.1. Now, most of the pathogenic variants are de novo, meaning that the risk of recurrence in subsequent pregnancies is going to be low. There's a very small proportion, no more than 10%, that is inherited as an autosomal-dominant pattern, and we are now also recognizing that [in] some of our patients, it is a mosaic that's inherited at a germline level. All of these families really do need to see genetics, particularly to exclude any potential mosaicism or autosomal dominant, because that would significantly increase recurrence risk for subsequent children.

And when we look at what that gene variant does, it results in SCN1A haploinsufficiency. That haploinsufficiency predominantly affects the GABAergic inhibitory interneurons and so there's reduced firing of these inhibitor interneurons. That leads to disinhibition of excitatory pyramidal tract neurons and that's what results in seizures. These children have sort of a hyperexcitable cortex. And, as well, it also can activate parasympathetic neurons and that's important because that can lead to suppression of heart rate and potentially an increased risk of SUDEP, and we know that patients with Dravet syndrome, one of the most common causes of death is actually related to SUDEP. This is a big concern for many families.

What's important to recognize is that not all SCN1A gene variants are going to result in Dravet syndrome. There are gain-of-function and there are loss-of-function variants. It is the loss-of-function variants that result in Dravet syndrome. Gain-of-function variants actually have been described in a very severe, typically neonatal onset epilepsy with developmental and epileptic encephalopathy, movement disorders and arthrogryposis. It is important to exclude those patients and not misinterpret that as Dravet syndrome. Loss-of-function variants also occur in a range of severities. Dravet syndrome would be the severe end of the loss-of-function variant, but other milder versions of loss-of-function variants would include children with genetic epilepsy, with febrile seizures plus, or just febrile seizures. Occasionally, this can even be associated with familial hemiplegic migraine without seizures. Again, it's important not only to identify the gene variant, but also look clinically at the child and really ask is there clinical presentation consistent with Dravet syndrome?

There have been several other gene variants that have been reported to be correlated with Dravet syndrome and, again, this is the minority of patients. But if you look at these patients with these other gene variants, many of them have a somewhat atypical phenotype of Dravet syndrome.

One of the challenges can be is if you identify an SCN1A loss-of-function variant and you identify that pretty early on, maybe when the patient has had 1 seizure or at most 2 seizures, they still appear pretty developmentally normal, it can be, I think, sometimes challenging for people to have the confidence to say, "Yes, I really do think this is Dravet," because obviously that's a big deal if we're giving the family that information. This SCN1A Epilepsy Prediction Model has been developed by Andreas Brunklaus and colleagues, and I find this pretty helpful. It is available online and what you do is you enter the specific genetic variant that was found. Dravet syndrome is associated with many different SCN1A variants, so you enter the specific variant that was found and you enter the age at onset, the age of the first seizure, and then you click this Calculate Probability button at the bottom of this form, and it will come out with a prediction. This child is 85%, or this child is 90% predicted to develop Dravet syndrome vs 10% or 15%. So that can help adding clinical confidence to your diagnosis.

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The disease burden is very significant. It is significant for patients because of the epilepsy, the frequent associated multiple comorbidities, as well as the treatment-related adverse events, because many of our patients require polytherapy. This leads to impaired quality of life in our patients. It is also very, very impactful for parents and caregivers as well as the rest of the family. Parents often have limitations now in their social interactions with other family members, and also with friends, simply because they have to spend so much time looking after their child with Dravet syndrome. The professional life is often significantly impacted. Studies have shown that in most Dravet families, at least 1 parent either takes a prolonged leave of absence from their work or, in fact, quits their job in order to be able to look after that child with Dravet. The personal life, professional life, and social life are significantly impacted. This also can cause significant financial strain on families. And then, for the healthcare system, these patients require multidisciplinary care. It is not only the seizures, it's looking after their sleep, it's looking after their GI issues, it's looking after their development.

The other big concern for families is the risk of sudden unexpected death in epilepsy, and this accounts for nearly half of deaths in people with Dravet syndrome and is estimated to occur about 8 per 1,000 person years. A very significant concern for persons or for caregivers of persons with Dravet syndrome. And I think there are still significant unmet needs. We need better management of seizures. Even with our current best therapies, most of our patients continue to have breakthrough seizures, although we've made a pretty significant headway with our new therapies. Many of our patients have behavioral comorbidities, or other comorbidities, and usually multiple. The caregiver burden is significant and so we need better ways to decrease that. While our current therapies really can reduce seizures in many patients, they do not prevent the ultimate developmental impairment that we see, and that's also very impactful on quality of life for the patient as well as their caregiver.

