Detect and Defeat: Improving Awareness of the Differences in Narcolepsy and Novel Strategies for Treatment

CMEO Podcast Transcript

Richard Bogan:

Hello, I'm Dr. Richard Bogan. On behalf of CME Outfitters, I would like to welcome you and thank you for joining us for today's educational activity titled Detect and Defeat: Improving Awareness of the Differences in Narcolepsy and Novel Strategies for Treatment. Today's program is supported by an educational grant from Avadel CNS Pharmaceuticals, LLC. Today's activity is brought to you by CME Outfitters, an award winning joint accredited provider of continuing education for clinicians worldwide. Again, my name is Dr. Richard Bogan and I am President of Bogan Sleep Consultants, as well as an Associate Clinical Professor at both the University of South Carolina School of Medicine in Columbia, South Carolina, and also the Medical University of South Carolina in Charleston, South Carolina. I'm very pleased today to introduce our faculty. Joining me is Dr. Clete Kushida, Division Chief and Medical Director at Stanford Sleep Medicine. He is also Professor and Associate Chair of the Department of Psychiatry and Behavioral Sciences at Stanford University in Redwood City, California. Welcome, Clete.

Glad to see you here. Also, we have Dr. Anne Marie Morse. She is Director of Child Neurology and Director of Pediatric Sleep Medicine at the Janet Weis Children's Hospital. She is also a Clinical Associate Professor at Geisinger Commonwealth School of Medicine at Geisinger Medical Center in Danville, Pennsylvania. Thank you for joining us, Anne Marie.

Excellent. So to frame our conversation and discussion today, let me begin with our first learning objective, which is to recognize the varied presentations of narcolepsy to facilitate a prompt and accurate diagnosis of narcolepsy. Let's begin our discussion with a seemingly simple yet complex question. What is narcolepsy?

Clete Kushida:

Thank you, Rich. So narcolepsy is a rare, by rare meaning about one in about 2000 Americans have this condition, and it's an often debilitating neurologic disorder. And as you can see on this slide, the prominent symptoms include dysregulation of sleep-wake cycles, also disturbed, disrupted, nocturnal sleep. The sleep becomes very highly fragmented. And then it also affects a lot of different organ systems and functions, such as it can affect the ability to think, process information. It can also affect things like mood and anxiety stability and also shown here, a big component also is metabolic and anabolic dysfunction as well.

Richard Bogan:

Yeah, I'm always impressed that the normal human is awake in the day and asleep at night. They have state stability, and narcolepsy patients have state instability, which we'll talk about. And when we examine these individuals, they give us a window into sleep-wake processes as we understand that. And so these individuals really have quite prominent symptoms. You want to explore that?

Clete Kushida:

Yeah, absolutely. Rich, thank you. So this slide shows the five major symptoms of narcolepsy. So many of you are probably familiar with cataplexy, which is a sudden decrement in muscle tone, typically affecting the axial muscles and often a response to strong emotions such as laughter, anger, or surprise. Also, there are hallucinations, and the hallucinations can be auditory, visual. It can also be sematic, feeling things on the body. A key prominent symptom is the excessive daytime sleepiness that will come on oftentimes in a very sudden sleep attack-type feature where the person has an irresistible sudden urge to sleep during the daytime. And then also there's sleep paralysis, which is paralysis of the voluntary muscles. And then as mentioned in the earlier slide, sleep disruption. The person has disturbed or disrupted nocturnal sleep.

Anne Marie Morse:

I would also like to add in that I think one of the things that is always very helpful is that when we're thinking about these five main symptoms, recognizing excessive daytime sleepiness is the most sensitive symptom. One-hundred percent of patients with narcolepsy are going to have excessive daytime sleepiness. And as you've described, Clete, cataplexy is one that many people are familiar with in term, but it's the most specific symptom, meaning if you're able to list that history for cataplexy, you're really looking at the diagnosis of narcolepsy. I really love the fact that the way that this slide is illustrated is actually even using this nice acronym, CHESS, with the little pieces from the chess board as well, to help with viewers who may be attending this effort to be able to more easily recall these symptoms by being able to potentially even remember this nice little acronym.

Richard Bogan:

Well said. And I think the disruptive nocturnal sleep, and we're going to explore all this as we try to dig into the pathology and the pathophysiology and how these symptoms manifest. And as you say, not everyone has all these symptoms except sleepiness. They all have sleepiness. So now we have an idea about narcolepsy, let's bring our audience in to see how well they feel about diagnosing narcolepsy. So I'm asking you the question, how confident are you in your ability to accurately diagnose narcolepsy?

Thank you very much. We'll come back to that in a minute because you get another chance after our discussion to let us know what you think. So Anne Marie, let's talk diagnosis. What are some of the challenges in accurately diagnosing narcolepsy?

Anne Marie Morse:

So even though we went over what are the pentad symptoms that we typically are encountering, we're thinking about an individual with narcolepsy, the challenge that many of these patients experience is that there's other things that can look like narcolepsy. What I mean by that is when we're talking about excessive daytime sleepiness, even though it's the most common symptom that we encounter, there's other things that can cause excessive daytime sleepiness. The additional factor that adds in another layer of challenge is that patients with narcolepsy have a very high likelihood of having other medical, even other sleep, conditions.

So up to about 25% of patients with narcolepsy may also have obstructive sleep apnea [OSA], which may lead some providers to just stopping there, of saying, "Your sleepiness in the constellation of symptoms you're experiencing is purely explained by having obstructive sleep apnea." In addition to that, many times patients may also receive misdiagnosis. They may receive a diagnosis of ADHD, depression, or some other condition, which may delay the diagnosis and ultimately identify whether or not they have narcolepsy. When looking at this, we recognize that about 82% of patients are experiencing a delay of greater than one year from the symptom onset to the time of diagnosis and about a third of individuals with narcolepsy are experiencing greater than 10 years between symptom onset and the time of diagnosis.

Richard Bogan:

Yeah, it impresses me that these people are remarkable in terms of the REM dissociative symptoms and the profound daytime sleepiness. Why don't we diagnose them earlier? But when you really look at the prevalence of sleepiness in the general population if you're sitting in a primary care practice waiting room, 30% probably. Maybe not quite 30%, but up to 30% are sleepy and maybe 8% to 10% are pretty profoundly sleepy and they have 2,500 patients in their practice per doctor. And narcolepsy's rare—it's only one in 2000. So they only have one narcolepsy patient amongst all those other sleepy people. And as you said, when you're sleepy, you have problems with executive function thinking, memory, attention, mood, motivation, et cetera. So oftentimes, they get diagnosed as something else, quite frankly, a mood disturbance or cognitive impairment. So how does this translate into our nosology?

Anne Marie Morse:

So when we're looking at narcolepsy, it is important to recognize that the International Classification of Sleep Disorders [ICSD] provides criteria for two specific types of narcolepsy: narcolepsy type one [NT1] and narcolepsy type two [NT2]. We previously termed these conditions as narcolepsy with and without cataplexy, and sometimes we'll even reference that. But our advancements in understanding some of the underlying mechanisms for narcolepsy type one has refined us calling it that. What I'm referring to is the fact that in patients of narcolepsy type one, there's spinal fluid testing that can be done—so looking at the cerebral spinal fluid—to look specifically at CSF hypocretin or orexin. It has two different names because in 1998, 2 different research groups identified this molecule. One called it hypocretin, one called it orexin. Throughout this presentation, you may hear us reference either one of those, but just be certain that it's referencing the same molecule.

Anne Marie Morse:

So in those with narcolepsy type one, they generally are going to have low to absent levels where narcolepsy type two will have normal levels. This is important because some of those individuals may not have a history of cataplexy just yet. Outside of CSF testing, the approach in considerations are very similar between narcolepsy type one and type two. So number one, excessive daytime sleepiness must be present in a chronic format, meaning that it should be present for at least three months. You can use validated questionnaires such as the Epworth Sleepiness Scale [ESS] or even just eliciting a history of whether or not sleepiness has been present. Sometimes people will describe this in falling asleep inappropriately in sedentary activities or just difficulty maintaining an alert weak state. Then we'll do sleep studies that will include polysomnography, which is an overnight sleep test, and a next day multiple sleep latency test [MSLT].

On that multiple sleep latency test, we typically are going to see that the average time to falling asleep or the average sleep latency is less than or equal to eight minutes. In addition to that, we'll then also see that there's at least two sleep onset REM periods, meaning that a person is entering REM within 15 minutes. This will be present in either narcolepsy type one or type two. If any absence of CSF testing, the distinguishing factor between narcolepsy type one and type two, is the presence or absence of cataplexy. So really refining your history taking skills to identify symptoms of cataplexy does become really critical in understanding which diagnosis your patient may have.

