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Addressing Insomnia in Patients with Alzheimer's Disease

Announcer:
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Dr. Neubauer:
Insomnia is often associated with Alzheimer's disease and has long been a burden for both patients and caregivers. And with new research suggesting there may actually be a bidirectional relationship between these two, it's time we take a deeper look into this connection and how we can better manage our patients. This is CME on ReachMD. I'm Dr. David Neubauer, and joining me in this discussion is Dr. Richard Isaacson. Dr. Isaacson, thanks for being here today.

Dr. Isaacson:
Thanks so much, David. I've been really looking forward to this chat. Um, hopefully we can learn a little bit from each other.

Dr. Neubauer:
Great. So why don't we start, Dr. Isaacson, with a brief discussion of Alzheimer's disease, including its definition, key characteristics, and prevalence.

Dr. Isaacson:
Sure. So, Alzheimer's disease is a progressive neurological disorder. It's a brain disease that affects a variety of things. I think some people think of Alzheimer's as a problem with short-term memory, and then changes in other thinking and cognitive skills, changes in executive function, changes in language, but really it affects the whole brain. So it's in some ways a neuropsychiatric disease. It can change a person's behaviors, it can change a person's, um uh, really anything, including sleep. And today, um, really one of the most, um, under really recognized aspects of Alzheimer's is the changes in sleep. And that's why I'm excited to be here. When it comes to understanding the key pathological findings, I think traditionally, and for me in medical school, I was taught that the things that cause Alzheimer's disease are amyloid. Amyloid is the protein – a protein that aggregates in the brain; these sticky plaques that build up in the brain. And amyloid beta is found, uh, when you look at the brain of a person with Alzheimer's disease after they pass away on an autopsy. However, we now have biomarkers, amyloid-based PET scanning for example, that can understand that we actually – that we know that there's amyloid in the brain, even before the person passes away. Another key pathologic finding is tau, and tau, or

neurofibrillary tangles that are made up of the tau protein are also a key pathophysiologic finding. However, we're really just not exactly sure what causes Alzheimer's disease, and some people even think that amyloid actually may not be a cause, but it may be a harbinger, or it may be a characteristic that builds up over time. And the – the sentence that I think characterizes this is that, you know, sometimes if you don't take the garbage out, you're going to get sick. And the accumulation of amyloid may be in response to something else, and the amyloid is just a garbage that accumulates that we can detect later. So whether it's problems with oxidative stress, inflammation, infection, uh, glucose hypometabolism, and um, really insulin resistance, I think there's a variety of likely possibilities that may promote pathology in Alzheimer's disease and may lead to some of the, uh, symptoms, as well as the increase in prevalence. When it comes to the prevalence in the progression, Alzheimer's disease is a slowly progressive neurodegenerative disorder. So when someone initially starts having those initial symptoms, they may have something called mild cognitive impairment due to Alzheimer's disease. This means that symptoms of cognitive dysfunction are beginning, but the person can still take care of themselves, so they don't necessarily have something that's called dementia. Alzheimer's dementia progresses over time. And when someone has MCI or the earlier first symptomatic stage of Alzheimer's, their range of about 15% per year a person can convert to Alzheimer's dementia. Uh, Alzheimer's dementia basically continues to decline through mild, moderate, and severe stages, and during these stages, uh, people become more dependent on others for care. These symptoms can progress over a few months, a few years, and sometimes over a decade or more. When it comes to care providers, you know, Alzheimer's disease doesn't just affect the fam – the patient, it affects the entire family. And it's really important for care providers, as well as, uh, the spouse, the children, uh, extended family members, and – and paid caregivers to understand all these idiosyncrasies and understand that there are many different characteristics of Alzheimer's, um, and that the person really needs supervision help. And finally, when it comes to societal burden, um, it's just shocking. I – I really believe, um, that Alzheimer's disease is really a public health urgency, if not emergency. For, in fact, the cost of Alzheimer's disease are, you know, billions of dollars every year, and it may bankrupt our entire medical system if some sort of therapy or some intervention isn't found soon. So, in keeping with that background and information in mind, Dr. Neubauer, let's move on to insomnia. What can you tell us about key features, its prevalence, and even possible causes?

