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The Future of Narcolepsy Therapy: Its Likely Impact on Disease Burden and Patient Outcomes

Announcer:

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Dr. Kushida:

Would it surprise you to learn that most patients with narcolepsy report being dissatisfied with the current management of their condition? Their frustration stems from unmet needs and their poor quality of life. But work is being done in cutting-edge clinical trials, and between June 10th and 13th, leading scientists and clinicians from all over the world convened at Virtual Sleep, the 35th Annual Meeting of the Associated Professional Sleep Societies. In this program, we will highlight the data coming out of that meeting to help you develop the best strategies for your clinical practice to effectively treat and manage your patients with narcolepsy.

This is CME on ReachMD, and I'm Dr. Cleto Kushida.

Dr. Thorpy:

And I'm Dr. Michael Thorpy.

Dr. Kushida:

So, welcome, Michael. Let's dive right in. As we're all too aware, conditions such as excessive daytime sleepiness, or EDS, and narcolepsy are seriously undermanaged and undertreated. What are the main barriers to timely diagnosis and treatment for patients with these conditions?

Dr. Thorpy:

Unfortunately, it's often very difficult for a patient with narcolepsy to get a diagnosis. Part of the problem is that sleepiness comes on very gradually for patients, and so patients may not be aware they really have a problem different from everybody else, even though they may be falling asleep in activities even such as driving. So patients are often hesitant to bring it up to their clinician. They think their physician wants to hear about more solid things like high blood pressure or heart problems but not sleepiness, and they don't realize that we regard sleepiness as just as equally as important as those other conditions. And so they need to bring it up.

Now many physicians and clinicians are not really trained to ask patients about sleepiness, and so they don't know how to do that accurately, and often, they may confuse tiredness, fatigue, and sleepiness of patients with other medical conditions. So there can be other comorbid conditions that are there. Now, during the Sleep Meeting, there are a couple of abstracts that were presented; one of them was an important abstract from the University of Arizona. And in this abstract, they questioned a community sample of individuals about sleepiness. And what they found is that a large percentage of patients with sleepiness think that they can just power through it, that they can handle it by themselves. The most severe ones, though, did recognize the fact that they would need some form of treatment and, fortunately, they are the ones that are more likely to come to physicians. But some patients, even though they have sleepiness that may be impairing them and affecting their quality of life, still don't tend to bring it up with physicians.

Another study that was presented at the meeting about physicians and patients, and they found that even though physicians were talking to patients and giving them information, patients often, when they left the consultation with the physician, just didn't remember receiving that information. I'm sure you've seen this, Clete, that you tell patients about the importance of sleepiness and need to get sleep studies, and then they go away and they just underestimate the severity of the problem, and they just don't think about it.

So it's really important that healthcare providers should be aware of the importance of trying to get accurate information to patients, and they can do this in part through organizations. One of the main ones in the country is the Narcolepsy Network, and patients can contact that Narcolepsy Network and get additional information about disorders of excessive sleepiness.

Dr. Kushida:

So now that we've identified these barriers to diagnosis and treatment, let's explore why it's so important to overcome these obstacles. Michael, can you tell us about the extent to which excessive daytime sleepiness, narcolepsy with or without cataplexy, and idiopathic hypersomnia, or IH, impact our daily lives for our patients?

Dr. Thorpy:

Sure, Clete. Well, first of all, let me just explain a little bit about what these different conditions are. There's narcolepsy type 1, which is narcolepsy with excessive sleepiness and cataplexy, and then there's type 2, which is narcolepsy that just has sleepiness. It's often a little bit harder to diagnose that condition because all patients have a sleepiness and may easily get confused with patients that are sleep deprived or have sleepiness for other reasons. Then there's a third category called idiopathic hypersomnia, and it's called idiopathic because we really don't understand what causes it, although we do believe that it is a central nervous system disorder. And this can cause severe excessive sleepiness, and there's a lot more interest and attention focused on this. But any of these conditions can adversely affect the quality of patients' lives. And there were a couple of abstracts that were presented at the meeting. One showed that these disorders of excessive sleepiness can be just as bad, if not worse, than many other disorders—medical disorders like epilepsy, multiple sclerosis, diabetes, hypertension, for example. So they are really important in affecting quality of life.

Okay. Let's move on to a different topic here and that's about diagnosing these patients with narcolepsy and excessive sleepiness. There are a number of questionnaires that we use and there are some objective tests that we can use to make the diagnosis. So, Clete, what are you using in your practice?

