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Understanding a Treatment Option for Excessive Daytime Sleepiness in Obstructive Sleep Apnea

ReachMD Announcer: Welcome to ReachMD. This medical industry feature, titled “Understanding a Treatment Option for Excessive Daytime Sleepiness in Obstructive Sleep Apnea” is provided in partnership with Jazz Pharmaceuticals, Inc. This program is intended for physicians. Here’s your host Michael Ayala.

Michael Ayala: Hello and welcome to ClinicalSeriesLive. Today's presentation is titled Sunosi for the treatment of excessive daytime sleepiness and obstructive sleep apnea. My name is Michael Ayala and I'll serve as moderator for the session today. I'm joined by our faculty, Dr. Russell Rosenberg and Dr. Michael Strunc. Dr. Rosenberg is the director of the Atlanta School of Sleep Medicine and Technology and the CEO of Neurotrials Research Incorporated. Dr. Strunc is the neurologist at Children's Hospital of the King's Daughters and assistant professor of pediatrics at Eastern Virginia Medical School in Norfolk, Virginia. Thank you both for being with us today.

Dr. Strunc: Sure Michael.

Michael Ayala: All right.

Dr. Rosenberg: Nice to be with you, Michael Ayala.

Michael Ayala: All right. We truly appreciate it.

Dr. Rosenberg: Yeah, we have a perfect topic for, for today, which is Sunosi and its treatment of EDS and obstructive sleep apnea and I'm sure the audience is going to really enjoy hearing more about this.

Dr. Rosenberg: Well, I'm really pleased to be here and to talk to you all today about Sunosi, which is indicated in, um, sleep apnea patients as well as narcolepsy patients to improve wakefulness in these adults, not children, just adults. The limitations of use, um, are that Sunosi is not indicated for the treatment of underlying obstructive sleep apnea. That is, the airway itself still needs to be treated. Now there are a variety of ways of doing that, uh, CPAP, Continuous Positive Airway Pressure, is certainly the most common approach to this and, and probably the most reliable. Um, so patients who are on CPAP for at least one month but who may still be sleepy are, are certainly eligible for using Sunosi and it's not a substitute for these other modalities.

I want to make sure that's perfectly clear in our audience is that, that if you have a sleep apnea patient, you still have to treat that underlying pathology. You don't just go right, to uh, uh, something that's more wake-promoting.

In terms of contraindications, the one thing that, uh, you need to know is that it's, it's contraindicated in those patients receiving MAOIs and, or within 15, 14 days, excuse me, uh, following discontinuation of use of those medications because there is a risk of a, of a hypertensive reaction and we want to make sure that doesn't uh, occur even though we think that's an older antidepressant and, and there aren't a lot of patients taking that, we still have to be very careful and to understand what medications patients are taking before Sunosi is prescribed.

Well, Dr. Strunc and I have worked together many times and it's a pleasure to be, uh, on the panel with him today. We're going to be going back and forth a bit on the different aspects of Sunosi and we're going to cover all the bases today.

So excessive sleepiness AND obstructive sleep apnea is, is the first topic. And I'd like to cover that particular topic if you don't mind, Dr. Strunc.

Dr. Strunc: Go for it.

Dr. Rosenberg: Okay great. Well, there are a variety of different studies that have looked at this. And one study I think, you know, is, this is sort of a high number, but about 52% of patients in this study with OSA reported subjective, excessive daytime sleepiness despite any amount of CPAP use. So that might be a little bit higher than what I see in our po- patient population, how about in yours Dr. Strunc?

Dr. Strunc: Uh, I would say, you know, it sort of depends on how, how you're asking and what you're asking. So it's sort of, uh, that same thing that we talked about with patients who might be treated with CPAP to some extent and their new normal is, I'm not falling asleep in traffic. And so they think I'm not really sleepy, but their wife might be like, ah, heck yes, you're still sleepy. So I think that the reports I think might be more like a third of patients. But I think again, that depends on how you're asking, what you're asking for patients. But it's not a small number. It's a pretty sizable percent that with any CPAP still have this complaint of excessive sleepiness.

