Project Sleep Narcolepsy Nerd Alert
"Types of Narcolepsy" (Season 1, Episode 14)
Transcribed by Mirela Starlight

Julie Flygare, JD is the President & CEO of Project Sleep, a leading narcolepsy advocate, speaker, award-winning author, and Stanford Medicine X ePatient Scholar diagnosed with narcolepsy and cataplexy in 2007. She received her B.A. from Brown University in 2005 and her J.D. from Boston College Law School in 2009.

Dr. Chad Ruoff, M.D. is an internal medicine physician specializing in sleep medicine. He enjoys evaluating and treating all sleep disorders such as sleep apnea, narcolepsy and idiopathic hypersomnia, restless legs syndrome, parasomnias, and circadian rhythm disorders. In addition to his clinical activities, Dr. Ruoff is active in research and education, providing mentorship to medical students. He has authored and coauthored numerous publications on various topics within sleep medicine including sleep apnea and narcolepsy.

In today's episode, Julie and Dr. Ruoff discuss narcolepsy type 1, type 2 and hypersomnia, the ways doctors look for differences in determining a diagnosis and whether your diagnosis can change, hypocretin and orexin and whether the MSLT has long term test, re-testability for people with narcolepsy and other sleep disorders.

The Narcolepsy Nerd Alert series invites listeners to dive deeper into specific topics relevant to living with Narcolepsy. This is a written transcription of the podcast "Types of Narcolepsy" (Season 1, Episode 14) from Project Sleep.

Project Sleep is a 501(c)3 Nonprofit Organization, dedicated to raising awareness and advocating for sleep health, sleep equity and sleep disorders.

All guests and speakers express their own opinions. While medical diagnoses and treatment options are discussed for educational purposes, this information should not be taken as medical advice. Each person's experience is so unique, which is why it's so important to always consult your own medical team when making decisions about your own health.

Julie in intro: What distinguishes narcolepsy type 1, type 2 and idiopathic hypersomnia? Can your diagnosis change? In today's podcast I speak with Dr. Chad Ruoff about the latest research and perspectives on this topic. Dr. Chad Ruoff is an internal medicine physician specializing in sleep medicine. He is active in research and education and has authored numerous publications in sleep medicine on topics including sleep apnea and narcolepsy.

Julie: Welcome, everybody! Today we're really excited to talk about types of narcolepsy— trying to better understand narcolepsy type 1 versus type 2 versus idiopathic hypersomnia. It can be really, really confusing and so we're just really excited to have this discussion, especially to have Dr. Ruoff walk us through this topic today. Hey Dr. Ruoff.

Dr. Ruoff: Hello, hello. Thank you so much Project Sleep for having me. Excited to be here and hopefully I can add some clarity and maybe a little bit of confusion to the picture but hopefully at the end a little bit more clarity for you, the patient. And caregivers. So, you know, really today we're going to be talking about narcolepsy type 1, type 2 and idiopathic hypersomnia. We're certainly not going to touch upon Kleine Levin Syndrome, that is an entity in and of itself. But you know hypersomnia due to a medical disorder, hypersomnia due to a medication or

substance. Hypersomnia associated with a psychiatric disorder— these are the challenges in diagnosing and differentiating these top three. So while we won't talk about these, this is really what makes you know coming up with a diagnosis challenging, in collecting the clinical history and whatnot.

Dr. Ruoff: Insufficient sleep, well that's fairly self explanatory I mean and it's certainly something we're concerned about more and more, just not getting enough sleep. Social jet lag. You know not getting enough sleep during the week and then catching up on the weekend and then the whole Sunday night, that's where some patients— people might in general have trouble falling asleep that night because they spent the whole weekend catching up on sleep. And so trying to normalize that sleep across the 7 day week, rather than the 2 day weekend playing catch up.

Dr. Ruoff: And then normal variants, but then long sleeper, this is another one. So long sleepers if they're given enough time to actually sleep and can ignore the societal pressures and whatnot, they feel fine if they get that. So, you know whether it's insufficient sleep that we're concerned about or long sleep, really the recommendation there is extend the sleep and see what it does for you. And with patients with hypersomnia, one of the really important thing like with insomnia patients— we wanted to find that optimal duration where they're not spending hours and hours lying in bed, so that makes the perception of sleep worse, right. The typical thing if someone's having trouble sleeping at night is to extend the time to get to that magical seven to eight hours of sleep. With hypersomnia it's really, what I recommend for patients is to define that optimal duration. What is that? Well it's where if you go over that, you don't feel any better but if you go under you feel worse. And that can be really important especially for some of the patients with long sleep or longer sleep. Trying to get by with maybe an hour less of sleep every day, that's huge to get an hour back. If you can really diligently do this kind of trial and say well, I usually get 10 but I think I feel the same with nine actually. So that's really an important point and the power of another hour during the day would be— [laughs] invaluable. Yeah.