Dr. Kushida:

Yeah, so a patient that typically comes in for any type of sleep disorder evaluation does receive the Epworth Sleepiness Scale, which is, as you know, a very common measure to assess daytime sleepiness. It is a subjective measure, and it just asks patients, what is their chance of dozing in 8 real-life situations. And if they score above a 10, we suspect they might have significant daytime sleepiness. In addition, we have a basic intake questionnaire like most sleep laboratories just to see if there's any symptoms of a sleep disorder including narcolepsy. Then, you know, there are other measures such as Ullanlinna Narcolepsy Scale, the Narcolepsy Severity Scale, which can be used for patients to have a deep dive into whether or not they might have narcolepsy and how severe it might be. But the objective tests are a nighttime sleep study and then a daytime multiple sleep latency test, a series of 5 naps to evaluate their objective daytime sleepiness. In addition, if, say, the multiple sleep latency test results are equivocal, then we might do orexin or hypocretin, lumbar puncture.

Dr. Thorpy:

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Michael Thorpy, and here with me today is Dr. Clete Kushida. We're just about to delve deeper into the latest research in narcolepsy and excessive daytime sleepiness.

Dr. Kushida:

Michael, can you tell us about the latest research on currently available and emerging pharmacologic therapies for patients with narcolepsy who present with excessive daytime sleepiness and cataplexy?

Dr. Thorpy:

Yes, Clete. It's a very exciting time in narcolepsy because there are just so many new medications that are out there, and there's a lot of research presented at the latest meeting on a whole variety of different medications that are being used for the treatment of narcolepsy. Of course, most people are aware of the traditional stimulants methylphenidate and the amphetamines, and really, these have been relegated now to a third-line treatment for narcolepsy because we have much better, more specific medications that are available to us. And so a number of the studies addressed new medications such as solriamfetol. Solriamfetol is a fairly new medication that's somewhat like the modafinil, armodafinil that we're probably all fairly used to using in the past. It's a dopamine, norepinephrine reuptake inhibitor that has slightly different effect and action than most of the other drugs for alertness such as dopaminergic medications. But the abstract looked at how it was being used by physicians and, interestingly, it showed that most physicians are using this to get improved efficacy with regards to daytime sleepiness. It has one of the advantages of not affecting oral

contraceptives, which is a bit of a problem with modafinil and armodafinil.

Then there's, a drug called pitolisant. This is an oral histamine H3 receptor inverse agonist. This helps both sleepiness and cataplexy in patients with narcolepsy. And there were several abstracts on the efficacy of pitolisant both in excessive sleepiness and cataplexy and showing that there are really good, meaningful improvements in those symptoms.

There's a number of drugs that are under investigation at the moment that were discussed at the meeting. We are pretty familiar with oxybates, and there were some studies talking about the new low-sodium form of oxybate, which is available and has been approved for narcolepsy, and it's just recently been studied in idiopathic hypersomnia. There was a lot of interest on this new low-sodium formulation of oxybate. And so there were a number of studies that looked at its effectiveness and looked at the side effect profile, and it seems as though it's just as effective as regular sodium oxybate that we're all used to and that the side effect profile is not greatly different, again, from regular sodium oxybate. But it has the advantage of being a low-sodium; it has 90% less sodium.

But there was also another form of oxybate that was presented at the meeting, and this was a form from Asia which has no sodium. No other cation associated with it, and that's associated with valine, so it's a different type of oxybate, and of course it's only undergone very preliminary studies. So it was really the first mention of this new drug at the Sleep Meeting. There's other forms of histamine antagonist, inverse agonists, such as samelisant, and there was data presented on that. It's just in early studies. Phase 3 studies just started, so there's still a little way away before we hear much more about that particular agent.

Dr. Kushida:

I just want to emphasize exactly what you were saying earlier, Michael, that these are very exciting times now for the management of patients with narcolepsy given all these options.

I'm going to cover this medication FT218, which is an investigational, once-nightly, controlled-release sodium oxybate formulation. And there was a pivotal efficacy and safety study of this medication for the treatment of excessive daytime sleepiness and cataplexy in patients with both NT1 and NT2. And all of the evaluated doses of FT218 showed significant improvement in the mean sleep latency on the Maintenance Wakefulness Test [MWT] also the Clinical Global Impression Improvement Scale of Sleepiness, as well as weekly number of cataplectic attacks. This medication was generally well tolerated, and the most common adverse events were consistent with the known side effects of sodium oxybate.