Dr. Rosenberg: Yeah, in fact, there was another study that showed about one in three patients who use CPAP equal to or greater than five hours per night, still reported excessive daytime sleepiness.

So, and patients are, really under recognize the degree of their excessive sleepiness or under-report it. They're not really sure how to describe their excessive sleepiness. You know, they might say, "Oh, I'm tired or fatigued," but who isn't? Everybody on this panel, we were talking earlier, you know, everybody on the panel here is working, you know, long hours spending time with their families and we're all tired and fatigued from time to time.

And patients adopt like coping strategies like excessive caffeine use. You know, they may, you know, drink five of the big gulp, uh, caffeinated beverages or they might go down to Starbucks and get a, you know, several cappuccinos with, with the, the oatmeal milk in it.

Dr. Rosenberg: So, so they adopt coping strategies and they're unaware of their chronic sleepiness or are they under report that. They're not really sure how to describe this to their physician. So the healthcare provider really has to dig in and really ask some specific questions and ask questions about their functioning.

So recognizing this excessive sleepiness can be challenging for a lot of healthcare providers. Uh, you have to be proactive. There's no doubt about that, you can't just wait until it comes to you, you have to dig in. And the Epworth Sleepiness Scale is a, is a good paper-pencil measure. And I think most of us in sleep medicine use this almost on every patient on, on every trip to their office. And there's this other test, which is an objective measure, the Maintenance of Wakefulness Test.

Uh, we may talk a little bit more about this later, but this is a very specialized test that's used in the sleep laboratory that most specialists are not going to have access to and it may not even be needed in some patients. So one of the things I think is particularly important with sleepiness and assessing sleepiness, is asking about what the patient can and can't do or what they say they might wish they could do, but they don't have the energy or the wakefulness that they need to. So how are they performing at work? How are they doing at school? What about social and family life? Do they put off social activities like going to the movies or being with other friends because they're too sleepy? And those are the things to ask about. Uh, you know, I think some patients, again, with those coping strategies I mentioned earlier, they mask their sleepiness. There's underlying pressure of sleepiness that persists and, and that has to be addressed.

Michael Ayala: Uh, next we'll dive into the pathophysiology of underlying EDS in patients with OSA. And for that, I'll go to Dr. Strunc. Doctor?

Dr. Strunc: So we're going to talk about EDS a little bit about the pathophysiology and specifically this is paying attention to patients with obstructive sleep apnea. We'll talk a little bit about what we know. So first we'll talk just briefly a little bit about the wake-promoting system of our brain. So wake and sleep are pretty interesting and the way that our brains do this. The main wake-promoting centers of our brain are tied to mainly these monoamine systems that run. They run sort of through a thalamic circuit and a frontal circuit. So the basal forebrain and through the thalamus, there's this circuitry and these amines acetylcholine, dopamine, norepinephrine, serotonin, histamine, as sort of the main wake-promoting neurotransmitters of our brain.

Um, and, uh, in EDS, in patients who have sleep apnea, there is some data that just look at some of the basic science research that patients who have chronic intermittent hypoxia or sleep fragmentation or both. Um, and then have EDS, um, in patients who have, uh, sleep apnea. Because of this, there may be injury to brain regions and wake regions that control wakefulness and that can be caused, uh, cause compromise, neuronal connectivity. And some of that's sort of born out and can lead to unstable sleep or sleepiness. Um, because of this dysfunction.

Michael Ayala: We will now introduce Sunosi and review key efficacy and safety data in the treatment of EDS in OSA and for that, I'll go back to Dr. Strunc.

Dr. Strunc: Thanks, Michael Ayala. So Sunosi is the first and only DNRI for the treatment of EDS associated with OSA. Although the

exact mechanism is unknown, it's thought to work primarily through dopamine and norepinephrine.