Julie: I was wondering too, where in the process of trying to diagnose someone with a hypersomnia do you think that clinicians are considering other things, outside of hypersomnias, as well? You know like other autoimmune conditions that might cause— you know we always think of how it takes so long for anyone with these conditions to get to a sleep specialist but at the same time I have heard of some cases where someone ended up with a lupus diagnosis that had been missed for many years and actually got on treatment for that and felt that their sleepiness resolved, so. Do you know how much they consider other things too?

Dr. Ruoff: I think it's important and when I see a patient I always encourage patients to talk about their fatigue, sleepiness with all health care providers and make sure that they're not missing something. I mean I've had, that certainly that can be Lupus, MS— MS has rampant fatigue, which fatigue and sleepiness sometimes even with the person in front of you, when you're trying to dissect, is it fatigue or is it sleepiness? Sometimes it can be challenging, yes sleepiness is the tendency to fall asleep— and fatigue is this tired exhausted feeling but not nodding off but— jeez sometimes it can be challenging to tease those two apart but, yeah I agree. You have to look for other conditions too. Especially you know when we see the word idiopathic, right. Idiopathic means that we don't understand why you have this condition, but you have this condition. And so this is where a lot of medical entities start, is as a syndrome. To place bins of patients that have similar symptoms and whatnot, and study them and try to figure out you know— make that pool as homogenous as possible, so we can learn from that group of patients and then come up with like narcolepsy type 1 with hypocretin orexin deficiency. Right, a

robust biologically confirmed entity, but it has to start somewhere. But idiopathic, so— just because you've been diagnosed with idiopathic hypersomnia, I wouldn't go through life saying, I'm sleepy because I have idiopathic hypersomnia, we just have to remind ourselves that it's idiopathic, we don't have a biologically confirmed understanding of the pathophysiology underlying idiopathic hypersomnia. You know if you follow those patients for a time maybe they would end up being diagnosed with something else. Just keep that in the back of your minds moving forward. Yeah, I don't know if that addressed your question but you pretty much answered it for me.

Dr. Ruoff: So next thing, so what are the symptoms when I'm seeing a patient that might have narcolepsy, IH or just hyper somnolent that I look for, so I always make sure that I address all five of these. Excessive daytime sleepiness which like we've already talked about that can be difficult to differentiate sleepiness versus fatigue, kind of a spectrum. Cataplexy, and really moving towards defining cataplexy as typical versus a-typical which we'll probably touch on later. Sleep related hallucinations, right. Hear things, feel things, see things as you fall asleep or wake up. Hypnogogic or hypnopompic hallucinations. Sleep paralysis, literally the inability to move even a finger as you fall asleep, as someone falls asleep or wakes up. You know this can be often misconstrued as just a compression or opothy where you know you're sleeping on your arm and you wake up and can't feel it or whatnot. That's not sleep paralysis. In my experience, within a few seconds of talking to a patient about sleep paralysis you can quickly— they usually will offer this up on their own, that, "Oh my goodness, yes I have that," the first time, the first couple of times that it— it scared me to, you know half to death, I didn't know what was going on— and then you ask about sleep duration and often times they'll say oh it feels like it lasts forever but it's probably seconds where they just have a very challenging time characterizing the duration.

Dr. Ruoff: And then disrupted nighttime sleep, there's really no well-defined clinical criteria for this, objective or subjective, but it's just really fragmented sleep during the night. So struggling to stay awake during the daytime and maybe struggling, this is exaggerating, but struggling to stay asleep in a consolidated fashion at night. And then some other symptoms when evaluating for this is of course sleep inertia, sleep drunkenness. This is this first thing when a patient gets up there's multiple alarm clocks, they have trouble waking up, extremely groggy, the somnolence is definitely more impactful in the morning hours when they're trying to get up. Sleep duration, long sleep, normal sleep. And the restorative nature of naps. Sometimes I'll look at that as well.

Dr. Ruoff: So what are our tools? This is probably, of this talk today, I think this is probably one of the more important, just for patient care— advocating for yourself, so just know what's out there. What— and make sure, if you're uncertain about your diagnosis, make sure that you've kind of at least engaged your health care providers to make sure that one of these tests isn't suitable for your condition. Or your situation. So, a solid history. I would recommend that a loved one, caregiver, especially at that new first consult, always shows up with the patient. Just to establish a repoire with patient family member, it just— it does so much for the health care provider in hearing not only from the patient but also a loved one, friend, family member— so that's just a tip I think that it can really help accelerate your care, and get things started. There's all kinds of subjective scales, I mean they're subjective, you know the classic one that probably every patient has had is the Epworth sleepiness scale. I don't know how many times I've had an Epworth sleep— the highest number is 24, right. How likely to fall asleep in this situation or that situation. I've had patients, and it goes both ways— they have an Epworth of 20— and my goodness you can't stay awake while reading— it's a 3, high chance of falling— "Oh well no, I

don't actually fall asleep." So, they're scales, you know they're not the end all be all but they can be helpful but what's a high chance of falling asleep for one person might not be at all for the next and so they have their limitations. But important. Actigraphy. Probably underutilized, for a variety of reasons we don't want to delve into but I think that we need to increase our use in the clinic of actigraphy. Actigraphy is nothing more than a medical grade you know, accelerometer. Placed on the non-dominant hand typically and wearing it for one or two weeks, the longer the better. Sleep diary, you know recording your sleep habits, how long you sleep, how long's it take you to fall asleep, naps, etcetera.

