Fine-tuning Diagnosis and Management of EDS in Patients with Narcolepsy and OSA

Matching Treatment Choice to the Pathophysiology of Sleep

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Richard Bogan:

Hello. I'm Dr. Richard Bogan and on behalf of CME Outfitters, I would like to welcome you and thank you for joining us for episode two of the four-part CMEOCast series, *Fine-tuning Diagnosis and Management of Excessive Daytime Sleepiness in Patients with Narcolepsy and Obstructive Sleep Apnea*.

Today's episode is titled, *"Matching Treatment Choice to the Pathophysiology of Sleep."* This activity is brought to you by CME Outfitters, an award-winning accredited provider of continuing education for clinicians worldwide. Again, I'm Dr. Richard Bogan, president of Bogan Sleep Consultants, Medical Officer at SleepMed Incorporated, now BioSerenity, and Director of SleepMed of South Carolina. I'm also the Associate Clinical Professor at the University of South Carolina in Columbia, South Carolina, and Associate Clinical Professor at the Medical University of South Carolina in Charleston, South Carolina.

I'm very pleased to introduce a national and international expert, Yves Dauvilliers, Professor of Neurology and Physiology at the University of Montpelier. This is a Southern fellow pronouncing French, so I apologize. And he's Director of the Sleep and Wake Disorders Center Department of Neurology at Montpellier in France. So Yves, welcome.

Yves Dauvilliers:

Thanks, Rick.

Richard Bogan:

So, let's get started. To frame today's episodes, let's start by reviewing our learning objective, which is to evaluate the significance of the mechanism of action when selecting optimal treatment of excessive daytime sleepiness in patients with obstructive sleep apnea, narcolepsy. In the sleep clinic, obstructive sleep apnea is really one of the most prevalent disorders that we see along with insomnia, but the majority of those patients are sleeping. Of course, narcolepsy gives us a window into some of the sleepiest individuals in the world, and Yves is going to walk us through basically brain states stability, how the brain stabilizes wakefulness. So Yves let's begin with a brief overview of the neurobiology of sleep and wakefulness.

Yves Dauvilliers:

Yes, thanks Rick. So I think we need first to divide the sleep and sweat regulation system in its two major pathways. First is arousal systems that include a lot of different neurons and related neurotransmitters with norepinephrine, acetylcholine, serotonin, histamine, dopamine, and orexin. And all of these neurons will be part of the game to induce your arousal, so the wakefulness. In contrast, there's the sleep onset systems, mainly driven by the VLPO, with one major neurotransmitter, namely the GABA. And to be awake or to be in sleep state, there is a competition and imbalance between the monoaminergic neurons. So again, histamines, serotonin norepinephrine, that need to be active when you are awake, all this is driven by the orexin activity. And in contrast, when you fall asleep, you will activate your GABA neurons, within your VLPO, to inhibit the orexin and the monoaminergic neuron. That explain how it works when you are asleep or awake during the daytime.

Richard Bogan:

Yeah. It's pretty clear that there's a lot of redundancy here in terms of trying to stabilize state, the brain obviously is mostly in one state or the other; awake or asleep. So it's obvious that this is very complicated. What actually happens in the neurobiology of narcolepsy type 1?

Yves Dauvilliers:

So in narcolepsy type 1, we know that since two decades right now, that there's a loss of orexin neurons in the brain and at the consequences when you measure orexin, also named hypocretin, your same peptide in the CSF, it is gone. It's no more. It's below one or a 10. And that explains in the patient with narcolepsy type 1, daytime sleepiness, sleep onset REM period, and the cataplexy. And it is really a nice discovery two decades ago. And because of what we discussed, that orexin will drive the monoaminergic neurons, if you have less orexin, you will have less norepinephrine, less dopamine, less histamine. And that explain especially the sleepiness we are discussing today.

Richard Bogan:

Yeah. When I talked to some of my patients, we talk about state instability, and patients with narcolepsy sort of oscillate back and forth between wake and sleep in the daytime and at night as well. And they have these brim intrusions around dissociative symptoms. And clearly in narcolepsy type 1, we have more insight, but narcolepsy type 2 and even idiopathic hypersomnia, which we won't get into, but narcolepsy type 2 is another disorder really. Do you want to expand on that?