Richard Bogan:

It's important for us to sort of think about the pathophysiology in orexin or hypocretin as a neuropeptide that you and I are really pumping out right now. That orexin is exciting other neuronal pathways and those neuronal pathways are dopamine, norepinephrine, serotonin, acetylcholine, histamine. Those are all real important to keep us awake. And in certainly type one narcolepsy, these individuals, the orexin neurons have been injured—probably in autoimmune abnormality. And so when you check their spinal fluid, they don't have orexin. And as a result, they have state instability, both in terms of sleep and wake, and they have a lot of REM pressure.

So that translates into our nosology. When you do an MSLT, you're asking, "Can you stabilize wakefulness in an environment where there's no sensory stimulus? What do you do?" Well, you fall asleep fast and you dream. And that's what we see. So it's an excellent explanation of the pathophysiology, which translates into how do we approach them both from a diagnostic as well as a therapeutic perspective?

So Clete, Anne Marie really provided us with an accurate diagnostic criteria that differentiate the two. But as we said earlier, if you sit in a primary care practice, there are a lot of sleepy people. So how do we dissect these overlapping symptoms as well as rule out other disorders?

Clete Kushida:

So Rich, for this slide, it shows some overlapping Venn diagrams. And you can see on the top that the blue is NT1, the green is NT2, and then the pink is idiopathic hypersomnia [IH]. And going from left to right to make it somewhat clear on this diagram, you can see that NT1 is characterized by the cataplexy. And as Anne Marie pointed out, that the CSF hypocretin levels are less than or equal to 110 picograms per ML. And then moving to that overlap between NT1 and NT2, you can see that they share certain characteristics. And one is the PSG REM latency. So this is the polysomnography REM latency on the overnight testing is usually less than or equal to 15 minutes. And then the MSLT, the multiple sleep latency test that is typically conducted on the next day after the overnight sleep study, will show greater than or equal two sleep onset REM periods on that MSLT. Also, there's the refreshing naps, the disrupted sleep, which was mentioned earlier. And the disrupted sleep is significant because it can be about two to three times greater compared to those without narcolepsy.

But also, the sleep paralysis and sleep-related hallucinations are shared. Now, if you look at the center of the diagram, you can see there's some symptoms or characteristics that are shared by all three conditions, and that includes excessive daytime sleepiness. Epworth Sleepiness Scale score greater than 10 out of 24 and a multiple sleep latency of less than or equal to eight minutes.

Moving onto the next category that is sharing between NT2 and idiopathic hypersomnia is characterized, as was pointed in the previous slide. No cataplexy. A normal CSF hypocretin one levels. There's a sleep inertia, so the sleep drunkenness or sleep confusion that appears immediately upon awaking from sleep. There's unrefreshing naps. And for both these conditions, you might have spontaneous remission. And then going onto the last pink area that shows characteristics exclusive for idiopathic hypersomnia, you have that less than two SOREMPs on the MSLT, and then you might have long sleep, which is defined as greater than 11 hours out of the 24 hours of a day. And typically, it's in the range of 12 to 13 hours.

Richard Bogan:

Yeah, these disorders of central hypersomnolence, they overlap and have different features. But the NT1 folks are the ones that we've done a lot of research on and have a lot of good understanding. The others, the pathophysiology is less clear. But let's explore the differential diagnosis.

Clete Kushida:

Yeah. So as Anne Marie had mentioned a little earlier, obstructed sleep apnea is a key condition that can also cause excessive daytime sleepiness. And as was pointed out, it's not unusual for an individual to have both narcolepsy as well as obstructive sleep apnea. And that's where the overnight polysomnography comes in handy as well as home sleep test because you can obviously detect if the person does have sleep apnea that might lead to excessive daytime sleepiness. But these other conditions also can cause the excessive daytime sleepiness such as just not getting enough sleep. Because as you know, the thing that can result in excessive daytime sleepiness is not only deficiencies in sleep quality as well as the sleep quantity. So the person just isn't setting enough time for sleep, that can cause daytime sleepiness. But other conditions such as medical disorders, psychiatric disorders as shown here, depression, they can also fragment the sleep and lead to the daytime sleepiness.

Clete Kushida:

Idiopathic hypersomnia, substance drug intake is also potential causes for excessive daytime sleepiness as well as things like Kleine-Levin syndrome, which can cause daytime sleepiness in sort of waves that appear periodic throughout the year, as well poor sleep hygiene. That overlaps with just not getting good habits in terms of sleep and resulting in daytime sleepiness. A periodic limb movement disorder can also fragment the sleep, leading to daytime sleepiness. And behavioral symptoms of daytime sleepiness, as you can see, these are some of the hallmarks of daytime sleepiness that can appear in patients that don't get enough sleep or have poor quality sleep. Now on the right side of the slide, you can see you can have a typical cataplexy as well as other causes that might be hard to differentiate, things like seizures, hypotension, and even a psychogenic causes that might mimic cataplexy. And lastly, in terms of hallucinations, there's conditions that can result in hallucinations at night, and those include schizophrenia, where hallucinations are a hallmark of the diagnosis, as well as you can have it also with sleep or night terrors, as well as panic attacks.

Richard Bogan:

Yeah, I think there are a couple of points also. The peak incidence is right in the teenage years, right around 15 plus or minus. And a lot of those individuals face delayed puberty. So insufficient sleep can really fool us, and that's obviously one reason we like sleep diaries and actigraphy and some other things. And then of course, the other point is when we are in REM sleep, we're paralyzed, we can't move. And because of this REM pressure or disinhibition, I should say, these folks may awaken with sleep paralysis, and they may actually panic or feel short of breath. So they may mistake sleep paralysis for sleep apnea, interestingly enough. They're saying they can't breathe, they're choking or whatever. But I think it's important for us to think about these REM dissociative symptoms. Vivid dreams, colorful. If you wake up and the dream is still going on, you'll hallucinate or you could have sleep paralysis as well. So when we think about the pathophysiology, it starts to make sense. So Anne Marie, what are some of the approaches in diagnosing narcolepsy patients?

Anne Marie Morse:

Just the same as in any patient that we see, a careful history is really quite important. Not only to elicit the history of those pentad symptoms and to distinguish the symptoms of narcolepsy away from some of those other differentials that Clete had just reviewed but also to understand the burden of the disease on the individual. One of the questions that I make sure I ask all of my patients who have hypersomnia is, “What can't you do because of your hypersomnolence?” This really helps frame the picture into individualized treatment strategies later on, and I think it's one that is an important seed the plant right now when we're talking about narcolepsy overall and what the burden of that is and how do we approach treatment. After a careful history and there's a suspicion for narcolepsy, the next steps are really that approach to figuring out is this existing, or is it one of those other differentials?

Anne Marie Morse:

Some steps we'll take is doing a sleep diary plus or minus actigraphy. Actigraphy is typically a wrist worn device that will help in monitoring what someone's sleep and weight patterns are. Some institutes have this, not all institutes. And so if it is available, it's something that we do encourage. We generally will do this for about two weeks, sometimes as long as four weeks, and typically right before we do the polysomnography or overnight sleep test and the following day, MSLT. When we're doing the overnight sleep test, some of the things that we're looking for is number one, are they sleeping at least six hours before moving on to the MSLT to enhance the reliability of the MSLT. Other features that may be present and give us some clues to the presence of narcolepsy may include, as has been mentioned earlier, a sleep onset REM period.

When they fall asleep, do they go right into REM sleep? This isn't present in everyone, but it is a key feature that if you do see it, it generally is really going to pique your index of suspicion that narcolepsy is existing. Some other things that you may see is a highly disturbed nighttime sleep. You'll see not only increased awakenings throughout the night, but you sometimes will also see very irregular sleep architecture, almost a blending of maybe NT2 sleep with REM sleep, which again can make it very difficult to score. Another feature does have to do with that REM dissociative phenomena. So many of these patients may also have features of something called REM without atonia or even REM behavior disorder being captured on the overnight polysomnography. Once you complete that overnight polysomnography, you're woken up the following morning, and then you are going to complete the multiple sleep latency test. This is four to five opportunities to nap where we're looking at do you fall asleep? If you do, how quickly do you fall asleep? And then do you go into REM sleep? Again, emphasizing that that typically is less than eight minutes and then that we typically are seeing two or more sleep onset REM periods.