Dr. Ruoff: And then of course you know a core part of the diagnostic criteria, the PSG, the overnight sleep study followed by the MSLT. The overnight sleep study is really to rule out other conditions, namely sleep apnea. Make sure there's a relatively normal sleep architecture. Looking very closely to see if there's a sleep onset REM period where someone might go into REM sleep very quickly. And then the MSLT, how I describe this to patients and other healthcare providers that aren't in sleep is, all we're doing is a series of four to five naps, ideally five. And answering some very simple questions. Do you fall asleep on each nap— 8, 10, 12, 2, 4. If you do, how long does it take you to fall asleep. And if you do fall asleep do you go into REM sleep. That's it! We tally that up. That's how we handle MSLT data. We tally that up and you know there's diagnostic criteria for narcolepsy and IH. A blood test for HLADQB1*0602. So this is not diagnostic. For the sake of this talk, I want you to leave today, or— when you put your head on the pillow, just think that— patients with classic type 1 narcolepsy, just think of them as 100% of them are HLA positive. Narcolepsy type 1. Because it really simplifies this discussion. So, if someone has a concern for cataplexy right, so typically cataplexy is going to be type 1 narcolepsy, and if we were to do a spinal tap, most likely they would be deficient in orexin or hypocretin.

Dr. Ruoff: So, if there's ever a concern as to whether this is cataplexy or typical versus a-typical cataplexy, which we'll go into a little bit, I'm sure later, this is a great place for your health care provider and you to advocate, I want to get an HLA test. I want to see what this is. If it's negative, it really would side with the fact that if we were to do a spinal tap that the orexin level would come back normal. So in type 1 narcolepsy there's orexin deficiency, if we check orexin it's less than 1/10th. And so, it's great if there's a challenging case, trying to differentiate, is this cataplexy, is this not? So for anyone you know with a questionable diagnosis of cataplexy even in your heart of hearts you're wondering, do I have cataplexy? I have this in this situation, but is it? My healthcare provider isn't sure. An HLA test is a great way to go. And then if it's positive then you might entertain the idea of getting a— talking to your healthcare provider, about the pros and cons of moving to the next step which would be an orexin test. This is finally commercially available, and so that's certainly important. Your healthcare provider just has to do a little bit of work to get it done but it's commercially available.

Julie: For the HLA marker—

Dr. Ruoff: Yeah.

Julie: Isn't it kind of a pretty simple blood test too, I re—

Dr. Ruoff: Oh my gosh, yeah. Yeah yeah yeah. It's so simple, so—

Julie: Any sleep doctor should be able to do this, right?

Dr. Ruoff: Unequivocally, yeah, absolutely. Widely available, they just need to make sure that they're doing the right one, that they're not actually doing the one for celiac, or— this is specifically so— at my institution it literally says "HLA test for narcolepsy". So yeah it's widely available, there's— at least in the United States this should be available everywhere.

Julie: Mm-kay. Just I feel like it is— I know it's not diagnostic in and of itself but it's a good clue and, um—

Dr. Ruoff: Yeah. Yeah.

Julie: —and I'm often surprised how many people, their doctors didn't even look at this and so I'm glad you have highlighted it here as something that a patient could probably ask their doctor for if they're in this confusing middle ground—

Dr. Ruoff: Yeah, yeah.

Julie: — and not sure.

Dr. Ruoff: It's an important point, so let me just— HLA, it varies by ethnicity but if you just go with say, maybe 25% of the general population walks around with this HLA positivity. Just because you're positive doesn't mean— doesn't immediately put you into the type 1 narcolepsy bin, but it doesn't exclude. If you're negative, it really just keeping it very simplistic, you know, however the— it really almost excludes orexin deficiency. So it immediately kind of makes the narcolepsy type 2 diagnosis, could make it more homogenous. Which is the goal in that if it's— if you're negative then you're more certain to be type 2. It does vary by ethnicity, so like African Americans they have a high positivity. Japanese ancestry have a low positivity of this. So, it can be— clinically it's very helpful when it's negative. If it's a challenging case of a-typical cataplexy. And don't forget there can always be some— psychiatry, antidepressants for example, are a great treatment potentially for cataplexy. So you know it's always this debate as to whether, oh my goodness, sleepiness started three years ago— patients been on an antidepressant for 10 years— could this antidepressant be masking the cataplexy. And that's where this might come into play, doing the HLA test. But widely available, and if you're confused about your diagnosis, your healthcare provider isn't sure— that might be a great place, especially if there's questions of cataplexy.

Julie: One other question, why is the actigraphy helpful, I— I am just not familiar with why that would be a helpful tool.