Another study looked at the results from this trial and suggested that FT218 could also offer a new once-nightly treatment option for disturbed nocturnal sleep. And, as we all know, it's a very common symptom of patients who have narcolepsy that includes just terribly fragmented sleep, and it also includes, oftentimes, frequent brief nightly awakenings in patients with narcolepsy, as we can see by the sleep study or polysomnographic measures.

Another study showed that FT218 had similar efficacy on excessive daytime sleepiness at the evaluated dose in NT1 and NT2 with improvement in both the MWT and Clinical Global Impression Improvement Scale in sleepiness greater than placebo. And additionally, FT218 also in a separate study had similar efficacy on excessive daytime sleepiness at all evaluated doses in narcolepsy patients who were with or without stimulant use with improvement over placebo on the same two measure, the MWT, as well as the Clinical Global Impression Improvement Scale.

And, lastly, another intriguing study showed that patients with narcolepsy are more likely to be obese compared with healthy controls. So patients who received FT218 experienced a significantly greater decreasing weight and body mass index compared to placebo.

Dr. Thorpy:

Patients with sleep disorders, and particularly narcolepsy, we're starting to recognize that there are a lot of comorbidities associated with these disorders so that they can have conditions such as obstructive sleep apnea syndrome, psychiatric disorders, metabolic disorders. So these patients are really at some risk for cardiometabolic problems. And to what extent do you think, Cleve, that clinicians need to consider this effect when prescribing medications for patients with these disorders?

Dr. Kushida:

It is well recognized that numerous factors can impact a patient's cardiovascular health, some of which are modifiable. One of the studies that was discussed at the recent Sleep Meeting showed that a real-world evidence study suggested physicians should consider the increasing cardiovascular risk when considering risk modification strategies and treatment options for narcolepsy patients. For example, in patients with narcolepsy, an additional factor that may impact cardiovascular health is the use of stimulants, which can lead to increased blood pressure with long-term use. Now, Dr. Alon Avidan and I published an article last year entitled, "The Sodium in Sodium Oxybate: Is There Cause for Concern?" in the journal *Sleep Medicine*. The goal of this article was to review the published data on sodium oxybate to evaluate whether there was evidence indicating an association of sodium oxybate with cardiovascular side effects. So what we examined was randomized placebo-controlled trials in 611 adults and 106 children with narcolepsy; we also looked

at open-label studies of twice-nightly sodium oxybate, and also post-marketing surveillance data in the US and Europe from 2002 to 2008. And overall, the evidence suggests that the incidence of cardiovascular adverse reactions with sodium oxybate treatment is low. So patients with narcolepsy, like any other patient, should be evaluated for cardiovascular disease risk factors, such as cholesterol levels, obesity, and diabetes. And the benefits and risks of the management options for their sleep disorders should be carefully considered.

Dr. Thorpy:

Well, that's most interesting, that we really don't have evidence of any significant cardiovascular risk following treatment in these patients with narcolepsy. However, I think, in general, people would think that, sort of, low sodium probably has some advantages over high-sodium intake, particularly if you have high blood pressure or heart disease or fluid retention or renal disease. But we certainly need more data on this to know just to what extent these cardiovascular risks are significant in the narcolepsy population.

Well, I think this has been an absolute fascinating discussion, Clete. Before we wrap up, do you have any take-home messages that you'd like to address with our audience?

Dr. Kushida:

Yes, absolutely, Michael. So as you mentioned, we are still understanding the pitfalls and gaps in the care of patients with this disorder that can have just such a profound deleterious effect on an individual's quality of life. But nonetheless, I believe the future is bright, given the amazing progress and research on the management of patients with narcolepsy type 1 and 2. And as discussed, there are several new and emerging therapies for our patients with narcolepsy and all these should be, in my opinion, carefully considered to determine the optimal treatment plan for our patients with this debilitating sleep disorder.

Dr. Thorpy:

I think it is a really exciting time because we have all these new medications becoming available to us that are more specific to the sleep pathophysiology, whereas the previous medications, as we mentioned, the amphetamines, methylphenidate, were like, sort of, blunderbuss approaches to causing stimulation of the whole body. But now we're getting more refined products, and so I think that's exciting. But it's also important for patients if they have problems with sleepiness, to bring them up with their clinicians and get diagnosed, find out exactly what's going on and then, you know, now with these new medications, we really are able to make very big differences in quality of life for patients in terms of their alertness and their psychosocial functioning during the daytime.

Dr. Kushida:

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and especially thank you, Dr. Michael Thorpy, for joining me and for sharing all of your valuable insights. It was terrific speaking with you today.

Announcer:

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