Dr. Neubauer:
So, we'll first talk about insomnia generally in terms of the diagnostic criteria. You know, first there needs to be that nighttime sleep complaint, which might be difficulty falling asleep, staying asleep, waking up too early. Now that's really a subjective complaint. We recognize that people with Alzheimer's disease, um, have, uh, quite a spectrum of their, uh, disability, and some, you know, on the extreme end are not really in a position to offer subjective complaints. And that's why in the most recent nosologies it's included care provider reports with regard to sleep-wake patterns, so it easily fits into this criteria. There needs to be some degree of daytime consequences associated with the nighttime sleep complaint. There needs to be the adequate opportunity for sleep to occur, as well. Finally, in terms of the diagnostic criteria, should be a problem three nights a week, uh, for at least three months. Now we recognize, uh, with dementia patients, oftentimes that's very long-term sleep disturbance. The prevalence is – is relatively high, at least, uh, half of individuals, you know, diagnosed with Alzheimer's disease do have a sleep disturbance and, uh, of course that goes along with the severity, as well, uh, increasing with worse severity. Now we recognize generally with regard to the prevalence of insomnia, it tends to get worse as people age, but we don't really think that – that bad sleep should be a consequence of aging; rather, it seems to go along with the comorbidities that increase with aging. So some of the possible causes, um, for – for that worsening of sleep as we age, might really just be circadian rhythm issues, so we know that circadian clock has a very robust effect on the timing of our nighttime sleepiness and daytime alertness. That whole pattern tends to shift a bit earlier as we age, and therefore, early morning awakening, uh, may occur more naturally as we age, but also, um, sleepiness in the evening may come on earlier, although people don't necessarily go to bed earlier. It's been speculated that, uh, melatonin is either lower or perhaps has an abnormal distribution with aging that might affect the sleep-wake cycle. The environment is a – is an important factor, as well. So we think that a lot of activity in the daytime and a lot of light exposure in the daytime is really good, and darkness at nighttime, but in some settings, people really are not able to take advantage of those regulatory processes of external factors that help maintain the robustness of the cycle.

Dr. Isaacson:
Thanks so much for breaking that down for us. Is there any bidirectionality in the relationship of sleep and Alzheimer's

disease?

Dr. Neubauer:
Well, that is exactly the current thinking, and that's relatively new. You know, we've known for probably a century or more that sleep difficulty accompanies dementia, Alzheimer's disease in particular. So we've known that – the one-way street of dementia leading to sleep problems. We now appreciate the fact that lack of sleep, uh, impairs memory and – and sleep difficulty seems to come on perhaps years earlier than other more obvious aspects of cognitive decline with Alzheimer's disease. And so we now appreciate this – this bidirectionality, and even have, uh, glimpses now of some of the mechanisms that might be responsible for that. So now that we appreciate the – this bidirectional connection exists, Dr. Isaacson, what possible mechanisms support the belief that insufficient sleep is a risk factor for Alzheimer's?