Dr. Ruoff: Yeah, yeah. Great question. So going back to the differential, right. So we want to look at insufficient sleep, we want to look for long sleep— potentially. So it immediately will give us an objective assessment of that. It also will look at, is the patient not getting enough sleep during the week and then playing catchup on the weekend? If the MSLT is negative and one of the core complaints of the patient is sleepiness and long sleep, they have to— they're sleeping long hours, then actigraphy is a way that you can actually cinch according to ICSD-3 a diagnosis of idiopathic hypersomnia. So somebody could have a negative MSLT, their MSLT

does not suggest a CNS hypersomnia like narcolepsy, idiopathic hypersomnia. But while wearing one of these for two weeks or— or coming in for an ad-lib 24 hour, 48 hour sleep study, which is near impossible in the United States unless it's research— you document that they're sleeping, you know, 600, 660 minutes, on average, each night. Which is a lot. So that's what, 10-11 hours of sleep a night on average. But that's where it can be very helpful and it can actually lead to an ICSD-3 diagnosis of idiopathic hypersomnia. But it's also used to rate— you know for ruling out things too, right. Is the patient just insufficient sleep, are they all over the map, going to bed late one night, early the next. They have a self inflicted perpetual jet lag. They don't know if they're coming or going, so it can be very helpful.

Dr. Ruoff: Diagnostic criteria, so for type 1 narcolepsy what do we need here. So, we need sleepiness for at least three months, and the presence of one or both of the following, so cataplexy and a positive MSLT. So I inevitably will say positive MSLT. So what does that mean? It means on those five naps, on average, the patient falls asleep in less than eight minutes, less than equal to eight minutes, and on two of the naps they immediately go into REM sleep within 15 minutes. And so we term that a SOREM, a Sleep Onset REM Period. So less than equal to eight minutes average sleep latency of falling asleep, and then going into two or more REMs on the naps. And also on the overnight test if they slip into dream sleep within 15 minutes, that can count towards this. This number, you know this eight minutes used to be five minutes, I won't go back too far historically— all the changes, but it used to be five minutes but it was increased to eight minutes to increase the sensitivity and it maintained about the same level of specificity.

Dr. Ruoff: Or, a lumbar puncture to check for orexin or hypocretin. Sorry, we love— in the medical community we like to have at least two names for everything, so hypocretin orexin. And so that can be diagnostic for type 1 narcolepsy as well. Without cataplexy. You don't have— 'cause it's one or both. So someone could not have cataplexy, but have orexin deficiency and be diagnosed with type 1 narcolepsy. Narcolepsy type 2, so same thing— first thing, at least three months of sleepiness, a positive MSLT. The overnight study, it's always important to have an overnight study followed by a day time MSLT. That is the standard. So anyone out there that had them separate, that's a problem. And cataplexy is not present. And if a hypocretin lumbar puncture was done to check orexin levels, it's normal. Or in more than 1/10th. And the sleepiness complaint is better explained by something else. This is what Julie talked about. Is there another condition? Is there any findings on the neurologics exam. Any medical disorder. Medications, psychiatric illnesses that might be contributing. Is there a circadian rhythm, is there delayed sleep phase, going to bed very, very late and then waking up, you know, later in the day. Yet societal pressures force those folks, or us, to you know wake up early. That's the goal here, in society, it seems. So looking for other possible explanations.

Dr. Ruoff: Idiopathic hypersomnia, so again— sleepiness for three months, no cataplexy. This is the difference right here, so right now in the current diagnostic criteria, idiopathic hypersomnia versus narcolepsy is simply differentiated by number of SOREMs. The sleep onset REM period. So both narcolepsy and idiopathic hypersomnia have to, on the MSLT, have to fall asleep on average in less than equal to eight minutes. But with IH there's not a REM propensity, so they have less out of all those five naps, there's less than two, so there can be one sleep onset REM period, but they can't have two. If they have two then that would put them in a narcolepsy bin. So this is the really the differentiating factor between narcolepsy type 2 and IH. And the presence of at least one of the following, this is what— this is to your question Julie, the actigraphy. So actigraphy, the actigraphy watch, the glorified medical grade accelerometer, demonstrates more than 660 minutes or you're fortunate enough to get a 24 hour overnight or 24 hour PSG polysomnogram, if you can cinch this 660, this is according to ICSD-3 supports a diagnosis of idiopathic hypersomnia. Hence my point that I don't think that we're doing

actigraphy enough. And then again, kind of the last number similar to the narcolepsy is, looking for other potential causes that might better explain this sleepiness.

Dr. Ruoff: So what are we left with? So, we're left with kind of two things, we're left with narcolepsy which we now differentiate between narcolepsy type 1 that typically can have cataplexy but it doesn't have to have cataplexy— and if a spinal tap is done they're orexin deficient, hypocretin deficient. And then idiopathic hypersomnia. How I differentiate in the clinic, so sleepiness with narcolepsy and sleepiness, brain fog— brain fog comes up more in the idiopathic hypersomnia literature, but certainly this is not absolute. Just kind of a clinical phenotype, I'm just trying to paint here. With cataplexy so we're trying to get in, typical versus a-typical cataplexy versus no cataplexy, right. So ideally with no cataplexy that's more of a narcolepsy type 2. And IH of course no cataplexy.