IMPROVING DIAGNOSIS

Looking at diagnosis, the initial presentation of patients is with seizures, and these are often called febrile seizures because they often are associated with fever. There are several key features that should or that could help us determine that this is really an unusual febrile seizure and maybe we should be thinking a little bit further and start looking for Dravet syndrome.

First of all, the febrile seizures are often more prolonged than you would typically see. Most febrile seizures are lasting less than 3 to 5 minutes. Children with Dravet syndrome often have seizures longer than that and many of them will have seizures lasting longer than 10 to 15 minutes, with about a third having their first seizure last longer than 30 minutes. Sometimes, seizures can occur in clusters, that's a little bit more common with Protocadherin 19 than it is with Dravet syndrome. The other feature with Dravet syndrome is that seizures often are hemiclonic or hemiconvulsive. They can be bilateral tonic-clonic, but the hemiclonic seizure, particularly if prolonged, should really raise concern that this can be Dravet syndrome. And then for subsequent seizures in children who have hemiclonic seizures, they often switch sides. They might come in at 5 months with their first seizure and it's a right hemiclonic seizure and then, at 6 months, they come in and it's now a left hemiclonic seizure. If you have those hemiclonic seizures switching sides, from one to the other, from seizure to seizure, that's a big clue. And then with time, children can evolve to other seizure types, including focal impaired consciousness seizures, many will develop myoclonic seizures, typically after the first year of life, absence seizures, occasionally atonic seizures and, as I said, status epilepticus is very common, about 89% of children with Dravet syndrome will have at least 1 bout of status epilepticus lasting longer than 30 minutes over the course of their illness, and most of them are having multiple bouts of prolonged seizures, lasting that duration or longer.

Triggers are very, very common, and while fever is a trigger, children with Dravet syndrome often seize at lower grade fevers. In your typical febrile seizure, we might see a bilateral tonic-clonic seizure lasting 2 to 3 minutes in a child with a temperature of 40 degrees. If you have a child who has a temperature of 38.1 who then is having seizures with that, think about Dravet. Those lower grade fevers triggering seizures is a sign. Other triggers can include hyperthermia or hot baths, vaccination, and again, about a third of patients with Dravet syndrome will have their first seizure following vaccination. Excitement is also a big trigger, and many families will tell you that they don't like to take their child to birthday parties or family reunions because they're worried with that excitement, that's going to trigger a seizure for the child.

The initial electroencephalogram (EEG) typically is normal and does not show any epileptiform discharge. Sometimes we do see some background slowing which can be focal and that's often more of a postictal slowing. But with time, typically after 2 years of age, we do see, even between seizures, some slowing of the background and we start to see epileptiform discharges and those are really nonspecific. In some children, we see focal discharges, and other children we see generalized discharges, and other children we can see more multifocal discharges. Some children will also show activation on their EEG with photic stimulation, so that can be a clue, particularly in young children. And the initial MRI should be normal. We should not see a causal lesion. As I mentioned, with time—typically over years—a proportion of patients can develop usually milder degrees of cerebral atrophy or hippocampal sclerosis, but that initial MRI should not show a causal lesion.

It is important to recognize that Dravet syndrome is a lifelong disorder, and this is an important feature to talk to about [with] the family when you're making this diagnosis. Symptoms will begin in infancy, but symptoms continue through into adulthood. And seizures do persist. There is some change in seizures as the child goes from infancy into adulthood. Oftentimes, we see a slight reduction in seizure frequency with age. We see evidence of less fever sensitivity with age. As adults, often seizures are not associated with fever. They still can be, but they often aren't. We see a lesser predisposition for those prolonged seizures, or status epilepticus episodes, and, in adulthood, most persons with Dravet syndrome are having predominantly nocturnal seizures. They're often convulsive, either focal convulsive or generalized tonic-clonic or bilateral tonic-clonic. But they tend to be brief, usually just a couple of minutes and often don't require rescue medication on a regular basis anymore. However, because of those ongoing seizures, patients with Dravet syndrome continue to require polytherapy lifelong.