So when we're talking about the efficacy of this agent and how it was established for the FDA to approve this for usefulness in EDS in sleep apnea, there are these trials here that we're going to talk about. So it's TONES three, four and five. So these were studies that looked at OSA in narcolepsy patients. Patients were randomized in TONES three as far as sleep apnea to a 12 week randomized, double-blind placebo-controlled trial of different doses and we'll talk about that. Um, and then phase three was a six-week withdrawal trial as well. And then there's this longer TONES five, which essentially looked at these patients. Those are narcolepsy and sleep apnea patients, and looked essentially out for about a year. There was a two-week randomized control piece in there. And then we follow them over a long period of time to see about the long-term efficacy as well as any side effects we would see on this agent.

And so for these trials, we'll talk about, there were a couple of measures that we use. So we'll just briefly mention those. So one is this Maintenance of Wakefulness Test, wakefulness test.

So Dr. Rosenberg mentioned this earlier, this is something I use all the time in my sleep lab, but in your internal medicine practice or in a family practice, you're not going to have this test likely available unless you have a sleep lab that you're tied to. Um, so the Maintenance of Wakefulness Test is different than the MSLT. A lot of people are familiar with that in, uh, narcolepsy. Um, we are trying to take a nap and see how fast you fall asleep. This is sort of the opposite. These are patients who have four or five opportunities to try to stay awake after they ha, have had a normal night's sleep. So you sit in a sort of a darkened quiet space, uh, and try to not fall asleep over 40 minutes.

And we do this several times and then the latency. How long do you stay awake? How long does it take to fall asleep? Are used as a measure of just how sleepy your brain is. And then we can trend that between any patient or any group of patients. Now the Epworth, which we also mentioned is a test that is sort of pen and paper. This is subjective, but again, I do this for my patients with every visit, uh, in my clinic regardless of diagnosis because it's a really good measure of how sleepy are you. So this is an eight-question scale. You can answer zero to three and essentially it asks a number of questions. For example, if I was sitting comfortably after lunch, if I was driving, um, uh, um, would I be likely to doze or start to fall asleep? Zero meaning never, three mean most of the time, um, I would doze if that situation occurred. Um, and we have a number of zero to 24, 10 being sort of a cutoff. So that's a test that sort of looks at how sleepy you are, and that's me filling that out if I'm a patient.

The last is this patient global impression of change. So this is sort of based on a Likert scale and then was, uh, drawn from that. It's essentially a patient self-reporting how am I? So, uh, if I'm on Sunosi or some other agent, my disease, how am I functioning? And so it's this global impression of me about my disease. So one of these is sort of subjective, I'm so- w- objective. The other two are sort of subjective tests that we used in these trials.

All right, so talking about TONES three, that's the first of these trials. And that's going to be Dr. Rosenberg.

Dr. Rosenberg: Thank you, Dr. Strunc. And, uh, I'm pleased to talk about these studies in which I was a principal investigator and, uh, and it's, it's really important to, to remember in this particular trial, uh, we had, uh, essentially five different arms of the trial. Uh, we're looking at placebo all the way, Sunosi all the way up through 300 milligrams, but, but I'll just stop here to remind everybody that Sunosi was only FDA approved to a 150-milligram dose, not the 300-milligram dose. And there were co-primary efficacy po- endpoints like the change from baseline to week 12 in mean sleep latency from the first of the four trials of the MWT. There were actually five trials that we conducted, but we only looked at, uh, from a statistical point of view, the four trials, the first four trials. And the change from baseline to week 12 in the Epworth sleepiness scale scores. And I just want to mention about the Epworth one more thing. And that is that, that we looked at, um, I've looked at the data from the Epworth scores here, uh, in terms of the reliability and validity, and there's, there's very high test-retest reliability, uh, with the Epworth.

I think the Epworth has gotten, uh, there had been a lot of pros and cons about its use, but I think is a highly valid, uh, type profile to use or, or test to use. There were key secondary efficacy endpoints like, uh, like you mentioned the PGI-C, this is what the patients think about their, their own improvement. And then last but certainly not least by any means are the safety evaluations, uh, which are very important in trials like this where we look at adverse events, as well as vital signs.