Dr. Ruoff: The restorative nature of sleep and naps, more so with narcolepsy phenotype. Less so with IH, right. So non-restorative long periods of sleep, naps are less refreshing, which in some instances when you get this history it's like, why did you take a nap to begin with? Because they almost wake up worse off than before they took a nap. And it sometimes can last hours with IH. Typically. Again, wake up feeling refreshed— the sleep intertia, sleep drunkenness in the IH phenotype, that's certainly a big one. A clue. More of the REM related phenomenon, the hallucinations we talked of, the paralysis, disrupted nighttime sleep, that fits more of a narcolepsy phenotype. And then IH more classically there's no REM related phenomena but REM related phenomena can occur in the general population so just because someone has sleep paralysis does not mean, oh my goodness they have narcolepsy. That's an important point. And depending upon the study you quote, maybe five, 10, plus percent of the general population have experienced sleep paralysis. And even higher with the hallucinations. So just because someone has sleep paralysis hallucinations and they're not sleepy, does not mean oh my goodness I need you to go see a sleep doctor to be evaluated for narcolepsy. But if they have those and they're sleepy, then you might have something there.

Dr. Ruoff: Comorbid sleep disorders, so in the narcolepsy phenotype, more REM behavior disorder, acting out their dreams, leg twitches, sleep apnea. In the IH, really kind of the cardinal rule is to rule out other sleep disorders. Because we don't understand the underlying pathophysiology it's difficult at least for me to say that there's, oh, in IH there's this comorbid condition. Similar to the narcolepsy type 2, until we understand the under— you know the pathophysiologic underpinnings, it's difficult to say, oh there's comorbid conditions. But in NT1 there's been plenty of comorbidities described and replicated, obesity, nocturnal eating, precocious puberty, psychiatric illnesses. And with IH, you just want to be— and narcolepsy type 2, you just want to make sure that, or I question that the comorbidities— they might be actually contributing to the clinical picture. So psychiatric overtones in IH and narcolepsy type 2. Autonomic symptoms, in the IH phenotype. For some reason a lot of the patients that I see have some autonomic symptoms, and ultimately go on to be diagnosed with IH.

Dr. Ruoff: So, kind of putting these into bins. Certainly I feel like there is a clinical phenotype when I'm seeing— evaluating patients for hypersomnia. But then ultimately we're left with the MSLT to differentiate these two. Another important point and I've highlighted it already, in patients with narcolepsy without cataplexy, so this is type 2 narcolepsy— if they undergo a spinal tap, if you had the HLA so you had a question of, do I have type 1 or whatnot, or do I have a-typical cataplexy and you got the HLA test, your healthcare provider ordered it for you— and it were positive, in some publications if you did a spinal tap, even though you don't have

cataplexy, 15-20% of those patients have a chance of being found to be orexin deficient. What does that do? Well that then changes your diagnosis to narcolepsy type 1. And I think this is an important point to mention as well, so in this study by Andlauer et al., African Americans were 4.5 fold more likely to be found to have orexin deficiency without cataplexy, compared to Caucasians. So, clinically if I'm evaluating a patient with a CNS hypersomnia and they're African American, I'm paying very close attention to the presence or absence of a-typical cataplexy and really thinking about this after the MSLT is performed, that maybe we should be doing HLA and at least talking about orexin testing. My goal as a clinician is to try to pull out as much— yeah just to— if we have a chance to do HLA and find orexin deficiency we should be doing that. To better define these conditions for patients, family members and for prognosis.

Dr. Ruoff: So what are some of the MSLT challenges, the daytime study. So these are the challenges, so the MSLT is positive for narcolepsy in the general population in six out of 100 men and one out of 100 women. That's a problem, see. You run the test on a random sample of the general population and 100 patients and six men and one woman are going to be positive for narcolepsy, regardless of symptoms. And—

Julie: This is the general population?

Dr. Ruoff: —general population, this is not people presenting for daytime sleepiness.

Julie: They would go and remind us, that would be falling asleep within eight minutes—

Dr. Ruoff: Less than equal to eight minutes and having at least two dream periods.

Julie: Wow.

Dr. Ruoff: So this gets to false positives, right. So if someone comes in complaining about fatigue and their GP sends them to a sleep doctor and they just are doing MSLTs a lot, there is a true risk based on this general population data to have false positives. False positive diagnosis. Maybe this isn't narcolepsy. So to your point Julie, it's always you know, making sure that if there are other symptoms you know delve into those other symptoms and make sure that there's not another explanation out there. Like you alluded to, Lupus or something like that. And, in the general population, the MSLT, so falling asleep in less than eight minutes, that was positive in these studies in about 22% of the general population. That's high. Remember that's the diagnostic criteria for idiopathic hypersomnia, less than equal to eight minutes. And so, that's you know if we just general population, had 100 patients come in from the general population, that the 22% of them would meet this criteria. Shift workers. So I use— use shift workers loosely, so if someone is having this social jetlag of being insufficient with their sleep during the week and then catching up on the weekend, that's essentially kind of a— a social jet lag is a kind of a form of— at least a circadian you know, irregularity. And, so that increases the likelihood potentially of a positive MSLT. 30 times more likely with shift workers to have a positive MSLT.