The maintenance of wakefulness test that is described here, we don't typically utilize as a part of the diagnosis but may incorporate this strategy as a part of the management, especially when we're looking at things like operating heavy machinery or driving, to really identify how well someone is able to maintain alertness. CSF hypocretin isn't used universally, but can be another strategy that you can apply to be able to identify those individuals with narcolepsy type one. It's not typically useful to be able to distinguish whether or not someone has narcolepsy type two or idiopathic hypersomnia because of the fact that those levels are going to be normal. So I always recommend that if you do use CSF hypocretin, to use it with some sensitivity that if it's normal, it still doesn't exclude narcolepsy type two. So that can still be on the table.

Richard Bogan:

Yeah, those are important points. And I think another important point is the disrupted nocturnal sleep because I have had patients present as insomnia because narcolepsy patients are very aware of their sleep. They wake up a lot, they dream a lot. And where most people go to sleep and wake up and there's nothing in between, they have busy sleep. So they interpret that as insomnia. So, "My sleep is disturbed, therefore I'm sleepy." Whereas in type one, the orexin deficiency creates state instability so they bounce all over the place. And I really like your call out on the short REM latency on the PSG. We actually looked at 100,000 sleep studies and saw a prevalence of close to 1% short REM length. When you see it's very specific, not very sensitive, but very specific. Discussing that, give us some patient reported outcome measures that we can use to guide us.

Anne Marie Morse:

Sure. When we're looking at, just as you've described earlier, trying to identify the patients who have narcolepsy, you really need to have that high index of suspicion. I recognize that there is competing priorities in everyone's clinical practice, and we're all having time crunches, so really trying to help us out, we can use some validated scales. Some things that I tend to find that can be helpful are something like the Epworth Sleepiness Scale. Most of our sleep clinics do utilize this to be able to identify and characterize the degree of sleepiness that may be present, not only in narcolepsy, but for a variety of different types of sleep conditions. This also can be useful in other clinical settings, such as in a primary care practice, to better identify and quantify the severity of sleepiness.

The Swiss Narcolepsy Scale, I will say, is not one that I typically will utilize in my practice, but I do find it's something that can be helpful, especially in a primary care practice or practices that have less comfort and familiarity with the diagnosis of narcolepsy. This is a validated, self-reported assessment that is five questions, and based on these five questions, can give you, "This patient is at risk for narcolepsy," or you can feel relatively reassured.

Richard Bogan:

It's obviously heavily weighted for cataplexy, but here's the Epworth score. My Epworth score is six. I don't know what yours is, but these people with narcolepsy have very high Epworth scores.

Anne Marie Morse:

You're correct. Patients who have narcolepsy very frequently will have elevated Epworth Sleepiness Scales. What is the Epworth Sleepiness Scale? This is giving eight different sedentary activities, meaning things that you're not very active, and asking the person to rate, "What is your propensity to doze?" It's important to recognize that dozing means you're having that inability to maintain wakefulness. It does also include and capture that you actually fall asleep. We ask, "Does it never happen, rarely happen, sometimes happen, or frequently happen?" Based on this scale, it's out of 24 points, those who are scoring greater than 10 is consistent with a pathologic degree of sleepiness. Most typically, individuals who have narcolepsy have very severe degrees of sleepiness and maybe scoring greater than 16. I say this with caution because of the fact that not all individuals identify with this way of screening for sleepiness. I know that in my practice, I've seen people who have fallen asleep at the wheel, are seeing me because they had a motor vehicle accident, and that was the call to action.

They come in and they have an Epworth of five, and it's because of the fact that they don't identify with these questions.

Richard Bogan:

Right.

Anne Marie Morse:

It's important to balance it again with that clinical history of what they're describing, in terms of sleepiness.

Richard Bogan:

Yeah. I think that's very important. And I would challenge the attendees, if you see tired people, if you see someone with executive function abnormality, if you see someone with a mood disturbance or attention problems… They might be sleepy, so do the Epworth. I would guarantee, if you do the Epworth score on any of those people over a period of two weeks, you're going to be surprised at how sleepy some of these folks are. I don't know if you want to spend much time on this, but this is the Swiss Narcolepsy Scale, the questions in specific.

Anne Marie Morse:

Sure. I always make the joke that, if you're going to use the Swiss Narcolepsy Scale, you do need a PhD in calculus, but the reality is that this is readily available online, and they can do all the calculations for you. As you can see, the scoring is a series of calculations in order to be able to create a more negative score that would make you more suspicious for narcolepsy. The reality with the Swiss Narcolepsy Scale, again, this is something that is really quite helpful for people who may have less of a degree of comfort, of even thinking of when to screen for patients with narcolepsy. A practical approach that many people could consider is that, if you have individuals that you're using the Epworth Sleepiness Scale, and you're identifying sleepiness is present, that you could potentially add this as a second layer to be able to help you to be able to bucket patients into, "Is this someone who I have to be worried about narcolepsy, because I still am having a developing comfort with recognizing those patients?"

This may be able to be a tool that will help in filling that care gap for you.

Richard Bogan:

Yeah. Questions four and five, where you ask about knees buckling and cataplexy when you're angry or, do you have symptoms in your face? That points out… Obviously, this is a European group of people, where they define cataplexy. That's heavily weighted, so it's important to ask very specific questions about cataplexy.

Let's bring our audience back in, I'm going to ask another question. How confident are you in your ability to accurately diagnose narcolepsy?

Anne Marie Morse:

Especially after all of this great knowledge that we've shared and contributed. Again, I really hope that the conversation that we're having today is actually creating some opportunity for people to fill some knowledge gaps that maybe they thought that they've had. I do hope that, so far, we're going to see some improvements here. That looks great.

Richard Bogan:

Yeah. I don't know that people that were not at all confident...6% drop down. Yeah, I like that. Somewhat confident, confident, and extremely confident. We're getting somewhere, this is encouraging. As a result, we're going to keep going.

Anne Marie Morse:

We'll keep the torture, right?

Richard Bogan:

There you go. Yeah, there you go. So Clete, let's begin our discussion with the neurobiology of narcolepsy. We've already alluded to that to some extent, and particularly how NT1 differs from NT2. This will help magnify some of the comments.

Clete Kushida:

Thanks, Rich. As you mentioned earlier, one of the hallmarks of NT1 is the loss of the orexin/hypocretin neurons. As you can see on this cartoon, this destruction is thought to be the principal cause of NT1. It's thought to be an autoimmune process, and with the destruction of these neurons, that leads to a lowering or absence of C-S-F hypocretin, which in turn can lead to the classical symptoms of NT1, particularly the cataplexy, as well as the excessive daytime sleepiness.

Anne Marie Morse:

Hey, Rich. I'm thinking that we may have just skipped an opportunity for the audience to tell us about their ability to consider a differential impact of narcolepsy type one versus type two. We would love to have this feedback, so this way we can see how we're able to impact their recognition and consideration of this. It's just this next slide right here.

Richard Bogan:

Yeah, I glossed over that, didn't I?

The question is, how often do you consider the differential impact of narcolepsy type one versus narcolepsy type two?

Excellent. All right, we'll come back to that in a minute, but again, thank you Clete for your discussion about the importance of the neuropeptide orexin. Let's explore this neurobiology here.

Clete Kushida:

Yeah. For NT2, as you can see by the slide, it's less clear. In particular, if you look at the lower left graph that's shown, you can see that the gray is daytime controls. I'm sorry, on the Y-axis are CSF hypocretin levels. As you would expect with the gray bar, with the control, it's within the normal range. Then you have narcolepsy with typical cataplexy, which is shown in the red. As you would expect from the prior slide, due to destruction of the hypocretin neurons, there's a decrease or even an absence of hypocretin that's shown in the CSF. The blue and the green, respectively, show narcolepsy with atypical cataplexy in the blue and narcolepsy without cataplexy. What you can see is that, for the blue and green bars, it's not quite getting to the normal range, but it's certainly above that of those with NT1.

It is very difficult to characterize at this point, in terms of what is a pathophysiology of NT2. Could there be a biological dysfunction? Shown on the lower right hand panel, we know that hypocretin, as well as in conjunction with the monoamines, dictate wakefulness or control wakefulness, but it's balanced by GABA, which is thought to influence sleep. All of these monoamines, hypocretin, GABA, certainly might play a role in the pathophysiology of NT2, but at the current time, it's not well defined.

Richard Bogan:

Yeah. It's important for us to recognize that this orexin/hypocretin is a really important neuropeptide for state stability, and these folks really have state instability as a result. Certainly, the type one narcolepsy, the others remain less clear. Clete, as a result we see disturbed nocturnal sleep, which is, unfortunately, very common in narcolepsy, maybe approaching 70%. Can you elaborate on the role it plays on the quality of life and functioning with these individuals?