Other diagnoses that we need to consider that might mimic Dravet syndrome. So, your typical febrile seizure, again that occurs in otherwise healthy, normal children, typically is brief, usually bilateral tonic-clonic as opposed to hemiconvulsive, and usually with a significant fever. And we've talked about how that's different in Dravet syndrome. Other conditions would include other developmental and epileptic encephalopathies. One of the things that sometimes gets mixed up is Protocadherin19-related epilepsy. This is a condition that occurs in girls, usually presenting sort of at the end of the first year, into the early part of the second year of life, and these girls ultimately will also develop some degree of developmental impairment. They also have seizures that are fever-related, but they tend to present more with clusters of febrile seizures than single, prolonged febrile seizures. Epilepsy with myoclonic-atonic seizures, or Doose syndrome, can also initially present with a febrile seizure, but then these children go on to develop the current, usually briefer generalized tonic-clonic seizures, myoclonic seizures, absence seizures, but their characteristic seizure type is what's called myoclonic-atonic seizure where they will twitch, and often, with their twitch, they have a little vocalization, and then they suddenly lose tone and fall. That very characteristic myoclonic-atonic seizure should suggest epilepsy with myoclonic-atonic seizures, as opposed to Dravet syndrome.

I think we're pretty good at getting genetic testing now in young children who present with difficult epilepsy. One of the challenges is, however, if we look at adults with drug-resistant epilepsy, most of those adults have not had genetic testing done, and it's really important to consider this in an adult who has had drug-resistant epilepsy from early on in life. I think we now have treatments that can really make a difference for our patients with Dravet syndrome. That is true also for adult patients and really thinking about getting that genetic testing done in those adult patients, and continuing in children to do that genetic testing early, particularly if they present with some atypical features of a febrile seizure or we see early life epilepsy without a clear cause.

OPTIMIZING STANDARDS OF CARE: EXPERT PERSPECTIVES

Looking at optimizing standards of care, looking at expert perspectives, when we think about seizure management, it's really important that we think really from that first presentation. If the child is presenting with a history that is suspicious for Dravet syndrome, if they have that prolonged seizure, hemiconvulsive at 6 months of age following vaccination, boy we're going to be really suspicious that child is going to have an SCN1A variant and so, for that child, we want to be treating as [if] that child had Dravet syndrome. Don't wait for the genetic confirmation, rely on your clinical suspicion and go ahead and treat that child as if this is Dravet syndrome.

What that means is that we want to use our best therapies from the get-go and, importantly, we know that sodium channel blockers, such as carbamazepine or oxcarbazepine or even lamotrigine, significantly worsen seizures in children with Dravet syndrome. So again, if we have that child with a prolonged hemiconvulsive seizure and we think this might be Dravet, we don't want to use a sodium

channel blocker. Also, I think levetiracetam is commonly used as a medication, a first-line medication, in children with seizures, and we know levetiracetam is not really a very good drug for Dravet syndrome. Not that it really exacerbates seizures, but it typically doesn't really do very much for them. And so, again, if we think this is Dravet syndrome, we probably want to be thinking about something other than levetiracetam.

A number of years ago, a group of experts got together and developed this International Consensus for Management of Persons with Dravet Syndrome and this was experts really from every continent, as well as involvement of expert families who are leaders in the Dravet Syndrome Foundation organizations in their region. And, at that time, what was developed was [as] a first-line we should be using valproate. Second-line, either fenfluramine, stiripentol or clobazam. Third-line was cannabidiol and here I'm talking about pharmaceutical cannabidiol. Fourth-line, topiramate or ketogenic diet. But also, importantly, was what we should not be using and those were the sodium channel blockers. Carbamazepine, oxcarbazepine, lamotrigine should not be used on an ongoing basis in persons with Dravet syndrome. Phenytoin, as well, should not be used, although, occasionally, phenytoin can be helpful in the acute setting when we're trying to manage status epilepticus. We don't think it's contraindicated in a child who comes in with status epilepticus acutely, but we do not want to be using that on a daily basis to try and prevent seizures.