Dr. Ruoff: Antidepressant use— 11 times more likely to have a positive MSLT, positive meaning for narcolepsy. And getting, speaking to the IH community— in this study, they really leveraged the power of doing ad lib overnight sleep testing, you know, 24— I think 24-48 hours. 44% and 39%, two different studies here of patients with IH had a mean sleep latency of greater than

equal to eight minutes. And so with additional tests, a 24 hour sleep study, they were able to demonstrate a diagnosis of IH. But if that clinician, if their healthcare providers had only done the overnight tests and the MSLT they would have been missed. And so this is where in the U.S., we don't have the luxury of 24 hour sleep tests and so. Yet, actigraphy can be helpful. And, in 71% of the IH folks with long sleep, 71% had a mean sleep latency of greater than equal to eight minutes. So on one hand given the general population 22% meeting this criteria, but in these folks they're not meeting this criteria. And so then over the last you know five years or so, another thing that's been called into question is the repeatability. How robust is this MSLT. So that if you do it today and then you do it two years, three years from now— does it end up with the same result? And so—

Julie: I meant to say this in the beginning, you know, your paper and your work in this area is why we really wanted to have you as part of this discussion, because of this research that you did and I think it's really helpful for people to understand, because they're often like, how could my diagnosis change? And thinking it's just them, and guys it's not just you. [laughs] If your diagnosis is changing, so anyway— go ahead, but I meant to say that in the beginning. [laughing]

Dr. Ruoff: Yeah, yeah. And so probably I should have probably presented this other information after this, as a potential explanation as to why this is occurring, or why we found this. So, three different studies, so it's been replicated. Now all these studies are retrospective, that is a huge limitation. So this isn't something perspective that I see a patient, we do an overnight test, an MSLT and then prescriptively we do a repeat MSLT six months, a year later, and see is the— is the repeatability of that stable across time. So a big question and limitation is why was the study repeated in these data. But, what we found across three different studies is that the MSLT and type 1 narcolepsy with cataplexy or hypocretin orexin deficiency— or typical cataplexy in HLA positive, that blood test positive— it's pretty test, re-test, the repeatability of it, 91% of folks that have a positive MSLT on the first positive test— on a first MSLT, they'll go on to have another one that's positive. That's what you want to see, right? So, when you talk to loved ones and stuff about your condition you want to say yeah, I had an MSLT and it showed this and it's a repeatable, reliable test and if I did it in six months it'd be positive again. That's what you want to see. And in this other group it was 81% likely to be— if you did a repeat it would be positive again. Whereas, in narcolepsy type 2 and IH, it's not a stable phenotype. If a patient is rendered a diagnosis of narcolepsy type 2 they meet the MSLT criteria, they don't have cataplexy, if they have the spinal tap and their orexin or hypocretin is normal, if you repeat that test, that MSLT, it could change. It could go negative, it can switch to idiopathic hypersomnia, and vice versa. Same thing goes with idiopathic hypersomnia. So, a patient has a daytime test, they're falling asleep less than equal to eight minutes. Six months, a year, two years, three years later, they repeat it— it'll be negative. And so this is extremely frustrating, not only for patients but healthcare providers. And this is the biggest challenge that we face in evaluating CNS hypersomnias. The MSLT is our best objective test to measure sleep ability, the likelihood if someone's told to fall asleep, to try to fall asleep— but there's huge limitations at least in type 2 narcolepsy and IH. And so while I believe just clinically my view is that there's a clinical phenotype I think with narcolepsy type 2 versus IH. Certainly with IH with long sleep. The MSLT I don't know if that's really the test in the future that we should be using to differentiate these conditions as we're doing today. So what to do. You know if you have an MSLT and you know your loved ones around you and everyone you know they strongly suspect a CNS hypersomnia, there's sleepiness, you see it with your own eyes— family members. The question is, to repeat the test or not. Certainly for clinical care and getting access to things it can be very helpful if the MSLT wasn't what was expected. It was negative, it was positive for IH. So this is a clinical

matter. But from a research perspective or just a diagnostic issue, this is troubling. The MSLT is not a reliable test according to these three different studies here. So these are three different you know research groups, with different patients, that came to very similar conclusions here. So that's the challenge. So the real question is, you know, where do we go from here? So the most or best, robust objective test we have— is not repeatable. At least in this data here.

Julie: Yeah. And I feel like it's just not fair to patients to have to feel like you're going into an MSLT and just hoping that your brain goes into the right forms and— because everyone's experience is very real, you know. And their symptoms are real like you said, family members— it's real. And so this kind of feels like you're throwing a dart at a dartboard, to see if— could get an MSLT result that's going to be helpful for medication and coverage.

