**CMEO Podcast Transcript**

Michael Thorpy:

Hello and welcome. On behalf of CME Outfitters, I'd like to thank you for joining us for episode three in this three-part CMEO cast series entitled, From Bench to Bedside: Applying Clinical Updates to Treatment Planning for Patients with Narcolepsy. Today's episode is entitled, Examining the Latest Evidence on EDS in Cataplexy and Narcolepsy. What are the implications to your practice? This podcast series is supported by an educational grant from Harmony Biosciences. I'm Michael Thorpy, professor of neurology at Albert Einstein College of Medicine and director of the Sleep-Wake Disorders Center in the Department of Neurology at the Montefiore Medical Center in the Bronx, New York. I'm joined today by my friend and esteemed colleague, Yves Dauvilliers, professor of neurology and physiology at the University of Montpellier and director of the Sleep-Wake Disorders Center, Department of Neurology at the Gui de Chauliac Hospital in Montpellier, France. Welcome, Yves.

Yves Dauvilliers:

Thanks, Michael. Happy to be on board with you today.

Michael Thorpy:

To frame the discussion today, let me review our learning objective. Our goal is that after the CMEO cast episode, you'll be able to utilize the latest clinical evidence to guide treatment planning for adults with EDS and cataplexy that's associated with narcolepsy. Yves, why don't we make a start? It's important as you know, to have goals in treatment. Too many people tend to pick just sort of one goal and go after that. But there are a number of different goals, aren't there for treatment? What are the ideal goals for patients with narcolepsy?

Yves Dauvilliers:

Yes, before initiating any treatment, we need first to define the treatment goals in narcolepsy. And the first step is always to reduce daytime sleepiness. Second is to manage cataplexy and third is to manage associated symptoms, hallucination, sleep paralysis, disturbed nighttime sleep and nightmare. This is to treat symptoms but we need also to manage quality of life to reduce psychosocial dysfunction and to improve the safety of the patient and the public awareness of the disease and the consequences on daily life of the patient and his relatives. And finally, we need to regularly assess the benefits risk ratio of different medication on the follow up.

Michael Thorpy:

Good. Thank you. One of the components of achieving good treatment goals is really to assess the value of the various medications that we're going to be using. In clinical trials, there are a lot of outcome measures that have been used. Would you like to discuss some of those outcome measures and which you think are the most important one?

Yves Dauvilliers:

Yes. Excellent point. I think endpoint in clinical trials differ than in clinical practice and we mostly do good clinical interviews, but to be sure that treatment is effective, we need to define treatment endpoints. Outcomes could be well related to cataplexy, as we discussed is the main issue to manage. It's mostly related to sleep diary and the weekly episode of cataplexy on the diary. It could be paper diary or electronic diary, so we can assess the frequency and the severity, so partial versus general cataplexy. We can assess the disease as a more general assessment with the CGI, the PGI, and we develop recently the narcolepsy series scale in adults and in kids to assess by questionnaire, self-reported questionnaire, the severity of the disease. For sure daytime sleepiness is key. We may assess regularly daytime sleepiness on clinical symptoms by the very known Epworth Sleepiness Scale in adults and in kids.

Yves Dauvilliers:

And we often like in clinical trials to objectively assess the improvement of daytime sleepiness with MWT or very rarely MSLT. And we need to think about other endpoint on as improvement or also to avoid any safety issue related as an example to the mood problem with the BDI and the global quality of life. And we will discuss that again later today with functional outcome of sleep questionnaire of the very well-known SF-36. This is a lot of different outcomes of interest in clinical trial to be sure that the treatment is really effective objectively.

Michael Thorpy:

Good. There are quite a number of new medications that we have available to us now that have been FDA approved. Can you tell us about the different types of medications and how do they differ?