Looking at the data on how well our medications work here I'm going to be talking about responder rates and that means greater than 50% reduction in seizure frequency. The data for valproic acid, clobazam, topiramate and levetiracetam is very limited. There has not been a really high-quality study done and this data is based on small observational studies. And, for valproate, the responder rates range from 22% to 48%, so not great. Clobazam, 28%. Topiramate, between 35% and 78% and levetiracetam only 11%. Our older antiseizure medications are not as effective.

Importantly, we now have 3 anti-seizure medications that have been FDA-approved for the management of Dravet syndrome and those include cannabidiol, and once again pharmaceutical grade cannabidiol, fenfluramine and stiripentol, and I'll talk a little bit about each of those.

Cannabidiol is now indicated by the FDA for treatment of seizures in persons with Dravet syndrome who are 1 year of age and older. It has probably several mechanisms of action. We don't know which is the most relevant and what we do know is that it has low affinity for the cannabidiol 1 (CB1) and cannabidiol 2 (CB2) receptors, so those are probably not so involved. The dosing that was used in the clinical trials was anywhere from 10 to 20 mg/kg/d. This medication is given twice daily, and it comes as an oral solution. The oral solution is compatible with ketogenic diet. Cannabidiol has significant drug-drug interactions and the most important one there is with clobazam. If you use clobazam together with cannabidiol, you get about a 2-fold increase in clobazam and about a 3-fold increase in norclobazam. And if you have a child who is already on high-dose clobazam, when cannabidiol is added, what you risk is that child will become excessively sleepy and probably toxic because of very, very high doses of clobazam and its active metabolite. It is really important to consider a dose adjustment in clobazam in order to ensure that the child will tolerate the add-on cannabidiol.

The studies compared 10 mg and 20 mg/kg/d of cannabidiol with placebo and what was found was that it was actually similar efficacy in seizure reduction, both for convulsive seizures as well as for total seizures with the 10 mg/kg dose as compared to the 20 mg/kg dose. And, importantly, both of those doses were significantly more efficacious than placebo in controlling seizures. Not surprisingly, safety and tolerability, how well the child tolerated that medication, was much better with the 10 mg/kg than the 20 mg/kg dose. In my practice, I think it's very reasonable to have your first target at the 10 mg/kg/d dose and then go up if you need further, up to 20 mg/kg.

Here is the data looking at side effects of cannabidiol that were seen in the trials and the most common side effects that we saw with cannabidiol were related to gastrointestinal (GI), including decreased appetite and diarrhea, as well as related to sleepiness. It caused increased somnolence. And you can see that the side effects were more common in the 20 mg as compared to the 10 mg/kg dose. What was also noted in a small proportion of patients were increases in the transaminases, ALT and AST. Again, that was more common with the 20 mg/kg/d dose and was more common in patients who were also on cotherapy with valproic acid. Now, none of those patients showed any evidence of other liver toxicity, of severe drug-induced liver injury and, in fact, [in] most of those patients, those transaminase levels came back down

to normal on their own, often with another reduction in cannabidiol or reduction in valproic acid.

Fenfluramine, or Fintepla, is now FDA-indicated for the treatment of seizures in people with Dravet syndrome over 2 years of age. And it has a number of different mechanisms of action. First of all, it is a serotonin agonist and it acts on a number of different serotonin receptors. It also is a positive modulator of Sigma1 and that is felt to sort of more stabilize the balance between GABAergic and glutamatergic activity and lessen seizures. Importantly, because it is an agonist at several serotonin receptors, there is a potential risk of serotonin syndrome and so many of our patients with Dravet syndrome may be on serotonergic agents for mood, for behavior issues, for sleep and so you need to be attentive to that and ensure that you are combining medications and doing so safely and try to reduce the use of other serotonergic agents with fenfluramine. The dosing of fenfluramine—so it is also available just as a liquid. If you're using it without stiripentol, the dose is up to 0.7 mg/kg/d to a maximum of 26 mg. For our older and bigger patients, over about 40 kg, they're going to top out at 26 mg. We're not going to be able to get them up to 0.7 mg/kg/d. And then if we're using it with stiripentol, there's a drug interaction between stiripentol and fenfluramine and you can use up to a maximum of 0.4 mg/kg/d to a maximum of 17 mg.