Dr. Ruoff: Yeah. And so, now some other explanations right, so we talked about shift work, that that you know is a high likelihood of a positive MSLT, right. 30 fold increase risk. So that's why you know that we recently came out with new guidelines for the MSLT and it's just so important that healthcare providers but also patients also kind of advocate and— Project Sleep and everything that we're doing, the overnight test and the MSLT, to a T. So we're getting the actigraphy for two weeks, you know. You're bringing family members, caregivers, family member, caregiver, friend, whatever, loved ones to those appointments to establish that patient doctor relationship, that repoire. You know, visit one. It's so critical because of these issues. You know some might argue that we should be really diagnosing this based on symptoms. Symptomatology. Which is challenging, because we really like to have an objective test to say, "Ah-ha! This test is positive." But that's out there, that we should rely more upon symptoms. Which having caregivers and patients and family members or friends there is very important in that situation. I'm not suggesting that we go to that, but— just emphasizing, yeah, it's challenging. So, where do we go from here, right? And I don't have the answer.

Dr. Ruoff: So what I didn't show here is— so historically right, so in like 2000, that's when it was discovered that narcolepsy in humans was due to— narcolepsy type 1 with cataplexy was due to orexin deficiency, hypocretin deficiency. So before then, you know we had HLA— some of these HLA findings that in narcolepsy with cataplexy, they were more positive for HLA markers, but it wasn't 'til 2000 where we were able to take these patients, say look! Ah-ha! We have a biologically confirmed entity here. So now we can define this group as a homogenous group. So we pull those out. And my feeling is, and this can be debated back and forth, but that really the next step as to what to do with this— these patients that have an MSLT that on one time it shows narcolepsy type 2 and the next time it shows IH and vice versa, what do we do with those patients. I think the first thing is that we pull— what else can we pull out? So, I highlighted— so African Americans, narcolepsy type 2, more likely not to have cataplexy. And yet have orexin deficiency. Take those out of there, right. So be more— when you're evaluating patients or you're advocating for a loved one, keep that in mind. And then long sleep. So there's been some of these really nice cluster analysis looking at— you know, symptomatology and clustering. And it does appear idiopathic hypersomnia with long sleep, my belief based on the data, is that that's a pretty homogenous group, so I think that intuitively that's the next step, is to take those patients and kind of put them in their own diagnostic entity. Which is why I think that we're not doing enough actigraphy, not doing enough prolonged PSG overnight sleep testing, to define that group of patients, capture that group of patients. And then what we're left with is this— potentially is— in my study I think maybe 30% of the type 2 narcolepsies— narcolepsy patients repeated both times positive. So maybe perhaps I'm not suggesting that we do two MSLTs to define this strong repeatable reliable phenotype, but maybe that is a reliable phenotype. Where if you have patients with two positive MSLTs for narcolepsy, maybe that's a

phenotype that we can study and learn from. So, you know there's been other studies looking at these conditions using tools like imaging, and a lot of the imaging findings in CNS hypersomnias are not consistent. And it's probably because we're not phenotyping these patients into homogenous groups. So until we can do that we really can't advance the field. I feel like.

Julie: Yeah, I mean there's a few proposals out right now about—

Dr. Ruoff: Yeah.

Julie: —what to, where to go from here, and— we'll make sure those are in our toolkit and you know, for our nerds that love reading papers, they're interesting and— and I think we will see some change, when they do the next ICD International Classification—

Dr. Ruoff: Hopefully.

Julie: Yeah. Because it just doesn't seem right that people should feel like, I mean you get attached to a disease name you know like, okay I figured it out. and these are already very stigmatized conditions and then to have your, like, disease name changed— it is a big change in people's sense of identity even though I think from a research side we'd say, you're still part of our club, don't worry! [laughs] you know you're part of our community, your symptoms are real, you're having a real experience and you know it shouldn't— it shouldn't be able to switch that easily I think, on people. Just from a personal perspective. You did mention a-typical cataplexy and I'm not so familiar with the use of that term, so.

Dr. Ruoff: Yeah. Yeah, so you know, the— clinically, you know when I'm asking this question, you know does anything unusual happen with laughter, saying something funny, coming up with a witty joke— that's usually how I ask it to a patient. And typically a patient that doesn't have a CNS hypersomnia doesn't have, you know, cataplexy— they look at me dumbfounded like, what in the world? Does anything happen? And typically the jokester says, oh— no one laughs. I'm telling a joke, no one laughs, that's what happens. Like ha, ha, ha. But the other thing that happens often is like, well what do you mean? When I laugh? You know so then so leading them— not leading them, asking in a very unbiased basis is really important. But typically after they're kind of looking at me like puzzled like, this guy's weird— some weird questions there— I'm like, such as— jaw sagging, knees buckling, falling to the ground, those kinds of things. And you know, in the Journal of Clinic you know 99.99% say oh no, no, not that. Occasionally you might get someone that says well yeah, when I laugh really hard or something like that, something might happen. Like the classic kind of cliche thing of, I laughed so hard I fell to the ground, right. So that's a positive emotion, laughter, right. So there's negative emotions too, right. Anger, startled, scared, these are all negative emotions. So, typical cataplexy is typically triggered by a positive emotion, so classically laughter. That is the right trigger, the duration is another thing, right. So duration, the typical duration is pretty short. And I'm not the one that should be talking to that, I mean that's the patients that should be talking to you about that but, you know it's a-typical for cataplexy to go on for prolonged periods of time, you know, hours. If that's there then we like to hear that oh, there's also you know, shorter— typical is a short attack. It's not typical to always fall to the ground, not to have any warning. Have an injury. So that would be a-typical. It can happen, but it's not typical and there should also be these more typical episodes triggered by a positive emotion. So, the classic thing, short duration triggered by a positive emotion, typically you know affecting the neck, the shoulders, the head bobbing,