Yves Dauvilliers:

Yeah. So unfortunately the neurobiology of narcolepsy type 2 is less clear. For narcolepsy type 1, it was in the past known as narcolepsy with cataplexy, and we were interested in assessing orexin within CSF. In narcolepsy without cataplexy and 20% only do have low level of orexin in the CSF. Today our name right now, narcolepsy type 1. So in narcolepsy type 2, by definition, there is normal orexin within the CSF. And we can speculate that a part of orexin neurons in the brain are gone, just 20%, 30%, but who knows exactly. So we may say that is almost a known. We work on histamine assessment, on MCH assessment, on orexin assessment, and right now nothing came up as a good biomarker to explain sleepiness in narcolepsy type 2. So the neurobiology of daytime sleepiness in narcolepsy type 2 remain unclear.

Richard Bogan:

Yeah. Thank you Yves. And then we move on to obstructive sleep apnea patients. Clearly, when patients present to us, they have fragmented sleep and oscillations. They have oxidative stress and many things because of the increase in upper airway resistance and obstructive events. But some of those patients, when we treat them appropriately, they're adherent, and their AHI is normal and airway resistance is gone. They don't snore, but some of them are still sleepy. Why is that?

Yves Dauvilliers:

Yes. Excellent point. So we do see a 10% probably of patient with sleep disorder, breathing with sleepiness, despite the fact that they are correctly managed with CPAP machine. But there's a lot of variability to explain this sleepiness that may be some comorbid depression, comorbid obesity, some drug intakes, or insufficient sleep syndrome, and central hypersomnolence disorders that may also co-exist with sleep disorder breathing.

Yves Dauvilliers:

So we need to really first to phenotype as best as we can, and to record sleepiness in those patient, and not only by a clinical interview or by questionnaire, to be sure that they are really sleepy and not just fatigue.

And in this population of selected target population, with really sleepiness assess, as for NT2 and you briefly touch, but IH is almost the same. We do not know. We may speculate that some orexin or norepinephrine also awakening neurons are gone because of hypoxia repetitively before being treated with CPAP. But it's not clear if this really happens in the brain of a patient with OSAS and especially in those who are sleepy, despite being treated with CPAP. So I think it's more hypothesis and speculation than really some nice results. So the pathophysiology to explain EDS is unclear and we really need to work on it to understand better this field.

Richard Bogan:

Yeah. I completely agree. It's interesting that the objective evidence is early, but there is some suggestion that some of these monoaminergic sites in the brain are more sensitive to oxidative stress, and that might have some influence in there. Of course, there's some evidence out of Chicago that showed conductivity issues as well in terms of how the myelin sheaths work in terms of communicating. But that's very early work. But what we do know is that as clinicians, we see patients that have excessive sleepiness and of course, many of those patients are significantly impaired. We have to make sure they're adequately treated and we have to rule out other sleep disorders, and medical problems, and psychiatric issues, but some of the patients deserve therapy. And we now have some therapies available. And since you've talked to us about these neurotransmitters, how does that inform you in terms of how you would treat these individuals?

Yves Dauvilliers:

Yes. I think we need to recognize that daytime sleepiness is not the same for all the different disorder. Again, NT1, NT2, OSAs and also IH, is they do complain about daytime sleepiness, but in different manner, in different phenotype. And it's of interest to understand better and better for which drug will be the best for which phenotype. And I think there's two thing we need to discuss on today. And we already discussed about what is the neurobiology, is still mostly a mystery in most of this condition.

But probably more and more we will know about that and that may explain for precision medicine who will need this kind of medication. This is our first step. And the second step is the severity of the condition. Severity of sleepiness is variable in term of the different background, and also within the same disorder. In narcolepsy type 1, as an example, we do have some mild cases, moderate cases, and severe cases for sleepiness. And we kind of decided to treat in the same way this different population. So I think that symptom severity and background of what may explain sleepiness in those population need to be the goals to better treat the patient at the end.

Richard Bogan:

I agree. Certainly we have drugs that have been approved to treat narcolepsy and certain drugs that have been approved to treat obstructive sleep apnea individuals with persistent sleepiness. Of course, we always want to make sure that they wear their CPAP device. You want to talk about those classifications of medications that are available?

Yves Dauvilliers:

Yeah. So there is right now some pipeline we can say, but there's a traditional stimulants, methylphenidate and amphetamine. There is the modafinil, and armodafinil, wake promoting agent, the solriamfetol, and sodium oxybate and the non-salt. So there is the different player that may improve daytime sleepiness in those different condition. And of interest, how it works is completely different and could be of interest for a target population. We need to use this medication for specific patient. And for methyphenidate or traditional stimulant, mostly work on that. So the transporter of dopamine, the transporter of norepinephrine called NET, and a transporter of serotonin called SERT.

And they do have a high affinity for this three transporter. In contrast, modafinil have a low affinity for one of these transporter named the DAT, so transporter of dopamine. And recently the solriamfetol have also a low affinity, but for both transporter, dopamine and norepinephrine. So it's different than modafinil and methylphenidate mechanism of action. And sodium oxybate is very known with high affinity for GABA B receptor in the brain, with selective activity. And JZP-258 is the same mechanism of action is just a low salt xyrem, so the same mechanism of action.