Here is the data looking at how well fenfluramine works and starting with fenfluramine without stiripentol. What we see is comparing the 0.7 mg/kg/d dose and that's in the blue line, the 0.2 mg/kg/d dose in the red line and then, in black, is the placebo response. Looking at the greater than 50% reduction in convulsive seizure frequency, that was seen in 73% on the higher dose, 46% on the lower dose and only 6% on the placebo. Very statistically significant. And even moving the bar up, looking at greater than 75% reduction, that was seen in nearly half of patients on the higher dose, just over a quarter on the lower dose and only 4% on placebo. That, I think, really kind of moved the bar as to what we might expect with regards to seizure reduction in Dravet syndrome.

Looking at the data on its use with stiripentol, and here they just compared the 1 dose, the 0.4 mg/kg/d, in black, to placebo in yellow. And looking at the greater than 50% reduction, they saw that in about 54% on the combined therapy vs only 5% of patients who had placebo added on to their usual antiseizure medications. And then moving the bar up to 75% reduction, they saw that in about a third of patients who used the combination of fenfluramine and stiripentol. Again, I think very beneficial in many patients.

Looking at the long-term benefit of fenfluramine, there has been a recent paper published really showing that efficacy is maintained over the long term. I think this is a very effective therapy for Dravet syndrome and one that really is maintained over the longer term. It has made a significant reduction in seizures for many patients with Dravet syndrome.

Looking at the side effects, fenfluramine was first used as an appetite suppressant agent back in the 90s and not surprising, one of the big side effects that we see is decreased appetite and that was certainly much more common on the fenfluramine doses and was more common on the higher than the lower dose. Otherwise, it seemed to be pretty well tolerated. There was a little bit of fatigue, a little bit of diarrhea and some lethargy reported, but most of the patients with fenfluramine adapt to these side effects pretty nicely in the first 1 or 2 months. The other thing that had been seen—and the reason it was pulled from the market for use as an appetite suppressant agent—is that it did lead to valvular heart disease in some of the patients, as well as pulmonary arterial hypertension that was not seen in the clinical trials. They were very careful and did echocardiograms and that was not seen. However, when we're still prescribing that, we do need echocardiogram monitoring of these patients.

Moving on to stiripentol, stiripentol now is approved by the FDA down to 6 months of age. It is really sort of the first Dravet-specific medication that we can use in very, very young children. Importantly, there's no clinical data to support its use with monotherapy and it's proved to be used together with clobazam. In many of the studies, it also was used in addition with valproic acid. It also has a number of mechanisms of action. It does potentiate GABAergic activity, and it does so at a site that is distinct from benzodiazepines, so it's not just adding to that effect. There probably is certainly an additional effect when we're combining it with clobazam. It also inhibits lactate dehydrogenase (LDH) and that can decrease neuronal excitability, and there is some evidence that it's also neuroprotective which is, I think, an interesting concept given that this is a disease with recurrent prolonged seizures.

The dosing for stiripentol is up to 50 mg/kg/d. We do need to use sort of higher doses, between 40 and 50 mg/kg/d in very young infants or young children, however as we get into sort of school age and older patients, they're not going to tolerate 50 mg/kg/d and as we go sort of into adolescence and adulthood, usually we're using doses that are about half of that because patients will not tolerate that

50 mg/kg/d. Similar to cannabidiol, stiripentol also inhibits metabolism of clobazam with elevations in both clobazam and norclobazam levels. Again, it's really important if you're going to start somebody who is already on relatively high doses of clobazam on stiripentol, you likely are going to need to reduce the dose of clobazam so the patient doesn't become toxic on that. Stiripentol also has the potential to inhibit valproate metabolism, that's to a lesser degree, but again in our patients who are on high doses of valproic acid, we can sort of push them to become sort of into the toxic range unless we adjust that dose slightly.

The efficacy of stiripentol was based on studies that were done back in 2000. They were called the STICLO studies and they were done in France and Italy. And they compared add-on stiripentol to patients who were already on valproic acid and clobazam to add-on placebo. The study included a 1-month baseline, a 2-month treatment phase and then an open-label extension. Again, looking at the data, what we see is, with the patients treated with stiripentol, and that's shown in the yellow line, we see again 72% reduction in convulsive seizures at the 2-month level compared to only 7% in the placebo. The data looked fairly similar to fenfluramine. Looking at the open-label extension, we see that once the patients actually moved into the open label and were taking stiripentol, they responded quite nicely. I think this is also a highly efficacious therapy and it is something that I think we should be considering, particularly early on in the course before we have availability to some of those other medications that we can only use at a year or 2 years of age.