Yves Dauvilliers:

Yeah, there's a lot that we are very lucky of because in recent years we have several drugs right now with different mechanism of action. Modafinil is very known for decades as dopamine reuptake inhibitors. There is also for sure amphetamine and methylphenidate with different mechanism of action that enounce the dopamine or epinephrine and serotonin release. And more recently we do have the solriamfetol and the pitolisant. The solriamfetol is a dopamine and norepinephrine reuptake inhibitor with a very typical mechanism of action and pitolisant is completely different than all the others because it's focused on histamine as histamine H3 inverse agonist. It's an isolated target drug. And for sure, completely different because it's given at bedtime and in the middle of the night, compared to all of the other. It's a sodium oxybate or the lower sodium oxybate with 92% reduce of salt.

Yves Dauvilliers:

We do have several drugs with several mechanism of action that may work on different symptoms and FDA and EMA approve most of these drugs, all of these drugs in adults but just sodium oxybate and methylphenidate in some countries and amphetamine in some countries for kids. And all of these compounds works on daytime sleepiness but very few were really affect cataplexy. Sodium oxybate for sure and the low sodium oxybate and the pitolisant with some studies and we will discuss that today.

Michael Thorpy:

Very good. Thank you. At the beginning, you mentioned that it was important to assess the risk benefit. What are the risks associated with these FDA approved agents? We have a list here of those risks that occur in at least 5% of patients in the clinical trials. Can you discuss these different risks with the drug?

Yves Dauvilliers:

Yes, for sure. When we prescribe a drug for a chronic disease, you need to be sure that the benefits risk ratio will be good. And we do see for all of these compounds, stimulants or wake promoting agents named modafinil, solriamfetol, pitolisant, some anxiety, some headache, insomnia, mostly related to the dose and also especially the first few weeks when you prescribe the drugs. For sodium oxybate and low sodium oxybate given again completely differently because at bedtime and in the middle of the night, we can see different safety concern with enuresis, with parasomnia and sometime decrease appetite. But that could be good as a good safety problem when you will decrease weight in patient with narcolepsy. And amphetamine and methylphenidate, often associated with more severe problem with a Schedule II for FDA and loss of appetite, headache but mostly is blood pressure concern with increase of systolic and diastolic blood pressure and heart rate. And also some mood change that may be more problematic again, depending on the dose. Yes, there is some safety consideration to take into account when you prescribe these drugs.

Michael Thorpy:

Now Yves, there are also some other safety considerations that need to be taken into consideration with these medications. Can you just touch on those for us?

Yves Dauvilliers:

Yes, for sure. We need to know that some specific AEs may exist for this wake promoting agent and stimulants. We'll sum up some of them. For modafinil and armodafinil, the main issue is that it may reduce effectiveness of contraceptive pills. A huge problem for young females. It may increase as well heart rate and blood pressure and for very, very rare cases allergic reaction and rashes. For solriamfetol, there is no concern at all on the birth control. That's good news but we need to be cautious of blood pressure heart rate. For pitolisant, there is a little reduction of effectiveness on contraceptive pills. There is no sign with vital sign, laboratory signs but it may increase QTC interval.

Yves Dauvilliers:

For sodium oxybate, there is a huge daily increase of sodium on a daily basis but mostly is not a problem but for patients at risk for cardiovascular disease, you need to switch to low sodium oxybate to reduce this kind of risk. Of interest there is one AEs, which is on BMI but is good AEs because it'll decrease BMI. And for amphetamine and methylphenidate, is Schedule II controlled substances and there is some high potential for abuse and some concern about psychiatric problem and cardiovascular problem related to increased blood pressure, especially stroke and myocardium factors.

Michael Thorpy:

Now, one of the neuro medications that we have available to us is pitolisant and what does the latest data show and tell us about this medication and the treatment of excessive sleepiness and cataplexy?