Clete Kushida:

Absolutely. This study looked at 57 participants with NT1. The mean age was about 46 years for this cohort. As you can see, when they looked at sleep, 71% of this group were unable to sleep without awakening and about 31% awakened at night to eat. It's a tip off right here that, either both were awakening and they would also have extended periods where they were unable to fall back asleep. Also, in this population, they looked at those with sleep apnea, of those with NT1, and 43% of the population exhibited loud snoring, which is one of the characteristic features of obstructed sleep apnea. And 21% experienced apneas or complete pauses in their breathing, and about 20% awaken with shortness of breath during the night. In terms of waking up, on the lower panel, you can see that 50% felt unrefreshed; it took them about 17 minutes, on average, to get up in the morning, and about 24% experiences sleep drunkenness, where, as was described earlier, upon awakening, it takes a while for their brain to become online, so to speak.

Clete Kushida:

They're confused. They're unable to think clearly. Their focus on attention is impaired. The top portion of the slide shows that there's definitely difficulty in both the fragmentation, the difficulty awakening, as well as the ability to have cognitive function during the daytime upon awakening. In a sample of close to about 250 patients with NT1, you can see that disturbed or disrupted nocturnal sleep severity was associated with higher scores on the Narcolepsy Severity Scale, which you would expect. As well as higher sleepiness, increase in anxiety and depressive symptoms, as well as on and off dysfunction, and overall just a worsened quality of life, because, as you imagine, these patients not only have the excessive daytime sleepiness, but if they're not kept fairly stimulated during the day, they can also fall asleep. But if they get too excited, they can have bouts of cataplexy. It's a very impaired quality of life for these individuals.

Richard Bogan:

Yeah. It raises the question or points us in the direction to know that this neuropeptide orexin is really important for state stability and it has a huge impact. It makes you breathe, and it has effect on hypothalamic pituitary axis and metabolic function. When we see these people who don't have orexin, we began to see how it might affect state instability.

What about the vivid dreams? I'm impressed with the title of, "Wide Awake and Dreaming," a book written by a patient with narcolepsy. Do you have any comments about the dreaming?

Clete Kushida:

Even people without narcolepsy can have these dreams. Most of the time, 90% or more, occur during REM sleep, which also have it in non-REM sleep. Individuals with narcolepsy, because of this REM dysfunction, it can create this borderland between the vivid dreams and the hallucinations.

Vivid dreams can occur, both in individuals without narcolepsy, but because of the sleep fragmentation, the sleep loss that occurs particularly in those with narcolepsy, makes these vivid dreams more apparent, because the REM sleep is fragmented. The person awakens and recalls, "Yeah, I just had this very pronounced, very vivid dream."

Richard Bogan:

I'm impressed with that, because normally REM latency should certainly be north of 60 minutes. I actually ask patients who have sufficient sleep, "If you do fall asleep in the daytime or take a nap, do you dream?" Oftentimes, in narcolepsy, patients say, "As soon as I fall asleep, I start dreaming and they're vivid, lucid dreams." Sometimes they even briefly hallucinate. That's the REM dissociative state, but I think you can see some issues of REM latency, if you want to talk about that.

Clete Kushida:

Yeah, yeah. This is a rather interesting study that was published in 2018. It was actually part of the European Narcolepsy Network. On the Y-axis, you see time in minutes, on the X-axis, you see number of SOREMPs. The number of SOREMPs went from two to five, but what is apparent on the difference between NT1, which is the pale blue, versus the NT2, which is the dark blue, you can see that there was a significant difference for the mean sleep latency between NT1 and NT2. Down the road, there should be further study looking at this, because it might lead, later on, to perhaps phenotyping NT1 and NT2, based on the mean sleep latency of the MSLT. What was further interesting about this study was that they also looked at hypocretin levels for the NT1, NT2. They found out that there was a significant correlation of the REM sleep latency shown on the slide with hypocretin levels for NT1 but, as expected, not for NT2.

Richard Bogan:

Anne Marie, I'd like to bring you into this discussion as well. What are some of the differences that you've seen in your clinic between patients with NT1 versus NT2?

Anne Marie Morse:

With NT1 versus NT2, we very frequently are trying to understand that burden of disease. Clearly, the most striking difference is the description of cataplexy and how that impacts day to day functioning. Many times, this can impact them emotionally, because a lot of people describe themselves as feeling as though they're clumsy individuals. They'll be derogatory of themselves saying, "I'm just stupid," and, "I make all these mistakes." That can be a struggle, but also, there's a safety hazard there. That is a major distinction that I may see sometimes between NT1 and NT2. When you're looking at this study in particular, what's very interesting and striking to me is that, if you reflect back on the question I ask all my patients, "What can't you do?" or, "How do you feel disabled from the symptoms that you're experiencing?", many times they will associate with symptoms like depression, anxiety, fatigue, or other type of functional impairment. When you're looking at this particular study that utilizes the PROMIS scale, which is a patient reported outcome scale, to try to really quantify what these differences are, you do see that there is a very high similarity between overall burden that narcolepsy type one and narcolepsy type two are experiencing, even though they may not have the same exact phenotype based on the pentad symptoms. There does seem to be a very similar experience in regard to overall disability that patients with narcolepsy type one and narcolepsy type two may experience.

Richard Bogan:

Yeah. I'm impressed with what you said about the cataplexy. You would think most people who had cataplexy, loss of muscle tone when they get excited, laughing, angry, or strong emotion, would recognize that as being abnormal, but so many times I've heard, "It's just me."

There's something interesting here, where the patients are before they enter a clinical trial. I would really encourage you to look at baseline data. It's boring, but it's how the patients present to us, in terms of their age distribution, their severity, and other demographic characteristics. Obviously, we examine where patients are after a treatment intervention compared to baseline, but I wanted to briefly point out what some of the baseline data may show. For example, in one clinical trial at baseline, 98% of patients were at least moderately ill. These individuals are significantly impacted. That means we have some pretty ill patients out there, who are pretty profoundly sleepy with these Epworth scores—16, 17, 18—and we need to do our very best to improve their symptoms and quality of life.

Anne Marie, you talked about the sleep symptoms and the mood disorders associated with narcolepsy, but how does narcolepsy impact quality of life and functioning since we've talked about that?

Anne Marie Morse:

I think it's important to recognize, when we're talking about a disease, we're talking about something that affects human lives. They're not in a bubble, and they don't only identify by those pentad symptoms or their disease state, but really describe what their everyday life is like. Because of the fact that you're talking about dysfunction that can really impact all different facets of life, you may see things like brain fog or memory problems. People will describe this cognitive dysfunction that, even when treated with stimulants or wake promoting agents and they're feeling more awake, there's still these residual symptoms of feeling like their cognitive processes aren't as sharp as what they would like them to be. They'll describe that they're having features of falling asleep throughout the day and clearly, this is going to really interfere with their ability to be at their top performance.

Many times, when I talk about narcolepsy, I always will reflect on the fact that it's a recurring theme, that patients will describe that time is of this critical essence in their life, and that they're being robbed of time by sleep. Because of this dysfunction, or this sleep state instability that you describe, patients are constantly having to make these decisions of where they're going to invest that time. That clearly puts a major strain on all types of relationships, whether it's business relationships, romantic relationships, or friendships. We see that these individuals have higher rates of non-marriage. We see that there are higher rates of unemployment. Why? Because of this struggle of needing to balance and figure out where they're going to invest their energies. Clearly, because of both the excessive daytime sleepiness, as well as potential cataplexy, this can have significant impact on the likelihood of having accidents, including motor vehicle accidents.

It is really important, when we're thinking about these patients with narcolepsy, it's not just a matter of treating a sleep disorder; it's a matter of impacting a more global impact that these individuals are experiencing on an every single day basis. Really, the call to action is trying to identify treatment strategies that are comprehensive and taking into consideration, not only those pentad symptoms, but also these more global psychosocial quality of life and work functioning considerations.

Clete Kushida:

If I can make a quick comment about that. Particularly in this first panel, it shows the brain fog. That has gotten a lot of press recently, because of the brain fog associated with long COVID. But it's actually one of the more frequent comments that patients with narcolepsy have, that they can't get their brain to function. What's interesting about patients with narcolepsy is, it appears that it affects the three major domains of neurocognitive function. It affects their attention and visual...as you would expect their ability to stay awake during the day, but also, as pointed out on the slide, learning and memory are also affected, as well as executive and frontal lobe function. That can cause impairments as shown in the last panel of the increased risk of accidents while driving. These accidents...it's been demonstrated that it can be caused by the daytime sleepiness, but there can also be some subtle impairments of their higher order function in being able to perform complex activities like driving.

Anne Marie Morse:

That's such a great-

Richard Bogan:

That's a very good point.