Looking at the safety of stiripentol, the most common side effects again related to GI. Some decreased appetite, reduction in weight. Somnolence was reported at 67%, but interestingly, in the studies that were done, they did not adjust the dose of clobazam down. It was not recognized they needed to do that, and I think if we are proactive about reducing the clobazam dose, we can see a much lower rate of somnolence with stiripentol.

The ketogenic diet has also been utilized and, again, this is more observational studies. It can be effective in persons with Dravet syndrome. This was a study based on a meta-analysis and they looked at 7 different studies reporting efficacy to the ketogenic diet. They defined responder rates as those who achieved a greater than 50% reduction in seizures and at 6 months, the responder rates are about 60%, dropping down to about 45% at 12 months. With the ketogenic diet, the side effects that were reported in persons with Dravet syndrome are quite similar to what we see when we use this with other drug-resistant epilepsies. Some GI symptoms, most common being constipation, sometimes weight loss or changes in lipid profile, that needs to be monitored in all children on the ketogenic diet. And then rare side effects include lethargy, some kidney stones, abnormal liver function. Again, pretty similar to what we see in other children treated on the ketogenic diet who do not have Dravet syndrome.

Multidisciplinary care is also really critical for these families. As we've talked about, these children have very challenging seizures, but they also have very challenging other comorbidities including sleep problems which are really impactful on quality of life, growth issues, endocrine issues, appetite and feeding problems and then the developmental issues and behavior issues, like autism, attention issues, gait problems. And, as they get older, there have been a small number of patients, in adulthood, who have more of a Parkinsonian gait and have shown potential benefit with levodopa. It is really about managing the seizures, but it's about managing all of those other things and I think, really importantly, supporting caregivers.

The Dravet Syndrome Foundation has created a transition guide that was an effort led by Danielle Andrade in Toronto and the guide actually provides information on clinical manifestations of Dravet syndrome, what are the important seizure triggers that we want to avoid, guidance with regards to vaccines and we do recommend that children with Dravet syndrome get their regular vaccines, but probably not 5 at a time and probably with some antipyretic prophylaxis. This guide also provides important information as you're transitioning into adulthood with regard to guardianship and other social considerations. It provides an overview of treatment, including medications to avoid, and the importance of identifying an emergency seizure protocol which is really a must for all patients with Dravet syndrome.

As mentioned, all persons with Dravet syndrome need a seizure action plan. These are going to be patients who are going to be prone to recurrent seizure emergencies. There needs to be a written action plan or Emergency Seizure Protocol because of the high risk of status epilepticus or cluster seizures. All patients with Dravet syndrome should also, I think, be offered an at-home rescue medication that can be given by their parent, by their caregiver or other

adult supervising them, with clear instructions as when do we use this. For some of our very young children with Dravet syndrome, every time they go into status we often give it at the first convulsive seizure. For adults, adolescents, we often are waiting sort of 3 to 5 minutes because many of the seizures will be self-limited. We also need to give instructions on can we repeat this and, if so, after how long and when to call 911.

Beyond Symptoms Control: The Need for Disease-Modifying Therapies

Moving beyond symptom control, the need for disease-modifying therapies, one of the therapies that's in phase 3 clinical trials is zorevunersen and this is an investigational antisense oligonucleotide. It works to induce alternative splicing. What's kind of interesting is when we look at patients with Dravet syndrome, most of those patients have their own private mutation, so the SCN1A gene is very large and when we look at patients with Dravet syndrome, there's multiple different allogenic variants that we see at various regions of the SCN1A gene. What this antisense oligonucleotide (ASO) does, [is] it actually targets the wild type gene and, in the wild type gene, there is this nonsense-mediated decay exon and this is present in the pre-messenger RNA. Now, if this is included in the actual messenger RNA, that messenger RNA disintegrates and we do not get functional protein that is made. What this drug does, or this agent does, this ASO does, is it uses the targeted augmentation of nuclear gene output, or the TANGO method to induce an alternate splicing and you can see that over on this slide, is that it induces that alternate splicing so that the messenger RNA that is made no longer contains that nonsense-mediated decay exon and so that is a productive messenger RNA and they can then increase the production of functional NAV1.1 protein based on doing that. Now, this ASO needs to be given intrathecally, and it also has a limited half-life, so it does require repeated doses. Currently, in the clinical trials, it's being given about every 4 months.