So now to the data itself, looking at the MWT data, it's, it's quite remarkable actually. Um, I've had the pleasure of working on a number of wake-promoting drugs in sleep medicine over the last, in my career over 30 years.

So, um, what we, what you'll see was the 150 milligrams and you look at the, well, this is least squared mean change. Um, and when you look at the amount of change it is, it is, uh, quite significant. Uh, not only is it statistically significant, but the effects size are really quite large. So 11 more minutes in that group from placebo, which is just, uh, absolutely nothing. So great separation between all the, all the different, uh, dose ranges and, uh, um, placebo here. So again, I would say robust effects on, on wakefulness, which is measured by the MWT.

Dr. Strunc: And I think, probably those numbers, what's impressive if you are involved in sleep research and I've been involved in research as have you. Um, and when you think about that MWT if you have experience with that, so folks in our audience, um, that number to go, to essentially almost double the time awake during that MWT that's really remarkable. And this, the statistic, statistics on there are crazy, the P-value, but that really is a number that I think is striking as well as sort of that curve. How quickly and how sustained it was.

Dr. Rosenberg: So we also did an exploratory subgroup, group analysis, looking at wakefulness and CPAP adherence and nonadherence. Um, I, I'm, I'm curious about what you would think about this Dr. Strunc and that is, you know, there'd be concerns about, um, you know, are patients really going to just give up their pap therapy because now they're awake? And, and the data shows from, from our perspective that that did not occur. There wasn't, there was no, uh, decrease, um, in the, uh, amount of pap use based on um, uh, them getting Sunosi.

Dr. Strunc: Yeah, I think that's really a fair question. People want to know if I could just take a pill 'cause CPAP is difficult. Um, so I think that proved that their compliance was the same. I think the biggest point here is the fact that those patients, so if you are, uh, compliant or not really compliant with CPAP, that didn't ma- matter a lot. In other words, this agent, uh, how it affects those wake-promoting neurons and that circuitry was really effective in both those groups. And so for the real world of our patients who have sleep apnea, who are using it from zero to eight hours depending on the day and it's very variable and we all know sort of the compliance numbers overall, um, that this therapy was very effective. So I think it really sort of shows the efficacy and why this is such a useful agent for those patients.

Dr. Rosenberg: Sure. And in this trial I didn't mention earlier is that the vast majority of patients, about, you know, three quarters were actually compliant. They came into the study being compliant, compliant, um, and, and compliance was, you know, sort of like the, the usual measures that most of us are familiar with in terms of equal to or greater than 70% of nights and equal to or greater than four hours of use. I think most clinicians would say, say that's inadequate, but it is a cutoff that's been used in a number of clinical trials. Um, and I think it's important to remember that. So, so some of these patients were not using it, you know, for eight hours, you know, seven days a week. Some, some were using it less than that, but we're still considered, uh, compliant in this trial. I think one other thing that I often get questions about, and that is what about the durability of effect during the daytime?

Because they have, you know, patients who are sleepy, and this is in any sort of disorders of hypersomnolence. They need to make it through the entire day. They, they, they, you know, you don't just want to make them feel better in the morning. You want to make them feel better in the afternoon as well.

And looking at the Epworth sleepiness scale scores, uh, with OSA across 12 weeks, it, it demonstrated, um, certainly that, that it was a durable effect. There was no decrement in performance or decrement in Epworth sleepiness scale scores, um, over time. So Epworth scores remained lower in the 150-milligram dose certainly than the placebo or the other two-dose, dose, uh, doses that were offered in this trial.

Dr. Rosenberg: And that's what we're concerned about. We, we're not, you know, yes, there's some studies and you know, that show a statistical difference with very small improvement. This shows statistical differences with very large improvements-

Dr. Strunc: Right.