Anne Marie Morse:

That's such a great point.

Richard Bogan:

Yeah. Yeah. Patients talk about speed of processing, so the brain is slow. Speed of processing is slow, so reaction times, divided tasks, all those things are significantly impaired, which obviously affects you all day long, whether you're working, social, or whatever. Anne Marie, this gives us a chance to hear from the patients, what they say. Do you want to share this data?

Anne Marie Morse:

Yeah. It's really important to always have the consideration of the patient's perspective. The reality is, we wouldn't be a field without the patient and without the patient contributing to us having more advanced understanding. In a survey that looked at 200 individuals living with narcolepsy, there was significant description of the disability they're experiencing. Sixty-eight percent say that they never feel like a normal person and these are taking into consideration individuals who are being treated. Eighty percent describe that it's a daily struggle, which would be why they're not feeling like they ever feel normal. Seventy-six percent are describing that it has affected very important moments in their lives. Being physically present is not the same as being emotionally or mentally present. So even when they are at a wedding, or an important birthday event, or any type of these celebratory experiences, they may be physically there, but sometimes will describe themselves as almost feeling like a shell of themselves and not even being able to potentially recall some of these things.

Anne Marie Morse:

Thirty-seven percent have described failing a class or withdrawing from school because of narcolepsy. It's important to recognize that as had been mentioned earlier, the typical most common time of onset is between the ages of five and 16 years of age. This is a critical neurodevelopmental period in life, where there is very common experience of having deteriorating grade performance.

There also is a critical period where if it's at teenage years where we're applying to school and we're falling off the cliff, that we may not end up going even into college. So, there are academic differences with individuals who have narcolepsy. And then 25% have been fired from a job or demoted because of symptoms. This is including people who even after the diagnosis and have been treated, may experience these same types of consequences. And 60% of those who are employed are worried about losing their jobs because of their symptoms. Because of this, many times, people won't even endorse that to their providers, recognizing that this is a condition that is protected by the Americans with Disabilities Act and would warrant in many situations, the ability to provide accommodations in a work environment. This again, is taking a look at narcolepsy on a more global scale and recognizing all these nuances that are so critically important for the patient. But sometimes we don't necessarily incorporate in terms of our treatment strategies.

Richard Bogan:

Anne Marie, it's interesting, and Clete alluded to this as well, but when we treat our patients, and we're going to talk about treatment, but when we treat our patients, sometimes the sleepiness certainly improves it's not normal, but the patients still complain of that brain fog and speed of processing. I've had them say, "Doc, I don't fall asleep." Or "I don't take a nap, but, but I'm, something's still not right. I don't feel good." And it's important for us to recognize that.

So we're going to go to another audience response, but before we do, I have two quick questions. Now I want them to be fairly quick. One goes to you, Clete. So I have a patient has sleep paralysis and hallucinations. Is this narcolepsy? But the patient is someone who has a history of drug abuse and insufficient sleep. They're not sleepy, but they do have these REM dissociative symptoms. Is that narcolepsy?

Clete Kushida:

That's really hard to tease apart sometimes because as you pointed out, with the history of drug abuse, as well as, some insufficient sleep, all bets are off because a person can have these hallucinations as well as sleep paralysis, just because of the fragmented sleep, the insufficient sleep. So that's where it would warrant a really deep dive in obviously the history, as well as, as probably getting a sleep log, sleep diary, just to see what the sleep is like. And then if it's inconclusive at that point, that would warrant bringing them in for an overnight PSG and possibly an MSLT to more actively characterize these patients.

It's really hard sometimes especially with an individual that has poor sleep habits, has fragmented sleep due to a whole host of other causes. Even things like obstructed sleep apnea, any type of fragmented sleep can also result sometimes in these hallucinatory behaviors, as well as some unusual sleep paralysis because of the apneas clustering around sleep and fragmenting sleep. So yeah, it's a real tough thing and you would have to use further tools.

Richard Bogan:

I think you answered it. Sleep paralysis, hypnagogic, and hypnopompic hallucinations are not definitive from narcolepsy. The general population can have that, particularly if they're sleep deprived, but, you can see it in general population as well. But cataplexy, that's narcolepsy.

Ann Marie, what about depression? So do you see much depression and anxiety? Is there a correlation in narcolepsy, and do we treat it?

Anne Marie Morse:

Sure. So what we do know about individuals with narcolepsy is that based on the literature review, there is a higher rate of seeing psychiatric comorbidity. About 30 to 40% of individuals with narcolepsy may also either come with a diagnosis, meaning that before they were diagnosed with narcolepsy, they had it or may develop it.

What is challenging about seeing the diagnosis of depression in patients with narcolepsy is understanding whether or not is this related to the diagnosis of narcolepsy. I have CNS or brain dysfunction and that is causing narcolepsy. Is that same brain dysfunction causing the depressive symptoms as well? Is it this the fact that I can't function the same way as my peers, is that causing depression or is it really a matter of stigma?

Is it because of the fact that when you look at narcolepsy, the media sensationalization of it is illustrated through movies like Deuce Bigalow, where the depiction of the individuals who have narcolepsy are relatively useless. They're clumsy, falling all over to place, always falling asleep in inappropriate situations, and really look as though that they don't rise too much. We do definitely see this when we do see depression, it's critical to treat it. When you're talking about the treatment of narcolepsy, you're treating the whole person, and if there's symptoms that are consistent with depression, you should partner with a psychologist and or a psychiatrist to really understand how to optimize those symptoms.

It is important to recognize that people who are depressed even without narcolepsy will also describe these features of brain fog and cognitive slowing and so that again may be another contributing factor to when we are seeing symptoms of brain fog.

Richard Bogan:

So now how often will you consider the differential impact of narcolepsy type 1 versus narcolepsy type 2?

So I think we're, we're getting it, we're beginning to see that sort of understanding this pathophysiology and seeing that there are differences in the phenotype. I think this is very helpful. So let's move on to our final segment, and we're getting lots of questions, great questions. I wish we had more time, but we'll get to as many as we can, but let's move on to our final segment where we will evaluate the latest safety and efficacy data on novel and emerging strategies to reduce the burden and impact of excessive daytime sleepiness and cataplexy in adults with narcolepsy.

Richard Bogan:

So how often are you using the latest clinical evidence to develop an effective treatment plan to reduce the burden and impact of excessive daytime sleepiness in patients with narcolepsy?

All right. Thank you very much. So Clete, as we begin to discuss treatment, what are the, what are our ideal goals for our patients with narcolepsy?

Clete Kushida:

Yes. Thanks Rich. So this slide is based on a publication by Dr. Michael Thorpy, one of our close colleagues who studies narcolepsy. As you can see one of the key things is to reduce the excessive daytime sleepiness and that's characteristic of both NT 1 and NT 2, and then to control the cataplexy of NT 1. Also, these symptoms like the nightmares, the hallucinations, the sleep paralysis, and disturbed nocturnal sleep [DNS]. You know, we've been focusing on a lot of the daytime sleepiness as well as the cataplexy, but, but these symptoms can also be as troubling sometimes as some of the other symptoms. So it's important to also think about a therapeutic approach, to work on the consolation of symptoms that the patient might be experiencing. Also, improving the psychosocial dysfunction and quality of life is key and as I pointed out by Anne Marie this is a substantial impairment in patients with narcolepsy.

In the back of your mind when managing patients with narcolepsy, you should always think of safety. Are these patients at risk at night or during the day, and are they at risk for the public? Oftentimes a difficult discussion is with driving. We all recognize that driving is a symbol of autonomy in modern life, but it is something that does carry a risk, particularly if a patient with narcolepsy, has a near miss due to the sleepiness, or has impairment in driving due to the cataplexy.

Also, very important is any of these treatments in these days of precision medicine and personalized medicine, you have to think of how to you weigh the risks and the benefits of each one of these pharmaceutical therapies. The good news is that there's a lot of new as well as emerging therapies for narcolepsy that are going on right now.

Richard Bogan:

Yeah, there are a lot of different approaches to the treatment and some are FDA approved. Some, as you say, are evolving, would you review some of our therapeutic options?

Clete Kushida:

Yeah. So, this slide summarizes the current FDA-approved treatments for narcolepsy. So the first column just shows the drug. The second column shows the mechanism of action. The third column shows the dose, and then it shows the indications, the excessive daytime sleepiness or cataplexy. And then also whether or not they're indicated for adults, children, or both.