Yves Dauvilliers:

Yes, there's two randomized control trials using pitolisant in narcolepsy with and without cataplexy. But this recent study reassessed the time to onset of response of pitolisant to treat EDS and cataplexy. Define for the daytime sleepiness with the Epworth sleepiness scale reduction of three and above from the scale, you can see that the effect in both studies, HARMONY I and HARMONY CTP for cataplexy start around week three and is even higher around week seven. And this is of interest to be sure that you need to wait at least three weeks to obtain a plateau for the good response to the drugs. And if we are looking at a cataplexy frequency rate, if the endpoint is a reduction of 50% of this cataplexy, it starts around week two, but its maximum is around week four. Again, you need to wait around one month to obtain a plateau. It's quite rapid but not on the first few days. You need to wait weeks.

Michael Thorpy:

Very good. Now how about, I think this medication's also been shown to be effective when you look at a group of patients that have high burden narcolepsy, that have more severe excessive sleepiness and cataplexy. How about those studies?

Yves Dauvilliers:

Yes. Excellent point, Michael. This again, there is just two phase three trial in using pitolisant in narcolepsy, but one of the question was that the patient with the more severe problem for sleepiness or cataplexy will be enough good responders to the drug. This study reassess the efficacy of pitolisant in the more serious subject. And for the more serious subject in terms of Epworth Sleepiness Scale, if you selected just patient above 16 on Epworth sleepiness scale in the trial, there's no differences at baseline but at study endpoint, there is a huge differences and significant differences for sure in term of decrease of Epworth sleepiness scale in the more severe subject compared to placebo.

Yves Dauvilliers:

And if we do the same for MWT, if we selected just patient with MWT latencies below eight minutes at baseline, we do see a significant differences at endpoint in patient treated with pitolisant compared to patient treated with placebo. For the more serious subject for sleepiness, subjectively and objectively assess, pitolisant is effective compared to placebo. If we do the same job for cataplexy, we will see the same results and patient selected with 15 cataplexy per week, so the more severe subject, at least two cataplexy per day, so it's very severe patient in term of frequency of cataplexy, again, we see no differences at baseline comparing placebo and pitolisant and a significant decrease in the frequency of cataplexy with pitolisant study endpoint.

Michael Thorpy:

And the clinical global impression scale of change showed a significant improvement as well, didn't it in those studies. Let's move on to the next medication, the new medication that's only been approved relatively recently called solriamfetol. And can you tell us a little bit about solriamfetol? What do you know about the efficacy of this medication?

Yves Dauvilliers:

Yes, we did publish together, Michael, the results of the phrase three trial on solriamfetol in narcolepsy with and without cataplexy and we did see a significant improvement on Epworth Sleepiness Scale and MWT but here in this recent study, we wanted to look at the effect of solriamfetol in patient with is cataplexy and without cataplexy independently. And we see a very effective dose response differences with solriamfetol in Epworth sleepiness scale on the complaint of data sleepiness in patient with and without cataplexy and the same results, those depend on again on MWT latency. To conclude on that, solriamfetol is efficient in treating the complaint of the daytime sleepiness and objectively assess some MWT inpatient with and without cataplexy, but we didn't find any efficacy results on the frequent of cataplexy per se.

Michael Thorpy:

And how about the global impression scale of change and work productivity with solriamfetol, Yves?

Yves Dauvilliers:

Yes, we wanted also to assess the patient impression of change and not just the scale on Epworth and MWT and the patient is very happy with the drugs in term of improvement of change in the true group with and without cataplexy. Of key interest as well in this study, we used a different questionnaire, related to quality of life but also on impairment related to work, impairment and activity, social impairment on daily life. And as you can see on the graph, patient manage with solriamfetol decreased the impairment related to work and activity at least from 25%. Using the scale, WPIA, we did see an improvement overall related to work and social activity with drug intake.

Michael Thorpy:

Very good. Sodium oxybate's been available to us for quite a number of years but there's a new formulation now that's available, isn't there? It has 92% less sodium than regular sodium oxybate. What do we know about this drug and its efficacy compared with regular sodium oxybate?