Dr. Rosenberg: ... Which is nice. And this, talks to you about the durability of the effect across the day, like how many hours post-dose is it still seem to be working? And when we looked at the, uh, wakefulness on the MWT, the Maintenance of Wakefulness Test that you mentioned, there were five trials in which people are asked to stay awake, you know, for a 40 minute period in a non-stimulating atmosphere. We, we saw that even across the day and, and even nine hours post-dose, they, you know, remained, uh, more wakeful on that Maintenance of Wakefulness Test.

Dr. Strunc: That's impressive. It really does have that durability. That's important when you're using this agent to know about sort of timing as well as dosing. So you know when to do it, when to use that. Because you're going to have this effect for that long.

Dr. Rosenberg: And across the 12 week period, uh, patients with obstructive sleep apnea, you know, remained adherent at the levels. Some would say, I'm too tired to use CPAP. Which is kind of funny because you know, they, they know what they need to use to feel better. But some, some in our trial actually slept a little bit better and use, we used a more pap therapy.

Uh, even though the results just showed that they remained a, uh, compliant. So, you know, efficacy was not dependent upon airway therapy adherence and that, and that's important, but, but I, I think our, our, our message to all of you is that yes, we want to optimize the pap therapy or whatever, uh, airway therapy they're doing and, and then add, uh, wake-promoting medication like Sunosi, you know, if after one month they remain, um, sleepy or not, not at i- ideal levels of alertness.

Dr. Strunc: So then when we look at the data, looking at the 12 weeks and we'll look longer as well, this is more than 2% of patients who are on Sunosi and how many si-, the side effects they had again, that were more than 2% in this 12-week placebo control. And this is the OSA patients. So if you look here, it's really going to be, uh, a few things that we'll mention a few times and a common theme here. So one is appetite that was decreased. Two was some anxiety and a little bit of irritability which we saw, um, and nausea was a side effect that we saw in some patients.

Those are the main things that we saw for patients. We'll talk about a couple of other things that were managed and checked as well.

Probably the biggest thing to think about in this study is that dropping out or discontinuing that medication, um, in those 12 weeks studies was really, really, uh, small numbers. So for all doses of Sunosi and this sort of dose-dependent, um, side effects you can see, the dropout number is just 3%, so very small numbers and the most common adverse results that led to that are what we just mentioned. Essentially headache, nausea, some appetite issues, anxiety, and some insomnia issues. So, uh, common things we see, but really very few patients dropped out and sort of demonstrates how well this medication is tolerated.

There's one important thing to pay attention to, and you mentioned it as far as agents MAOIs as well, but it's really important to be aware that Sunosi definitely did have some increases that we saw in the study looking at blood pressure. That is systolic blood pressure, diastolic blood pressure, and heart rate. And again, as I mentioned, as far as side effects, this was dose-dependent. So this is important that pay attention to our patients, particularly if I'm a family practice doctor, internal medicine, they have a lot of patients that have multiple issues and have some of these issues that would increase this MACE that is, uh, major adverse cardiovascular events, and paying attention to those risks. So assessing blood pressure, making sure we're controlling blood pressure, is really important for our patients who are on this agent. When they start it and once they're on there you want to monitor them and make sure that you're, uh, checking that. Would you add anything to that?

Dr. Rosenberg: No, no, I think that's absolutely right is that, uh, and I think many practitioners are aware of, of medications that they've given patients. Any wake-promoting drug I think is, it's worth checking blood pressure and making sure that cardiovascular issues are not in play and, and that that just increases the safety, uh, of the, of the use of the drug.

Dr. Strunc: Right. And monitoring that's really something that's important for Sunosi, like any of these other agents.

So there's blood pressure, heart rate increases, moderate or severe renal impairment could be at higher risk. And we'll talk about renal disease for patients, psychiatric issues that is that irritability, anxiety or mood issues, any drug that affects your brain can affect that. So those were pretty small numbers, but of course, it behooves us to make sure for our patients we're paying attention to that. And caution if there's a significant disease that would be mental health disorders, that is psychosis or bipolar disease. It is not contraindicated. It's important that those patients would be man- monitored appropriately for that. So for moderate or severe renal impairment, they would be at higher risk of those issues. And so we want to make sure that we're paying attention to blood pressure, but also mood issues that could affect our patients.