So you can see going down from modafinil, armodafinil, as you would expect, the primary action would be for indication for existing daytime sleepiness in adults. It shows a mechanism action here. Solriamfetol is a dopamine norepinephrine reuptake inhibitor. Primary indications for excessive daytime sleepiness for adults. Pitolisant is a histamine H3 antagonist, also an inverse agonist, and it's indicated for both excessive daytime sleepiness and cataplexy. And both sodium oxybate (SXB) and the lower sodium oxybate preparation (LXB), the mechanism of action is a GABAB agonist. And you can see it's indicated for both excessive daytime sleepiness as well as cataplexy in both adults and children. And lastly, there's the amphetamines and methylphenidate, and what's important about this particular slide is right now they're approved for narcolepsy, but not specifically for either cataplexy or EDS. That's why there's not a checkmark under, under the fourth active columns.

Richard Bogan:

Yeah. So, it's interesting, we don't orexin on here. So these are all downstream receptors, and I remember your seesaw with dopamine, histamine, all those promoting wakefulness. So we're downstream targeting some of these wakefulness promoting neurons, exciting them, but oxybate is a GABAB agonist. You give it at night. How does that work?

Clete Kushida:

Yeah, so, obviously the main source of action is with the excessive sleepiness as well as the cataplexy, but it also does a very good job in improving the fragmentation of sleep at night as well.

Richard Bogan:

Mm-hmm (affirmative).

Clete Kushida:

So it does help to consolidate sleep and that's why it interplays with a gap assistant. And one thing that ducktails on this, that's kind of a very important point that you've jogged my memory about is that if you look at the side effects of these medications, all these medications with the exception of oxybate do have insomnia as one of the side effects. Whereas with the oxybate, as I was just discussing, insomnia is not one of the common side effects and in fact, as mentioned, it does tend to consolidate the sleep at night and reduce the fragmentation, reduce the disturbed nocturnal sleep. If you look at things like delta power, particularly in the first third of the night, it actually has been shown to enhance the delta power as well in the first half of the night.

Richard Bogan:

Well, you talked about safety. Anne Marie, all of the FDA-approved agents for narcolepsy have some side effects and safety considerations. So, can you review that for us?

Anne Marie Morse:

Sure. So when we're looking at the medications that are available to treat narcolepsy, we generally are kind of packaging them out to saying wake promoting agents. So in this slide, pitolisant up, your oxybate agents. So sodium oxybate and lower sodium oxybate, which is as just been described those nighttime medications, and then your traditional stimulants, such as your amphetamines and your methylphenidates.

As have been described, all of them really have a characteristic in regard to potentially augmenting or increasing the likelihood of experiencing insomnia. So someone with a primary complaint of there being significant disturbed, nocturnal sleep, I'm definitely going to be leaning more towards the sodium oxybate or low sodium oxybate for treatment for those individuals.

Now, it is important that when you do have individuals who have preexisting comorbid psychiatric concerns, that you are having a very open dialogue about the potential of any of these medications exaggerating those symptoms and so really having a tightknit relationship and conversation about anxiety and any other of these mood disturbances. You also will see that some of the other things that may occur include decreased appetite or dizziness, headache, things like that, a piece that I always do like to call out is that in the studies looking at oxybate and sodium oxybate both in the clinical trials, as well as the open label extensions. We did note that there was a decrease in weight that was really noted more so in the pediatric studies than the adult studies. Although we do see a similar signal there, and I always like to call that out because we have talked about the metabolic differences in the adult, in patients with narcolepsy.

One of the things in the pediatric side of the world is that we do commonly see that in individuals that have narcolepsy, that we can experience precocious puberty, as well as significant weight changes. It's not uncommon when I have a patient in front of me who has narcolepsy, that I can look at their growth chart and predictably tell when the onset of their symptoms were. So, although it's listed as an adverse event for many patients, this is actually a welcomed symptom to experience because the fact that it does help them with another area that they may be struggling with.

Richard Bogan:

Yeah. I think these are all seen as active drugs. They probably can increase sympathetic tone and their nuances here in terms of how they're metabolized. Solriamfetol, for example is excreted in the kidneys, so less drug-drug interaction. So there are all these nuances that can be discussed. Clete, we're getting short on time, so I'm going to ask the faculty to be very precise. Let's talk about the efficacy of these various agents let's begin with solriamfetol.

Clete Kushida:

Yeah. So just very briefly as you recall solriamfetol is a norepinephrine-dopamine reuptake inhibitor and it's indicated for both the excessive daytime sleepiness and narcolepsy type 1, as well as obstructive sleep apnea. And as you can see here on the left panel, on the Y-axis is the maintenance wakefulness test in minutes and on the right it's the Epworth change from baseline. So, what's demonstrated here very nicely, is the dose dependent relationship for those with cataplexy and without cataplexy who are taking solriamfetol. You can see that there is an improvement, both in objective, as well as subjective of daytime sleepiness.

Richard Bogan:

Yeah. I'll point out those 300-milligram dose is not FDA-approved, but it was in the research study. So, take that into account.

Clete Kushida:

Right and this further just shows on the left panel, it's a patient global impression of change [PGI-C] versus placebo, and what's demonstrated really nicely here is you can see that with solriamfetol there's higher scores that correspond roughly to the dose in terms of the CGI scores, and then on the right panel, which shows work impairment. So you can see the baseline in terms of mean overall impairment was reduced for both the work impairment as was activity impairment across the 40 weeks.

Richard Bogan:

Yeah.

Clete Kushida:

Right and so then, and next slide also very briefly because of the interest in time, as you recall, the Pitolisant is an H3 receptor antagonist or reverse agonist. What it shows over here, is that there's two placebo-controlled stud[ies]. One is HARMONY, one HARMONY CTP. For both these, it shows the percentage of patients with an Epworth Sleepiness Scale score reduction of greater than, or equal to three points across the two-to-eight-week period of time. It's comparing both pitolisant versus placebo. I've shown on the left two panels, a strong improvement in percentage of patients in terms of the Epworth Sleepiness score reduction compared to placebo.

On the right-hand portion, it's greater than a 50% reduction in the weekly rate of cataplexy attacks and you can see that over time, there was a significant improvement in total pitolisant versus placebo in the percentage of patients that had this decrement in cataplexy attacks. This response for the excessive daytime sleepiness, it was mainly in week three and for week two in the complexity.

This slide just shows the efficacy of narcolepsy with high EDS burden both by the Epworth Sleepiness Scale, which is shown on the left side as well as the objective as seen sleep in minutes. And as demonstrated by end of treatment significant improvement in pitolisant in reducing the Epworth Sleepiness Scale, score and significant improvement in improving the sleep latency compared to placebo.

Richard Bogan:

Yeah, this is histamine and I think it's good to point out that this is one of the two drugs approved by the FDA that treats cataplexy. The other drugs are more wakefulness promoting, but the oxybate molecule pitolisant, both treat sleepiness and cataplexy, both approved by the FDA. So, speaking of the lower sodium oxybate trial. Clete, twice-nightly, lower sodium oxybate 92% less sodium than sodium oxybate. Tell us about that.

Clete Kushida:

Yeah. You can see that the left panel just shows a change in Epworth scores to subject to measure, as well as on the right side, it's a number of cataplexy attacks. And you can see that the lower sodium oxybate compared to placebo, there was a significant improvement in the change, in the Epworth Sleepiness Scale score, the right side, a significant decrement, as well as in a number of cataplexy attacks. So the lower sodium oxybate similar to just regular sodium oxybate has a positive effect in both the subjective sleepiness, as well as the cataplexy attacks.

Richard Bogan:

Yeah. I want to remind the listeners, this was a double-blind withdrawal so, patients were on stable dose and then they were withdrawn placed on placebo for two weeks and so, when you look at the effect size, the p values are quite high, but you're like, wait a minute, that's a signal that is not as impressive, but it's because of this double-blind withdrawal. What about the cataplexy?

Clete Kushida:

Yeah. So this slide shows on the Y-axis cataplexy free, and then on the X-axis, it shows the week. What you can see at the stable dose period, at the end of it, when all the participants were on the stable optimized dose of lower sodium oxybate that there were greater cataplexy--free days of the week with not only sodium oxybate but also with sodium oxybate other anti-cataplectic drugs, as well as those that were anti-cataplectic naive and were placed on, on lower sodium oxybate. So it was a very positive outcome in having on average about six cataplexy-free days per week.

Richard Bogan:

Yeah. I'll point out for the listeners. There's some really rich data here because some of the patients were on off-label anti-cataplectics, which are typically the SNRIs and could be tricyclics as well. But you can see that pale green line where the patients came off, the anti-cataplectics and their days free, decreased, but when they were on the lower sodium oxybate over time, as you say, clearly they reached stable state. So Anne Marie, each of these therapies have proven beneficial in improving excessive sleepiness, quality of life, and functioning in patients with narcolepsy, but there are some challenges with them. You want to comment on that?