Dr. Isaacson:
Yeah, so I think this area of the science has just evolved so much, you know. When I was in residency in – in med school, there was no – nothing. Nothing in the textbooks, nothing in, you know, journal articles; nothing. But over the last decade, you know, I really feel this whole area has evolved. And you know, whether sleep is a risk factor for Alzheimer's disease, which I think it is, and sleep disturbance meaning, or whether it's just a part of the disease that's manifesting, you know, years or even decades prior to the actual symptomatic phase of Alzheimer's, meaning maybe sleep is a non-cognitive symptom, a disturbance that happens decades before the typical symptoms. You know, we're really trying to elucidate this. So what I would say is that the most exciting aspect of our understanding about the relationship between sleep and Alzheimer's is this mechanism and this, uh, pathway, and this concept called the glymphatic system. And when I first heard this, I kind of, you know, turned my head a little bit and I said, 'What's the glymphatic system?' You know, I understand about the blood stream, and I understand about the lymphatic system when you fight an infection and the lymphatic drainage and all that, but the glymphatic system is really a pathway and a, uh, system that I don't think most people were really aware of at all that existed. And I think it's really been this new area of science. So the glymphatic system is really what is used in the brain to clear metabolic byproducts, or basically, you know, the analogy I used earlier about amyloid potentially being a reactive, uh, you know, protein, that – that changes as confirmation, and then basically it's a garbage that gets accumulated over time. You know, believe it or not, during deep sleep is actually when the garbage or the amyloid gets taken out, and in – in the setting of, you know, clearing these metabolic byproducts, inadequate phases or inadequate lengths or quality of sleep, specifically deep sleep, may be one of these pathophysiologic, um, avenues that we can try to, um, both A: intervene on, and B: try to further understand about the relationship between taking the garbage out, um, if the person is going to be sick, and maybe if we can, you know, promote glymphatic drainage through whatever process; whether through medication, whether through, uh, lifestyle changes, whether through nonpharmacological approaches of sleep. Even I've heard of sleep positioning. Maybe sleeping on your side versus sleeping on your back has different, um you know, effectiveness when it comes to this glymphatic drainage. So, uh, oftentimes I talk to my patients, um, about this, and I really underscore how important sleep is. Um, but I often say, uh, you know, exercise. Exercise is the number one thing a person can do, for example, to – uh, in terms of the evidence, to reduce a person's risk for Alzheimer's disease and to support brain health overall. And you know, as a, you know, colloquially speaking, maybe the exercise loosens up the amyloid and, you know, we've actually seen this in – in mice for example, with reductions of amyloid accumulation, in mice that exercise versus mice that don't. But maybe this glymphatic system is, you take the exercise or whatever else to loosen up the amyloid, and then you take the deep sleep and the glymphatic drainage to loosen it up, and now we're going to get rid of it. We're going to take the trash out. And maybe that's how we can support brain health and, you know, slow Alzheimer's progression. Or um, even reduce risk before symptoms. So, um, you know, this is a complicated topic, and I think it's one that's evolving literally weekly. I see some new studies on this. But Dr. Neubauer, I would now like to ask you what specific sleep problems occur in patients with Alzheimer's disease?

Dr. Neubauer:
Well, from a clinical point of view, I think the best word is fragmentation. You know, sleep deteriorates in a lot of different ways. Um, people have more difficulty falling asleep. Once they get to sleep, they tend to be lighter, easily disrupted, and perhaps the individual is waking up too early. Many people sort of have a flattening of the differentiation between nighttime sleep and daytime alertness, such that they're awake more at nighttime, but then sleeping a lot during the daytime, so no

longer is there that robust differentiation between the nighttime and the daytime. And I think that sort of fits in with the, um, bidirectionality that we're now appreciating. You know, there's less opportunity if there's less deeper sleep for that amyloid clearance to be – to be taking place. Um, there are other aspects of difficulty that people may have at nighttime. There may be wandering behavior. And it might even be that some of the sundowning that can occur in the evening, and into the nighttime, you know, may have relationship to the circadian cycle, and perhaps to, uh, melatonin rhythms, as well. But what excites me so much now is this appreciation of the glymphatic system, because we know that, uh, beta amyloid is better cleared during sleep and, while we're awake, more of it is being produced. And obviously we want to have it cleared out as much as possible. And we think that part of the bidirectionality is really like – like a vicious cycle with, um, poor sleep is leading to, uh, less amyloid clearance, and we think as a result of that, more, um, amyloid beta deposition is actually impairing the functionality of – of the sleep-wake mechanisms.

Dr. Neubauer:
For those just joining us, this is CME on ReachMD. I'm Dr. David Neubauer.

Dr. Isaacson:
And I'm Dr. Richard Isaacson. Together, we're reviewing the latest research on the bidirectional relationship between insomnia and Alzheimer's disease.

So, Dr. Neubauer, continuing right along with our discussion, are there any sleep architectural changes that occur in Alzheimer's patients? And if so, are they different from other forms of insomnia?