maybe a little bit of knee buckling. And it's not so rapid that there's not time to prevent injury. I equate it to like an accordion collapse. And so that's typical versus a-typical. So a-typical would be a negative emotion only, long duration, those kinds of things. Whereas typical would be a positive emotion, you know, 10 seconds, short duration— those sort of things.

Julie: I feel like I hear from a lot of people, very subtle, even more subtle than the jaw dropping— people saying like, a pa— like having to sort of pause, you know and this is true to my experience living with severe cataplexy, is that when I'm on medication you know those are kind of your internal coping is like, oh I kind of just— kind of like, pause myself, to not make it worse sort of, or— someone had described that they lose their smile, you know. They say, oh you lose your smile when you laugh and that's cause she's having a hard time with her jaw, but not necessarily like dropping open. So it is really interesting to think about, I like how you present more from the idea of like, what happens when you laugh, as opposed to going from the perspective like, are you falling down. Because I think there's a lot of subtlety in many people who have mild cataplexy. Yeah, I'd argue— [laughs] personally, that the idea of positive emotions being typical, is— a little bit of a misnomer? I mean, I think that is because it's unique, whereas, and I've talked to Dr. Scammell about this, negative emotions could cause— you know some sort of like fainting, other things.

Dr. Ruoff: Right.

Julie: And so the positive emotions are more— unique, to cataplexy— but I don't think that that necessarily means that they're entirely more typical, I know annoyance and— were— were early ones for me.

Dr. Ruoff: Yeah, yeah. I think it's just, if there are negative— it's more of a typical case if there's also positive. If there's only negative, and that's it— that would be classified as a-typical. Now, regardless of if that's typical or a-typical, if as we know it now it's kind of on the typical and that's where the HLA testing that we talked about earlier can come into play. The orexin testing, especially if you in your heart as a patient say, "This is cataplexy." Then engage, advocate for yourself and go down this path of HLA. Especially if your MSLT is negative, my goodness gracious.

Julie: You talked a lot about the spinal tap or you know the hypocretin— yeah, there's a real word for it, what did you call it? The—

Dr. Ruoff: Orexin, or hypocretin— spinal—

Julie: The— well— the spinal tap, thing—

Dr. Ruoff: Yeah, yeah, yeah.

Julie: —you know it's used more in Europe now than in the U.S., it's not obviously a comfortable procedure— to have done so, do you think there's any hope for some other ways of measuring— [laughs] hypocretin, or—

Dr. Ruoff: Yeah it would be great, it would really—

Julie: —is this kind of the main one, and—

Dr. Ruoff: —it would revolutionize evaluation and diagnosis if we had a blood test, but— that's an important point, the HLA is not diagnostic, right, that we talked about. There's not really a blood test that diagnoses narcolepsy or IH yet. So I'm not aware of you know, any developments in this space. There's nothing coming to us in the near future, that's for sure.

Julie: Right, so do you think that the—-

Dr. Ruoff: Not that I'm aware of.

Julie: —that we will like, that there's going to be increased use of that spinal tap, in the U.S.?

Dr. Ruoff: So it's been part of our diagnostic criteria since 2014, right. So, 2000ish, this is how history— research, unfolds, so— 2000 we see, we find orexin deficiency in humans for narcolepsy, right. 2014, it finally makes it into the diagnostic criteria. 2019, at least in the United States, it's now commercially available. That's great that it's now commercially available, but— it took us 19 years to get it to where it's not just research, it's commercially available.

Julie: Thank you so much, Dr. Ruoff, for coming in and tackling this challenging topic, I know it's a lot. Really quick, just want to of course mention the patient organizations because they are incredible and they are important and they have so many different great resources, so. Especially when you're thinking about hypersomnia, check out the Hypersomnia Foundation, has so many incredible online resources. Narcolepsy Network, of course us, and Wake Up Narcolepsy has a lot going on all throughout the year. So check these out. International ones are online. Everybody, thank you, Dr. Ruoff!

Dr. Ruoff: Thank you so much.

Julie: Alright, bye for now.

Access the toolkit for this episode here.

Narcolepsy Nerd Alert episodes are available in many formats to listen, watch or read.