Anne Marie Morse:

Sure. I think we've already highlighted that comorbidities can definitely impact the treatment selections. We are going to think about cardiovascular comorbidities. You're going to think about psychiatric comorbidities. You're going to think about anything else that may be going on. So, that's going to definitely impact your safety decisions. The biggest challenge is that we see that adherence is highly variable and many times not as great as what we would like it to be. So clearly we're not going to make the impact we'd like if people aren't using the medications that we're prescribing. And so when looking at wake-promoting agents, their good adherence is only seen about 55%. And then when you're talking about oxybate therapies, 27% are describing that they're not taking it in the prescribed schedule. So in terms of dosing there's customizations as necessary. And then also when you're talking about the oxybate therapies, there is twice-nightly dosing, which very frequently may lead to patients not taking that second dose.

Richard Bogan:

Yeah. And then we have obviously modafinil, armodafinil and its induction of enzymes if you're on oral contraceptives. So you have to know the drugs, the pharmacokinetics and pharmacodynamics effects. Clete, did you want to add anything?

Clete Kushida:

Yeah. No, I just wanted to dovetail on what Anne Marie was saying, because it's such an important point that, those with sodium oxybate—particularly, those that are adolescent young adults. As you had mentioned earlier, Rich, there's also some phase delay going on and having, if they're placed on oxybate, it is a challenge because they have to awaken about two and a half, four hours later to take that second dose. So, even for medications that have been shown to be very highly effective such as oxybate, for the daytime sleepiness, the cataplexy, the disrupted daytime sleep, as Anne Marie pointed out, is still a challenge especially for the adherence, even with such a debilitating disorder.

Richard Bogan:

So, Anne Marie, treatment adherence dosing regimen is among the challenges that we discuss. FT-218 is an emerging one-dose formulation of sodium oxybate that may address some of those issues. Fortunately, for our audience, we have new data that was just presented at the 2022 World Sleep Congress two weeks ago, Anne Marie?

Anne Marie Morse:

Sure. So when we're looking at the study that was described, we're talking about using once-nightly, there was a baseline period and then a one-to-one randomization of once-nightly sodium oxybate versus placebo. Then there were safety and efficacy assessments that were done at different periods during it. And so that was done at week three, week eight, and 13. On this side we're looking at the maintenance of wakefulness test results, the number of cataplexy attacks in the Epworth Sleepiness Scale. And one of the themes that we're seeing across all of these is that we are seeing benefit when we are having an individual on the once-nightly sodium oxybate, most typically in the seven and a half and the nine grams, we're seeing that escalating in terms of continued benefits.

Then when you're looking at outside of what we're typically measuring, which is your excessive daytime sleepiness and cataplexy, we also are focusing on our patient-reported outcomes. And so again, we're seeing the same benefit carry through when we're talking about refreshing nature of sleep and sleep quality. And again, as we're going between six and nine grams, which is that therapeutic window that many times we're trying to reach, you see that there's a significant performance that is superior to those who were randomized to placebo in both that the refreshing nature of sleep, as well as the sleep quality.

Richard Bogan:

Yeah. It's apparent that this drug was effective in sleepiness and cataplexy and disruption of nocturnal sleep and REM dissociative symptoms implied. Clete, you were involved in this trial. Is there anything that you would like to add?

Clete Kushida:

No. The only thing that I was just going to add is that the once-nightly sodium oxybate was, I generally well tolerated it as well. The adverse drug reactions that were noted in the trial were mostly related, just mild or moderate in severity. So not only was it obviously highly effective but also safe as well. Yeah.

So this, on the left hand side, it just shows a change from baseline in sleep state shifts by narcolepsy type. And it just shows that over the pattern of different weeks, and it does show the different dosages and basically on the Y-axis, it's just a change from baseline and the sleep state shift. So you can see that you're roughly a dose dependent relationship also in terms of the improvement in sleep state shifts. And then on the right-hand side is a change from baseline in nocturnal paralysis narcolepsy type and just by our prior discussions, this very much goes hand in hand with that. That shows the change from baseline and the number of nocturnal paralysis by PSG were significantly improved compared to placebo over the weeks of the trial. And also in terms of the different dosages. So the take-home message from this is that this FT-218 did show improvement in both the sleep state shifts as well as the nocturnal paralysis. So in general, it improves the disruption in the nighttime sleep, reduces the fragmentation of sleep, which in turn will translate to improvement in the daytime sleepiness, as well as most likely cognitive improvement.

Richard Bogan:

Yeah. Two things. One is a dose response relationship and the other one is state stability, both wake and sleep seem to be more stable. So, thank you Anne Marie and Clete for summarizing the latest clinical data on both the current and emerging treatments for narcolepsy. Clete, what factors do you think about that are important to consider when developing personalized treatment plans for your patients with narcolepsy?

Clete Kushida:

Yeah. So you've already kind of alluded to that or mentioned that earlier certain medications in particular, you mentioned like modafinil and armodafinil, you wouldn't want to necessarily prescribe to women of childbearing age because it would have an adverse effect on oral contraceptives. And even things like, for instance, solriamfetol, it does have an effect on blood pressure and heart rate, so that would also be something to consider. Cardiovascular risk is something that you should be also kept in your mind. Dr. Avidan and myself published an article looking at the impact of sodium on patients with narcolepsy. And there really wasn't a strong signal there. And when you consider low sodium, in fact, even in heart failure patients, those would be kind of the patients that you would think of as, oh, you have to be a little careful about sodium.

But what was interesting was just within the last five days, it was published in Lancet, of patients with congestive heart failure. It was an international study looking at about 806 patients. And they were randomized to either 1500 milligrams per day of sodium versus usual care. And the outcomes were cardiovascular and ER visits as well as hospitalizations, as well as all cause death. And the results of the study showed at this point that there was no significant difference in those outcomes. So, we do know that sodium can have an effect on cardiovascular events, but certainly it was kind of an eye opening experience to see this recent article that showed that really wasn't a risk. And then all the other things on the slide like comorbidities, the severity of daytime sleepiness, the convenience of use adherence carryover effects definitely play a role in this personalized management of narcolepsy patients.

Richard Bogan:

Yeah. Like Anne Marie's comment earlier, how is this sleepiness affecting you the most? And you can use that as a target to monitor the success of your therapy. So thank you for those comments.

So let's bring it back to the audience and see what they've learned here, or have comments on. How confident are you using the latest clinical evidence to develop an effective treatment plan to reduce the burden and impact of EDS in adults with narcolepsy?

I like the one not at all that goes at 30%. I mean, goes down. This is excellent. So, yeah. Thank you all for your attention. And we will take this into consideration. And Anne Marie and Clete, I mean, thank you so much for your expertise and impactful discussion on the importance of early diagnosis of narcolepsy. Again, realizing that this is happening around puberty or before in these individuals, as well as the insight into what is on the horizon in terms of emerging therapies. Would you like to make any concluding remarks, Anne Marie?

Anne Marie Morse:

I would just like to reinforce the fact that really I'm so appreciative of seeing how people's impressions of narcolepsy, ability to diagnose has increased, but also just reinforcing the idea of treating the whole person, making sure we're looking at those pentad symptoms, but also taking into the consideration of what else they're struggling with.

Richard Bogan:

Clete?

Clete Kushida:

Yeah, the only thing I just want to mention is that this is really exciting times for not only researchers within our field of clinicians but also for patients as well, because there's so many medications now that are being looked at, and there's various companies that are exploring these new technologies and new pharmacotherapy. So it really is an exciting time. And there's much more to look at down the road because it just offers more opinions for clinicians to decide what is the best treatment for the patients, in collaboration obviously with a discussion with patients.

Richard Bogan:

Yeah, I'll echo that because I think that these patients are a window into sleep, wake processes and how the brain controls that. And all of us are impaired at some point. And for us to understand that, I think is extremely useful. And these people are profoundly sleepy and the ones who have cataplexy and worried about muscle loss and its impact on quality of life is significant. And the REM dissociative symptoms, the disturbed nocturnal sleep, all of those are important for us to consider as we look at the treatment options in these patients.

So use the SMART goals that we're going to use here, that are specific, measurable, attainable, relevant, and timely. Use the ICSD-3 diagnostic criteria to accurately diagnose NT1 and NT2. Assess the presence, quality of life impact, and efficacy of the treatment on EDS and REM dissociative symptoms and importantly, disturbed nocturnal sleep in our patients with narcolepsy. Use the latest clinical data to develop personalized treatment plans, consider updated clinical parameters and newly approved and emerging narcolepsy treatment medications. And hopefully we've covered a lot of that.