Dr. Neubauer:
Well, the quick answer is yes and no. Um, they are similar to other types of insomnia, but much more extreme, and in extreme versions of what we see with a lot of other, uh, elderly individuals with sleep problems. I mentioned fragmentation from a clinical point of view, um, earlier, but also we recognize when doing a sleep study, that sleep is quite fragmented when we're looking at the EEG pattern. There tends to be much less slow-wave sleep, slow-wave activity; both in terms of the amount, but also the amplitude of the actual slow-waves occurring, there tends to be less REM sleep, as well. But also the whole differentiation of sleep stages tends to – to break down. And when we think about just solid sleep being stage 2, where we have spindle activity and K-complexes, those aren't – those don't really have the same sort of, um, morphology as individuals, uh, with healthier brains, uh, who don't have, uh, any sort of dementia. So there are some pretty clear, uh, characteristics that occur. One other interesting aspect of this is that if you look at the power spectrum of the EEG in dementia, it tends to be shifted towards the higher frequencies, and you know, representing the fact that there's less slow-wave activity. And this higher frequency, you know, goes along with greater brain activity, and probably with greater deposition of the amyloid, and less clearance, as well. So it's all part of that – of that vicious cycle that we see.

Dr. Isaacson:
Interesting. And just a quick question, in terms of changes in sleep architecture and changes in REM sleep, dreaming changes, what are your feelings on, you know, I've had patients that have talked to me about changes in dreams, vivid dreams; is REM sleep impacted as much? Or is it each person somewhat of an individual?

Dr. Neubauer:
Yeah. So there's a lot of individual variation. And it's really a tendency for decrease in REM sleep, but it probably is not as, uh, as significant as the decrease in the slow-wave activity. And since sleep is lighter when people are in REM sleep, they may be more aware of that dreaming, and they may complain of vivid dreams and even nightmares, as well. You know, in – in the broader discussion of – of dementia, there also are, um, parasomnias like REM sleep behavior, uh, that occurs of course during REM sleep.

Dr. Isaacson:
And that makes a lot of sense because during slow-wave sleep, or deep sleep, that's when the glymphatic system is most active, so if we have decreased deep sleep or slow-wave sleep, then maybe we have problems with getting rid of the

amyloid, and the person is not doing as well. So that makes a lot of sense.

Dr. Neubauer:
So let's shift gears here and talk about the treatment of patients. Um, can you comment on what nonpharmacologic insomnia treatment options are appropriate for our Alzheimer's disease patients?

Dr. Isaacson:
Oh boy. The nonpharmacologic approaches, um, are just so, so important. And you know, we give these talks and grand rounds and other things, and there's a great paper from several years back by, uh, Cohen Mansfield, that really goes through all of these, you know, uh, aspects that we should think about, both for, you know, people for example with some behavioral changes, as well as sleep disturbances. And, you know, the list really goes on and on, and it's so important, you know. Treating with a medication or a supplement or this or that, sure, important; and there's evidence, and I think it's, you know, a vital part of the picture. But these nonpharmacological approaches are absolutely necessary. So, uh you know, caregiver education is key. Um, spending time with the caregiver, uh, and also the care team to – to help explain this. Recommending books, um, meeting with a social worker, um, probably is among the best things a person can do. Or, you know, sending a person for an actual, you know, uh, discussion with a sleep psychologist is one example. But when it comes to the actual specific things, reinforcing daily routines is key. Um, using environmental strategies, you know, as you alluded to before, um, you know, people that sit in the dark all day, um, how are we going to expect their circadian rhythms to be in order? Well, we probably won't, so making sure to balance the light and darkness, you know. A person with Alzheimer's disease, um, if they're sitting in a dark room, why don't we move them to a lighted area. Maybe put some music on. Maybe put some activating something, um, you know, to keep – keep a person awake and have the person's circadian clock refreshed a little bit with daylight and sunlight. During the night, well, it should be darkness, um you know. I think, uh, oftentimes we have a little crack in the window that lets the light in. Well, maybe we should put some – put something there. You know, in my bedroom, my blinds have that little space, and I decided to put something against the wall to reduce that light coming in to bother you. And it's the same kind of thing with a person with Alzheimer's disease dementia; we want to really try to stimulate these. When it comes to daily routines, you know, being active during the day, listening to stimulating music, listening to the television or something on in the background. But then when it comes to the nighttime, maybe quiet music, calming music. Maybe we shouldn't have loud sounds, um, around. These are things to help balance things. Then finally, you know, cognitive behavioral therapy for insomnia is certainly, uh, a technique that can be used. Um, you know cognitive behavioral therapy has tons and tons of evidence, and especially in what I would say is the most earliest stages, really mild dementia, as well as even mild cognitive impairment due to Alzheimer's disease. These may be the more effective, um, intervention times to consider cognitive behavioral therapy for insomnia.