This was data based on the early study, the phase 1b and phase 2 trial, and this was a trial that was done both in the US as well as in the UK. It included 81 patients between the ages of 2 and 18 years of age. All of these patients had drug-resistant epilepsy and were having on average 1 major motor seizure per week or more, to get into the trial. And this was children and teens who were already on our best therapies, so many of these patients had been or were on fenfluramine or stiripentol or cannabidiol and still having this frequency of seizures. Patients received either single or multiple loading doses of zorevunersen, less than 70 mg or equal to 70 mg. The doses were started low and then, as the trial progressed and we saw that it was safe, the doses were increased and then those patients were maintained on a dose of 45 mg or less every 4 months. And they evaluated convulsive seizure frequency, including—or as well as—some behavioral issues. looking at the median percent change from baseline, those patients who received the 70 mg dose in the initial clinical trials had a significantly greater reduction in seizures. 75% to 80% reduction in seizures and, again, these are patients on our best current therapies. There was reduction in seizures on the lower doses, but it did not achieve the level seen at the 70 mg. For the phase 3 trial now, they are starting with 2 doses of 70 mg because of that.

They also looked at Vineland scales. They had done the previous natural history study, the Butterfly study, and they saw that children with Dravet syndrome often kind of more plateaued in their development compared to neurotypical children. What they did is they looked at the Vineland, they also looked at the Bayley Scales and this study shows improvements, the least scores mean change from baseline at the 12-month level, at the 24-month time period and then at the 36-month time period. We see improvements in these Vineland raw scales over time, and this was different than what was seen in the natural history study. I think, importantly, they really could have combined all of the doses, starting at sort of 20 mg all the way up to 70 mg and this was seen in this whole group of patients. I'm hoping that we are actually going to see even more impactful outcomes on development now that we're into the phase 3 trial looking at the higher dose.

They also looked at quality of life, and this was assessed about 9 months after starting therapy in the phase 1 and 2a trials. With the higher dose, the 70 mg single ascending and multiple ascending dose, there was sort of the best improvement in quality of life, but we still saw improvements in quality of life even at the lower doses.

Looking at safety, this was generally well tolerated. The most common side effect that came out were elevated cerebrospinal fluid (CSF) protein levels, but this did not have any significant clinical manifestations associated with that. That is something that is going to need to be watched, particularly as we're going into phase 3 studies. There was 1 patient who experienced an unexpected serious adverse reaction. There were 3 deaths reported, but none of those deaths were felt to be related to the zorevunersen. Two of the patients died from SUDEP which we know is a risk in Dravet syndrome and 1 patient unfortunately died of malnutrition.

Beyond Seizures: Addressing Neurodevelopment, Quality of Life and Emerging Therapies in Dravet Syndrome Patients

This agent has now moved into a phase 3 trial. This is the EMPEROR trial which is currently ongoing. It is a double-blind, sham-controlled trial and is evaluating efficacy and safety in persons with Dravet syndrome between the ages of 2 and 18 years. These patients are randomized 1:1, they either get zorevunersen or the sham procedure, and they are in that sort of double-blind phase for 52 weeks. Those who are receiving the zorevunersen are getting 2 70 mg loading doses 8 weeks apart and then are maintained on 45 mg doses every 4 months. The primary endpoint will be change in baseline in major motor seizure frequency at week 28, and they are also looking carefully at secondary endpoints being developmental outcomes. This trial is enrolling very quickly, and we expect the results probably in mid-2027.

Another agent that has been looked at is clemizole hydrochloride. Clemizole hydrochloride is a histamine receptor antagonist, but it also modulates the $5HT_2$ serotonin receptors and has demonstrated antiseizure activity in Dravet syndrome. It is also given as a liquid twice a day. They have completed the phase 3 ARGUS trial. This was children with Dravet, 2 years and older, and their seizures were not controlled on their current regimen. They were treated 1:1 with clemizole vs add-on placebo, and this was a 16-week trial. They were then able to enter into a 3-week open label extension, and in the open label extension, patients were noted to have about a 50% median reduction in seizures compared to baseline. Overall, this appeared to be very well tolerated. No deaths were reported.