We've got a lot of questions. We have, gosh, almost 40 questions from the folks here. And they're all really good. The most recent one was how does the Swiss Narcolepsy Scale differ from the Epworth Sleepiness Scale, Anne Marie, and does it matter?

Anne Marie Morse:

So in terms of the Swiss Narcolepsy Scale, that is something that you're going to use where you're not certain if a person has narcolepsy. They may have features of excessive daytime sleepiness. You're kind of trying to enhance your understanding whether or not they have narcolepsy. The Epworth Sleepiness Scale is something that we utilize really to just qualify how sleepy someone is. Again, if they're scoring greater than 10, that's pathologic. And so the goal that one would look at is saying, I want to see that that number starts to go down with treatment, so you can use the Epworth as a screener. And then you can also use it in partnership with the patient as you start treatments to see that it also improves.

Richard Bogan:

Yeah, my clinic, they fill out the Epworth score every time they come in. They also do an insomnia questionnaire and a quality of life modified FOSQ. So it gives us a way of patient report outcome measures to use it. So anytime you have a patient who that you think is sleepy, you can use the Epworth score to quantify. It's just you check their pulse and heart rate and you check their Epworth score. So any data on improving cognition with sodium oxybate or FT-218?

Clete Kushida:

Yes. I believe there's some data, but it isn't really well or systematically studied because certainly during the domains I mentioned, there is more of a focus on attention and vigilance, particularly with the daytime sleepiness, but the higher order functions of the learning and memory, to my knowledge, it hasn't really been looked at in a real systematic, organized fashion, but that certainly offers a lot of potential for future studies.

Richard Bogan:

Thank you. Yeah. I think that's, again, reaction time speed of processing that... Some patients do have automatic activity. So they do things. They're so sleepy, they kind of oscillate, micros sleeps, and you have to be awake for a certain period of time to remember things. So individuals may have automatic activity, they may do something and don't remember doing it. And they were oscillating back and forth between wake and sleep. And they're worried about their memory. A lot of times the automatic activity will significantly improve. So from that perspective, they remember what they did. They don't have automatic activity. So the question is does narcolepsy tend to worsen as somebody gets older?

Anne Marie Morse:

I think one of the things to remember is that individual life circumstance changes. And so the studies that have evaluated symptom stability tend to suggest that there is some degree of stability after two to four years of symptom onset. However, the thing that is not fixed, or meaning that it's always changing, is that zero to 25 years of age, we're undergoing neuro development, after 25 unfortunately we're on the wrong side of things. We're undergoing neurodegeneration. So not only is that changing, but also social circumstance and the demands that are put on you. So if you're a child that is going to school, those are different demands than an adult who may have a job and a family. And so it's very difficult to make that comparison, one to the other. There also is differences in coping development. And so those all are other factors that may contribute to the evolving experience that an individual may have.

Richard Bogan:

So, Anne Marie. This is a trick question. Not exactly. So you have someone in front of you who develops sleepiness at age 15, and they have classic symptoms of narcolepsy, EDS. We'll say not cataplexy.

Anne Marie Morse:

Okay.

Richard Bogan:

So, but you do an MSLT and they have a mean latency of one minute and three sleep onset REM episodes but the urine drug screen's positive for cannabinoids.

Anne Marie Morse:

So there is... There's some debate about this because of the fact that a use of marijuana could potentially cause a false positive. I would say to you, however, that if I have a pretty convincing story for narcolepsy, have excessive daytime sleepiness, other REM dissociative features, and that MSLT, I probably would be convinced that that patient may have narcolepsy. The piece that we have to remember about individuals with narcolepsy, is that sometimes they are at higher risk for substance use and abuse. And part of that is their own self-treatment of the symptoms that they're experiencing. So sometimes cannabis may be utilized because of that disturbed nocturnal sleep. Other times you may see things like illicit acquirement of prescribed stimulants. So getting them from other countries or using things like illicit substances like cocaine. So it is important to kind of really look at the full picture to approach that diagnosis in that consideration.

Richard Bogan:

Gotcha. Clete, since you did some of the research on the once-nightly, there's a question. What do you think the latest research on once-nightly sodium oxybate will mean for the management of narcolepsy?

Clete Kushida:

So, I mentioned earlier that one of the struggles from patients, and in fact, when patients have been surveyed to see what can be factors with the current landscape of treatments, one of them is the ability to take the medications at the prescribed times. So to go from a twice-nightly dosing to once-nightly dosing, I think is huge, just because I've had patients that would have to set their alarms to wake them up a few hours later to take that second dose. And when you think of patients who have narcolepsy, who already have fragmented sleep, who have a lot of sleep pressure, that's no easy task. And when they wake up, they have to get the formulation ready, they have to sit up and all that. So, that itself can also be affected because as was discussed, they'll have this sleep drunkenness or confusion arousal, and they would be at risk for falls. So this is kind of a long winded discussion, but bottom line is I think it will substantially improve the adherence of particularly oxybate in general to patients that have narcolepsy.

Richard Bogan:

Good point. As you said earlier, it's really exciting that the medication research that's going on right now as we attack different neurotransmitters and different receptor sites, and to see what evolves is pretty exciting. And this is one of the drugs is now soon, hopefully, is something that we'll be able to use.

So, here's a question about sleep inertia. Anne Marie, do you want to comment on sleep inertia? What is that? Is that, I mean, we're all sleepy in the morning looking for a cup of coffee. What's the difference?

Anne Marie Morse:

So sleep inertia is that very strong drive to wanting to go back to sleep. So many times people describe sleep inertia as when someone is trying to wake someone up and it's like feeling like you're waking the dead. That person is really having that significant difficulty and being able to get themselves up and ready to go. And it many times is driving them to going back to sleep. So we more commonly see very, very strong sleep inertia in our idiopathic hypersomnia patients. We can see that our patients with narcolepsy do have this urge to falling asleep and they sometimes get to the tipping point where they just need to go to sleep. The main difference is that usually patients with narcolepsy, they can kind of almost reboot with very short periods of sleep and be able to kind of get back to it, as opposed to those with a very strong sleep inertia, like our patients with idiopathic hypersomnia. Generally, whether it's 15 minutes or five hours, they still wake up feeling like they've never been refreshed and are falling right back to sleep.

Richard Bogan:

Good. Oh, here's a question for you, Clete. I mean, how do you differentiate cataplexy from seizures or syncope?

Clete Kushida:

Yes. So for cataplexy, you're taking a careful history is very important for you to see if there are triggers for the event and to have a good description of what occurs and then for a differential, like seizures. Obviously in the history you would delve into here is a history of trauma. Are there any focal neurologic signs on the physical exam? And for younger individuals, were there staring spells, anything like that at night? Is there periods where there's bedwetting, things like that? So all these things would point out whether or not they're seizures. Now for hypotensive events or cardiac arrhythmias that could also be considered a differential, that would also be potentially uncovered by history. But it's easy to be fooled. I mean, even sometimes I've had patients that come in and they have an attack right in front of me. And then being somewhat skeptical, I've often questioned you, is that really cataplexy? Because sometimes it's hard to even tease that apart, but doing a careful history I think goes a long way in kind of-

Richard Bogan:

The other thing is these folks are paralyzed, but they're awake...

Anne Marie Morse:

Yes.

Richard Bogan:

... when they have cataplexy. Now they can transition into sleep, but they're awake. They're aware of the environment, they're areflexic if you check reflexes. Most time they're areflexic because they're paralyzed. And so there you go.

Unfortunately, we've reached the end of our program. Lots of questions left, good ones. And one, Clete, there's one about how do you transition from twice-nightly to once-nightly? I'll do that parenthetically, but unless you can answer it in five seconds.

Clete Kushida:

Yeah. Not really. I mean, there's actually a protocol for being able to switch over from, depending on the specific dose of twice-nightly to once-nightly. So...

Richard Bogan:

It's not an easy answer, but sort of close to dose equivalent. But I'd like to encourage our audience to visit the Sleep Disorders Hub for additional information, clinical guidelines, resources, and patient education about sleep disorders and to receive this CME CE credit for today's program, complete the post-test and evaluation, and you'll be able to download and print your certificate immediately upon completion. And I'd again like to thank Anne Marie and Clete for joining me today for this very important discussion. So, thank you Clete.

Clete Kushida:

Thank you. Thank you.

Richard Bogan:

Thank you, Anne Marie.

Anne Marie Morse:

Thank you for having me.

Richard Bogan:

And I would also like to, again, thank you, our audience, for participating and for providing the best care for your patients with narcolepsy. Thanks again.