Dr. Neubauer:
Yeah, I agree. And clearly it needs to be targeted to, uh, to the individual patient and what their capabilities are. But I agree with all of that. I think of it as, uh, as really the infrastructure of treatment of insomnia, and it's – much of it is very applicable to the Alzheimer's population. So let's talk about pharmacologic management. Can you comment on the risks and benefits of, uh, using a medication in this population?

Dr. Isaacson:
Sure. So this is – this is a tough – tough area because we really have to balance the risk versus benefits. And you know, from a practical clinical perspective, uh, whether it was this morning, whether it was last week, I mean, almost every week something comes up with a person with dementia, um, and really balancing, you know, what can we use, you know. What kind of, uh, should we start – always – we always talk about starting low and going slow, but what do we start with? So, first of all, I'd like to just touch on the importance of using caution in cognitively impaired individuals. You know, traditional sleep-inducing medications, um, have a much different effect on someone with cognitive dysfunction than someone without. And also, of course, there's an age effect. You know, older people and more frail people are going to have potentially a much more, um, you know, likelihood for risk rather than benefit from drug interventions from pharma – pharmaceutical intervention supplements, you know, that can maybe promote sleep and – and make someone feel tired, but that hangover effect, uh, may be much worse. And in someone with dementia, the last thing we need is someone to wake up in the middle of the

night, have that hangover effect, be groggy, and then fall or hurt themselves. Um, the other part about this is, you know, kind of along the same lines of the importance of using caution in patients with physical comorbidities. Um, someone that has motor difficulties as it is, you know, when we use certain medications that have sedating side effects, um, they're going to be much more likely to fall. Dr. Neubauer, you know, I'd love for you to kind of give us, uh, you know, a one-by-one overview of some of the medications, supplements, um, some of the over-the-counter things I think, uh, we've seen, um, that people use on their own, the risks and benefits, uh, you know, and of course the FDA-approved medications. There's a lot of emerging therapies, a lot of exciting stuff. Again, when I was in medical school and residency, we just like had almost nothing. We had limited options. Um, I'd really love your – your input here.

Dr. Neubauer:
Sure. Happy to do that. And let me say that, uh, you're exactly right. I agree with you 100% about the caution; both for pharmacodynamic and pharmacokinetic reasons since our older patients are metabolizing medications more slowly often, and the blood levels can build up and be prolonged into the daytime. So, people take so many different things or are given so many different things to try to help with their sleep. I like to put them in four categories; first, there are the dietary supplements. So these are completely unregulated by the FDA. Most of them are pretty benign. Um, the one that FDA has issued warnings about is kava kava. But things like valerian, hops, and these various other things, um, that are promoted for sleep, uh, probably don't do a whole lot in terms of efficacy, but then again, um, the – they're probably relatively safe. The other odd thing that falls into this category though is melatonin, which, you know, we know that melatonin plays a very important role with our circadian system, and our melatonin level comes up in the evening, that helps to quiet down our arousal and help facilitate sleep onset. So it kind of makes sense that people may use that to help them get to sleep. The problem with a lot of older individuals, including the Alzheimer's population, is melatonin already is coming up early, taking more is not likely to have more of an effect. And there are a lot of new questions coming up about, you know, perhaps, some safety issues with melatonin. So, um, it may be benign, it may not. I think the near future is going to teach us a lot more about it as more research is done. The next category is the formal over-the-counter preparations; even the ones that are regulated by the FDA. All of these are antihistamines. Um, they are marketed as sleep aids. So there are two of them: diphenhydramine, doxylamine. They're relatively long-acting, so the effects can linger into the next morning. The real problem with these with the Alzheimer's population or truly for any older individual, is there are also anticholinergic effects, which is exactly what you don't want with an older individual. Uh, that can lead to memory difficulty and confusion and delirium, and so, uh, those are best avoided in older individuals. The third category are the prescription medications that are not approved for treating insomnia, but may be sedating; and therefore are pretty commonly, uh, prescribed. Some of them are antidepressants, some of them are antipsychotics. Really in this category, the one that stands out is trazodone because it's so widely prescribed, and it may be somewhat sedating. And may be beneficial for some people, but I think we should be cautious with older individuals, especially because of the pharmacodynamic activity. So there's a lot of, um, serotonin blockade postsynaptically, but there's also alpha-1 blockade, which can lead to, um, lower blood pressure, orthostatic hypertension, increasing the risk of falls. In fact, there was a study that came out last year. It was a large retrospective, um, case matched control study looking at patients in nursing homes that were either started on trazodone or started on a benzodiazepine receptor agonist medication for their sleep, and the fall risk was about the same in both of those groups. So trazodone did not represent a better alternative for those individuals.