Yves Dauvilliers:

Yeah, so this low sodium oxybate is of interest to reduce the salt on a daily basis for a patient that may be at risk of cardiovascular disease. It's of interest to prove that it's still efficient in the same way as sodium oxybate. We were not able to compare lower sodium oxybate and sodium oxybate per se, but we compare lower sodium oxybate to placebo. Based on these complex studies, in term of the design, it was an escalating drugs dose for several weeks. And after two weeks stable dose period and after we randomized for two weeks patient to continue the drugs or to be treated with the placebo. And we can confirm on the Epworth sleepiness scale, that patient randomized to placebo increased the Epworth Sleepiness Scale and patient that continued the LXB drugs at stable complain on daytime sleepiness based on Epworth Sleepiness Scale. And for cataplexy is almost the same story. Patient randomized to placebo increase the severity of cataplexy in term of the number of attacks per week, in contrast to patient that continue to be managed with LXB with no change in the frequency of cataplexy.

Michael Thorpy:

To what extent does it actually reduce cataplexy? How many cataplexy free days do patients get from low sodium oxybate?

Yves Dauvilliers:

Yeah, so this paper is not yet published but we were interested in epilepsy to assess the number of days without any cataplexies, another way to assess the cataplexy endpoint contrast to the weekly rate of cataplexy as we discussed already. And in this complex study, with different strategy to be managed at baseline, patient may be managed with sodium oxybate, sodium oxybate and anti-cataplexis with mostly antidepressant or they can be drug naive for cataplexy at baseline. And at baseline, we do see a lot of change from three days of cataplexy without any cataplexy in the group of drug naive subject but in the group treated with SXB, there's five to six cataplexy free days per week. And at the end of the stable dose period, after more than 10 weeks it's mostly around 14 weeks, we do see that all of the subjects, all of this group go around six cataplexy free days per week. Of interest, everybody regardless of treatment intake at baseline reach a nice plateau of six cataplexy free days per week. Almost all the days.

Michael Thorpy:

Very good. Well, we've shared with the audience about some of the newer medication that are FDA approved that are available for narcolepsy and also their safety but now we've got to apply those medications to treating actual patients. When we come to treating patients, there are certain subpopulations that we need to make some special considerations for. Do you want to discuss some of those subpopulations before we talk a bit more about the treatment rationale for these medications?

Yves Dauvilliers:

Yes, Michael. This is an excellent point and we need to think about that patient. We manage the for decades, it's chronic disease but we cannot treat in the same way patients with huge comorbidities, patient during pregnancy, patient in childhood or even patient after 65, 70 years old, often associated with more comorbid cardiovascular disease. And also, on the long-term management, we do see a lot of co-medication that are required to manage correctly the patient. We discuss step by step, one drugs per one drugs compared to placebo mostly but in my experience after five years, 10 years, you're often oblige to combine drugs, to manage correctly patient with narcolepsy. Obese patients, patient with sleep disorder breathing, patient with high blood pressure, patient with depression, need to be managed differently in a clinical routine.

Yves Dauvilliers:

And when patient is pregnant and is very often the case because narcolepsy often start around 15 or 20 years old so we do see a lot of female that want to be pregnant and you need to avoid most of the drug but especially modafinil, amphetamine, and methylphenidate. Another example is for kids, we do see a lot of obesity unfortunately and sometime even precocious puberty associated with obesity and for this subject is nice to propose Xyrem because it is the only drug that will decrease the BMI. And for depression, you need to take care if you prescribe sodium oxybate as example and for blood pressure and patient with high risk of cardiovascular disease, especially in elderly patient, you need to take care that amphetamine, methylphenidate, and solriamfetol as well.

Michael Thorpy:

Well, thank you. Which really is personalized medicine, we have to take a lot of things into consideration in treating our patients. Not all patients can be treated the same. Yves, why don't you discuss with us the various strategies that we might use in selecting medications for patients with narcolepsy.