And this was ambulatory monitoring. It's just important that we're paying attention to that for these patients.

Dr. Rosenberg: But in this population, in obstructive sleep apnea population, it's particularly important because cardiovascular disease, you know, is comorbid often with obstructive sleep apnea.

Dr. Strunc: Absolutely. Yeah, no, I think you're exactly right. So this small change is something we have to pay attention to in our patients.

Um, this is dose-dependent adverse reactions, again in that trial. And again, these numbers, these, uh, items are what we already mentioned about. And again, they're dose dependent so this changes as you change, uh, change the dose, but headache, nausea, appetite, anxiety, these are the things that we saw most commonly for these patients.

With Sunosi dosing can be adjusted to find the right balance for efficacy and tolerable- tolerability for your patients. Patients are started at 37.5 milligrams a day. Typically after three days, you would titrate to 75 milligrams and then three days later can titrate to 150 milligrams a day, uh, to obtain the right balance again between efficacy and side effects for your patient.

So a couple of other brief safety issues, in that 12-week placebo-controlled trials, uh, and for doses, we saw the dose-dependent side effects as I mentioned. I mentioned renal impairment. It's most important to know that if you have end-stage renal disease, this is not an agent we would use. And so dose adjustments would be used otherwise, but that's a population that would not be, it would be not recommended to use, uh, the agent for.

Uh, mentioned a couple of these before as well, the monoamine oxidase inhibitors are a drug that we do not want to use with this agent. So again, it's a couple of weeks of coming off that agent before you would use that. We, we already talked about blood pressure and

heart rate. Dopamine agents are certainly not contraindicated, but if you are using a dopamine agent, uh, either either side of that, it's just important that you'd be monitoring your patients if they were on Sunosi to see how that affects them.

And lastly, it's not metabolized hepatically, it is not a big inhibitor of our enzyme systems. Excreted mostly unchanged in the urine, this goes to that renal issue, but minimal metabolism and low plasma protein binding.

Very low safety, as a schedule four agent. Um, so not a big abuse potential for Sunosi. Similar to other sce- schedule four, uh, agents and lower than many others, uh, is what we saw.

And there's no evidence of tolerance, dependence, or withdrawal, uh, in these studies that were conducted. So again, uh, for these extended trials, we did not see any issues there for Sunosi.

When we get to, uh, using Sunosi for our patients. Sort of the take-home messages that we'd hope to leave you with, um, would be one that this is a unique agent. Sort of new, something new that's in your toolbox as a DNRI, a selective inhibitor that, uh, affects dopamine and norepinephrine.

Um, apart from those, a couple of exclusions we talked about as far as MAOIs and, uh, renal disease. Is proven effective across the measures that we talked about. Those both subjective and objective and really at those higher doses at 150 milligrams, remarkable changes in the Epworth and the MWT as we saw. At week 12, we saw that that, um, uh, drug worked well, and in fact, not only did it work well, it worked well for this nine hours. And that's really very different than most of the agents that we used for patients who would have EDS, uh, with sleep apnea and the most common adverse, uh, reactions we saw. Headache, nausea, some appetite change in, uh, anxiety, insomnia, we need to pay attention to those. But it's important that we're paying attention to that as we use this agent.

All right. And I think, uh, now we can talk about a case.

Dr. Rosenberg: That'd be great because I think case studies are really illustrative of, of how to manage patients and sort of the typical patients here. Um, so in this particular case, we have a 53-year-old grade school teacher with EDS and obstructive sleep apnea.

But anyway, the patient, uh, is struggling with sleepiness despite CPAP use, um, was diagnosed with obstructive sleep apnea three years ago and has been using CPAP for two years. Manages sleepiness just like many of the pages that we all know by, uh, you know, cups of coffee and energy drinks throughout the day. She has an Epworth score of 16. So, uh, she's pretty in this, in the, you know, more moderate to severe range actually, right there on the cusp. She sleeps about eight and a half hours per night, which would be very happy with and, and as everybody in this audience knows, not only do we have to think about what pathology is going on, but is there some self, you know, sleep restriction, uh, self-imposed sleep restriction. Not the case here.