Another agent that's currently in clinical trial is bexicaserin. This is also a highly selective $5HT_{2c}$ agonist. Why is that important? It does not bind at $5HT_{2A}$ or $5HT_{2B}$ and the $5HT_{2B}$ receptors are most important for the cardiovascular risks. As you recall, fenfluramine is also a serotonin agonist. It binds at also the $5HT_{2B}$ and so there's a potential, albeit very small risk, of cardiovascular side effects. That's not the case if we have a very highly selective 2C agonist. There was a phase 1/2 Pacific trial done. These were individuals with developmental and epileptic encephalopathies of various types. There were 36 who completed the trial. Only 3 of those patients actually had Dravet syndrome and all of them were actually in the treatment group as opposed to the placebo group. Of those 3, there was a 73% reduction in motor seizures. Looking very exciting, although very small numbers for Dravet. It appeared to be well tolerated and there's currently a phase 3 clinical trial ongoing.

Another very exciting therapy is ETX101. This is a gene therapy. The thoughts are that this is going to be a 1-and-done approach. It uses adeno-associated virus serotype 9 (AAV9) gene therapy and because that SCN1A gene is very large, they can't fit that all into an adenovirus vector, they had to kind of pick and choose and what they have is an engineered transcription factor and that enhances production of the SCN1A gene, and then they also have a piece of genetic material in there that really targets the expression to the GABAergic inhibitory interneurons which are the main cells in the brain that are affected in Dravet syndrome. This enhances transcription of SCN1A within those GABAergic inhibitory interneurons. This is currently in clinical trials. Patients in the US between 6 months and 4 years of age and they are given this therapy as a single intraventricular injection.

This is the POLARIS study. There is an ongoing phase 1/2 trial. This is in the US, ENDEAVOR. In Australia, it is WAYFINDER and in the UK, it's EXPEDITION. In Australia, they're including children up to 7 years of age, but in the UK and the US, it's up to 4 years of age who have a documented pathogenic SCN1A variant associated with Dravet syndrome and are on standard of care antiseizure medications. As of June of 2025, they had included 11 participants with follow-up for up to 58 weeks. They did not see any significant treatment-related serious adverse events or dose-limiting toxicities. And the early efficacy data does show dose-dependent reductions in seizure burden, reductions in the use of rescue medication and an increase in seizure-free days. Dose escalations are continuing and this trial also looks very exciting. I think the benefit that this would have over potential ASO therapy is this is really a single dose, 1-and-done therapy, as opposed to needing recurrent lumbar punctures (LPs) for ASO administration.

Key Concepts

Dravet syndrome is a lifelong and severe developmental and epileptic encephalopathy. At the time of initial presentation, infants' development is normal and that should not dissuade you from thinking about Dravet syndrome or from doing genetic testing in children who are presenting with a very characteristic seizure in the first year of life. With time, all patients will develop variable degrees of developmental disability or other comorbidities, and the epilepsy is drug-resistant and quite difficult to control. Importantly, I think, identifying those pathogenic variants in

SCN1A early on is really critical. If we can identify that this is Dravet syndrome, we can really target our treatment appropriately. We can avoid using medications that actually worsen seizures and we now have a number of currently approved medications which really, I think, significantly reduce seizure burden, and we have some very exciting therapies in clinical trials. We really want to be initiating treatment for Dravet syndrome as soon as possible.

Looking at management, we have several Dravet syndrome-specific therapies with proven efficacy that have recently been approved, including fenfluramine, stiripentol and pharmaceutical-grade cannabidiol. Use of the ketogenic diet is also a reasonable option and, because of comorbidities, these patients also require a multidisciplinary approach. As I mentioned, several additional disease-modifying therapies are currently in the pipeline, including precision genetic therapies, gene therapies, as well as antisense oligonucleotype therapies that I think really offer potential benefit not only just to improve seizure frequency, but also to improve cognition, behavior, overall function, improved quality of life, and potentially lessen the risk of SUDEP.