Yves Dauvilliers:

Yes. I think you give a very good yield on personalized medicine. We do have several drugs on the market right now, so we need to propose the best drug for the best population and not by chance. There is modafinil, pitolisant, solriamfetol, oxybate, which is the best drug for which population? And we can define several target population at risk to be good responders to specific drugs. One example is modafinil, it is effective for moderate daytime sleepiness, mild cataplexy, very low cardiovascular risk but that exists, is just low, is not at all. An untreated patient with a sleep disorder breathing may be managed with modafinil without too much risk.

Yves Dauvilliers:

For pitolisant, it works on moderate daytime sleepiness and moderate cataplexy. We are very lucky because there is no interaction at all, as far as I know, on my clinical experience and also on the results of phase three trial on cardiovascular risk and psychiatric problem and sometime we do see a patient with severe depression or severe anxiety associated with narcolepsy and pitolisant is nice because there is no interaction with that.

Yves Dauvilliers:

For oxybate, is used to manage severe cataplexy. It works quite well as well on moderate daytime sleepiness. It is very effective on the disturbed nighttime sleep and on obesity. But you can prescribe the drug for obesity narcolepsy just in case of no OSAS or if the OSAS is well managed with CPAP machine. Patient need to be able to comply with drugs because it's given twice at bedtime and in middle of the night, so twice at night. And LXB, so the lower sodium oxybate is nice for comorbid cardiovascular disease because there is a huge, as we discuss already, 92% reduction of salt.

Yves Dauvilliers:

For solriamfetol, is for resistant and severe daytime sleepiness because it's very effective drugs to manage MWT latency as an example. It’s for resistant cases and severe daytime sleepiness. There is no effectiveness, unfortunately on cataplexy. And there's some concern about the blood pressure so we need to keep the drugs till 150 milligram at maximum. And for methylphenidate and amphetamine is nice to propose the drugs to resistant cases and severe daytime sleepiness to young female for oral contraception. But you can also do that with solriamfetol, there is no interaction with oral contraception. And methylphenidate is good as well as you are probably aware of to treat comorbid ADHD that maybe comorbid to narcolepsy. I think personalized medicine to have a good benefits risk ratio is a good way to go to propose the best decision making strategy to treat patient with narcolepsy.

Michael Thorpy:

Well thank you, Yves, you've really given us a great overview of the latest clinical evidence with regards to efficacy and safety of these FDA approved drugs and also how our audience can use that information to make the best decisions regarding the treatment of their patients.

Michael Thorpy:

Let's summarize with our SMART goals, SMART being specific, measurable, attainable, relevant and timely. And that's what we hope our audience will take away from this presentation and apply to their practice. We hope the audience will identify the individual goals for patients with narcolepsy, considering the primary symptomatic complaints of the patient, assess the current comorbidities that that patient has and then the individual patient characteristics and also how these medications might interact with other medications. We should use the latest clinical data to develop a personalized treatment plan, considering updated clinical practice parameters that become available and also be aware of the new medications that are being approved for narcolepsy.

Michael Thorpy:

Thank you for joining us today for episode three of our three part CMEO cast series in additional episodes on the burden posed by narcolepsy and on the neurophysiology of sleep and cataplexy, they can be viewed by visiting the sleep disorders hub at www.cmeoutfitters.com. All three episodes and a wide variety of educational resources on sleep disorders are available on the CME Outfitters sleep disorders educational health. And this is for both healthcare providers and for patients. Yves, thank you again for joining me today.

Yves Dauvilliers:

Thanks, Michael. Hopefully it was appreciated by our colleagues as well.

Michael Thorpy:

Great. And I'd like to thank our audience for joining us. Be safe, take care of yourselves so that you can provide the best care for your patients. Thank you.

Yves Dauvilliers:

Thanks.