Um, and uh, her attempts to use CPAP regularly but wakes up in the morning to find that she's no longer wearing the mask, she's pushed it off or doesn't put it back, you know, in the middle of the night. And she's only using the CPAP three hours, which I would think most healthcare providers who are involved in sleep medicine would say, uh, "Not enough, I'm going to keep encouraging my patient to try to use it more and more." But what's great is we get the downloads every day. She can transmit those or report those into our care manager or nurse. And this will all figure in later to her treatment plan.

She was prescribed, uh, Sunosi and after seven days of taking the 37.5-milligram dose, her Epworth score had improved from 16 to 12, which I'd be happy with that. I don't know if, she's perfectly happy with that. In fact, she wasn't, she liked, she said, "I'm still a little bit more sleepy. I want to, I'm getting there, but not all the way there."

She hasn't noted any headaches or any allergy-like symptoms over the past week. Um, when she came back the third time, uh, she had used, uh, uh, the 75 milligram dose and her Epworth improved just a slight bit more down to 11. Again, I think we're getting there, if she went from 16 to 11 and, and that's a clinically significant, uh, drop. Um, despite, she says she's still a little bit sleepy.

Dr. Strunc: Yeah, I would say, uh, you know, 85% of my patients, uh, that are on Sunosi end up at 150 and honestly they tolerate it very well. So I've had a couple of patients who are uh, who are below that. But um, I would say that the, what, what, what's born out in the data of those TONES trials is really born out clinically. Um, that sort of significant drop in Epworth and that change, all what you see clinically. So I really, our patients, we sort of try to get them there because the clinical benefits what you see is more impressive for them at that. So that's where most of my patients end up.

Dr. Rosenberg: So do you feel timid at all about going to the 150? Going 75 to 150?

Dr. Strunc: I would say clinically what I tell my patients, this is what we're doing. We're going to be here for three days, here for three days, but also tell them that side effects are dose-dependent.

Dr. Rosenberg: Right.

Dr. Strunc: We're always monitoring blood pressure and those things. So I think the goal is sort of get there knowing the data from these studies. But if we get there and we have trouble or if you went to the 150 said, "I gotta tell you, man. This is no better than 75," like, sounds good, we'll back down. So I think it sort of depends on when you get there. And, and then it just sort of depends on how you're doing clinically, kind of once you're there.

Dr. Rosenberg: Sure. We've had some patients that went to the 150 said, "You know, I think I'm doing really, I did really well at 75," they go back down to the 75 and they say, "Hey, wait a minute. I think I was better at 150." So until they have sort of a reversal trial, they don't recognize how much better that they were doing at the higher dose.

And so here's some of the pearls from Vicky's case. You know, we want to make sure that we've treated the underlying obstruction, um, for one month prior to initiating, uh, Sunosi. And, uh, I would say that her three hours for most patients would be inadequate and we'd be finding out if the mask is fitting, is there mask leak, you know, what are the problems, if she got humidification. Um, so we'd advise her to use the CPAP more often while taking Sunosi.

By no means is Sunosi, um, you know, a substitute for treating the upper airway, and prior to initiating the Sunosi make sure you measure heart rate and blood pressure as you said, Dr. Strunc you've got to uh, monitor blood pressure and there were some increases in, in diastolic and systolic blood pressure as well as heart rate, they're, although they're small, we need to monitor that. And certainly, you know, obstructive sleep apnea patients do have cardiovascular, a lot of them have cardiovascular disease so we don't want to exacerbate that. We evaluate patients for a history of drug abuse and observe them for signs of misuse or abuse and that was not the case here with Vicky.