Richard Bogan:

Yeah. It's interesting because you pointed out that each of our patients are different. And for example, I remember a patient who came to me with narcolepsy, who said, "Doc"... he managed his sleepiness, but he said, "Doc, I dream all night. I'm very aware. I go to sleep and I'm aware of my sleep. I dream all night, I wake up a lot and this is what bothers me." So we obviously have to listen to our patients and fashion and recognize that some patients respond in one way and other patients respond in another way. And part of that is based on these mechanisms of action. Would you comment on histamine because that's a new drug that we now are using in terms of pitolisant.

Yves Dauvilliers:

Yeah. So there's a lot of, as we discussed, different transporter of this monoamine and histamine are also with own transporter, is name H3 at the presynaptic level. And if you block the reuptake of histamine at the presynaptic level, you will increase histamine in the synaptic cleft. And that will be metabolized to [inaudible] histamine, being a more stable metabolite of the histamine. So pitolisant is on that block exactly as I'm discussing on, this H3 presynaptic receptor, it will increase the level of histamine. And if you increase the level of histamine, you will decrease the sleepiness, increase the REM sleep latency and decrease the partial cataplexy. So I think it is again, one of the big player like norepinephrine, dopamine, orexin, and it's nice to have a new compounds will work in this direction.

Richard Bogan:

Yeah. We have a lot more opportunities now in terms of our treatment. So interestingly, when we attempt to use sodium oxybate or now the low salt oxybate preparation in patients, it's difficult to explain that to the patients sometimes. They're like, "Wait a minute, you're going to give me something at night, I already I'm sleepy. How does that work?" And I sort of tell him, it turns off the awake circuits and then when it wears off, they upregulate. But obviously the science is more sophisticated. Would you talk about GABA receptors. GABA A and GABA B, but obviously GABA B receptors.

Yves Dauvilliers:

Yes. It's mostly GABA B because GABA A is for benzo, and it will reduce your slow wave sleep and induce sleepiness during daytime. So GABA B is actually the target of sodium oxybate and also JZP-258. And it is very selective, high affinity with this receptor, and it works in activate these at night. And because you activate GABA B, you will change your dopaminergic level in the brain, and mostly inhibiting it at night and there is a shutdown, so there is a rebound during the day, and you will increase your dopamine tones during daytime that may explain the efficacy on sleepiness and decrease of cataplexy. And of interest, we need to stress on the activation of GABA B, so namely the sodium oxybate pathway is the only drug so far known to increase slow wave sleep. And this is a good target for many patients to improve their bad sleep at night, mainly for narcolepsy. And who knows about other conditions, but for narcolepsy is quite clear.

Richard Bogan:

Yeah. I wish we had time to kind of go into the pharmacokinetics because it's a very short acting molecule. Has a short half-life, so you have to take two doses. And yet the next day, the patients have less sleepiness and the cataplexy is significantly improved. So it's a very interesting molecule. But I think what you've done is phenomenal presentation in terms of helping us understand the neurobiology of sleep and the science behind this targeted therapy. So let's close with our smart goals. That is very specific, measurable, attainable, relevant, and timely goals. And Yves, what we hope that the healthcare practitioners listening today will take away from this podcast?

Yves Dauvilliers:

So, yes, I think we need to clearly identify the key neurotransmitter that is involved in sleep-wake regulation and particularly dysfunctional in patient with narcolepsy type 1, type 2 and OSAS. So we know quite clear on NT1, less on the two other condition, but we need to work more in this direction. And the second goals is to recognize that many different drugs target exactly the key neurotransmitter we just discuss on and that explain how it works to manage sleepiness in patient with narcolepsy and patient with OSAS in different manner.

Richard Bogan:

Yes. Thank you very much. To receive CME CE credit for this activity, click on the link identified here to complete the post-test and evaluation online. Please visit the sleep disorders hub that's CMEoutfitters.com, sleep disorders hub for additional educational activities, resources, and tools to improve the care of patients with excessive daytime sleepiness. Thank you for joining us today for episode two of our four-part CMEOCast series. If you additional episodes on an overview of EDS and the burden it imposes differentiators when choosing novel treatment options for EDS and diagnosing and treating pediatric narcolepsy with cataplexy, please visit CMEoutfitters.com. Thank you again for participating and thank you for providing the best care for your patients and a special thanks to Yves for this phenomenal scientific presentation.

Yves Dauvilliers:

Many thanks Rick.