And we observed patients treated with Sunosi for the possible emergence of psychiatric symptoms and consider dose reduction if they start to have any problems with anxiety and with insomnia. With some of our patients in the trial, um, they had insomnia, uh, some of our clinic patients have had insomnia. We've just made sure that they don't wait too late in the morning to take the, their 150-milligram dose. That we want them to take it immediately upon awakening, um, you know, even clinically we've had patients, you know, uh, just just take a little bit even before they're normally, their normal wake-up time so that, so that it's not affecting their nighttime.

Dr. Strunc: Yeah, no, I think that's an important point. This drug, this nine-hour window is awesome that your patients have that sustained effect. But that's probably one of the other key points I would say to my patients is, uh, you take it when you start your day, when you're getting up, you don't want to wait. Um, and I'll, I'll tell you one of the other things is that, um, a number of some mild anxiety, some irritability that is also a thing that I'm sort of like hang in there. So if you're more awake and alert, you might be a little anxious because you're so awake and the world's a crazy place.

But I think sort of time is also one of the things that is helpful. This is a marathon, not a sprint for treating our patients. So sort of time helps us a lot I think.

Dr. Rosenberg: Well I think this is where the real art of medicine comes in where you decide when did these patients get their drug and you know, how much and what are the side effects.

Dr. Strunc: Yeah, I agree.

So I think this has, uh, been a lot of fun. Uh, I hope everyone has enjoyed this and, uh, a couple of summary of things to go over for our patients. So one is if you have someone who has OSA and has residual sleepiness, we want to make sure that we sort of screen them. Are there any things that get in the way? So for me, monoamine oxidase inhibitors, their blood pressure, renal function, those things, and then starting at the doses that we talked about and sort of how we titrate most of our patients.

I think what we just mentioned, take it the first time and when you start your, your day in the morning, you need that nine hours. And also making sure that we're treating the underlying sleep apnea as you mentioned as well. Those are your, the key points, uh, to be successful with these patients.

Dr. Rosenberg: Yeah, this is a once a day dosing, right?

Dr. Strunc: Yeah.

Dr. Rosenberg: So it's not one that they can split. They may be more familiar with medications that had to take an afternoon dosing and no, that's not the way this works. It's a once a day dosing.

Dr. Strunc: That's important. I think that's really actually a critical thing to make to for patients 'cause again, a lot of our patients who use other agents are maybe in the habit of saying, "Well, I took one so I took another one midday." Or I've, they may adjust it that's really not an option here and it shouldn't need to be an option because of how this drug works. That's something, something to make sure our patients understand.

ReachMD Announcer: Now let's review some important safety information for Sunosi.

INDICATIONS AND USAGE
SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use
SUNOSI is not indicated to treat the underlying obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI. SUNOSI is not a substitute for these modalities, and the treatment of the underlying airway obstruction should be continued.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS: SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS
Blood Pressure and Heart Rate Increases: SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms: Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders, as SUNOSI has not been evaluated in these patients.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Observe SUNOSI patients for the possible emergence or exacerbation of psychiatric symptoms. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop.

MOST COMMON ADVERSE REACTIONS
The most common adverse reactions (incidence ≥5%) reported more frequently with the use of SUNOSI than placebo in either narcolepsy or OSA were headache, nausea, decreased appetite, anxiety, and insomnia.

Dose-Dependent Adverse Reactions: In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg/day of SUNOSI to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth.

DRUG INTERACTIONS
Do not administer SUNOSI concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

Concomitant use of SUNOSI with other drugs that increase blood pressure and/or heart rate has not been evaluated, and combinations should be used with caution.

Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with SUNOSI. Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

USE IN SPECIFIC POPULATIONS
Renal Impairment: Dosage adjustment is not required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m2). Dosage adjustment is recommended for patients with moderate to severe renal impairment

(eGFR 15-59 mL/min/1.73 m2). SUNOSI is not recommended for patients with end-stage renal disease (eGFR <15 mL/min/1.73 m2).

ABUSE
SUNOSI contains solriamfetol, a Schedule IV controlled substance. Carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of SUNOSI (e.g., drug-seeking behavior).

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