Dr. Neubauer:
So then the fourth category are the prescription medications that are, in fact, approved by the FDA for treating insomnia. So, there are four of those, pharmacodynamically that is. So there are the benzodiazepine receptor agonists. Um, some of them are structural benzodiazepines, some of them are the newer generation non-benzodiazepines, but it's working very similarly pharmacodynamically. So there are five benzodiazepine receptor agonists that structurally are benzodiazepines, and then there are three other newer generation ones that we call non-benzodiazepines; either zolpidem, zaleplon, eszopiclone, but all of these work in a similar manner. The newer generation are somewhat shorter acting, so that is a benefit. But all of these can be associated with some memory difficulty, uh you know, excessive sedation, ataxia, as well. So as a class, they're far from ideal for our patients with dementia. There is a melatonin receptor agonist, ramelteon; works in a similar way to melatonin, helping to quiet down the circadian arousal in the evening, so may be beneficial for sleep onset. Um, there is a histamine receptor antagonist. So this is low-dose doxepin in 3 and 6 mg, uh, which can be beneficial

for sleep maintenance. And these very low doses have the advantage of not incorporating the anticholinergic activity of some of the other products. Finally, there are orexin antagonists. And there is one on the market now, Suvorexant. And interestingly, this has actually been studied in, uh, Alzheimer's patients. Uh, there was a phase 3 study looking at I think 277 individuals, placebo controlled, and the individuals taking the Suvorexant had a significant improvement in their sleep duration, a decrease in the wake-after sleep onset, was pretty well tolerated. So it's really interesting that this has actually been studied in this population. There are several other orexin antagonists that are in the pipeline, and some may be available soon. One – one reason that these might be particularly beneficial is there are reports suggesting that there is increased orexin, uh, measurable in the brains of people with Alzheimer's disease. And this may go along with the fact, um, uh that there is still so much stimulation during that time. So in addition to these treatment options, Dr. Isaacson, what type of interprofessional collaboration among healthcare providers can help address sleep problems in patients with Alzheimer's disease?

Dr. Isaacson:
So honesty, interprofessional collaboration is so important when it comes to managing people with Alzheimer's that have sleep disturbances. And just like the conversation we had today, David, um, you know, we learned a lot from each other. And even a cognitive neurologist or Alzheimer's specialist jumping on the phone with a sleep specialist, um, even for a few minutes, I think can really hash out a really, uh, more elaborate plan and really understand what outcomes to look for and what treatment options may be the best bet. Um, the other aspect is to really incorporate, uh, um, you know, a social worker. Social worker can really talk about some of the nonpharmacological interventions, um, and also give guidance on an ongoing basis. And then further, physicians extenders, you know, nurse practitioner, physician assistants can also aid in the overall, uh, patient and caregiver educational approaches. And really, education about the variety of options from pharmacologic and nonpharmacologic are really key.

Dr. Neubauer:
And as our discussion comes to a close, let's each sum up the most important take-home messages from today. Dr. Isaacson, I'm going to open up the floor to you first.

Dr. Isaacson:
Sure. So I really learned a lot. Um, I think, the – there's really two take-homes. Number one is that there are things that physicians can do to try to help their patients with Alzheimer's when they have sleep disturbances from a pharmacologic perspective, from a nonpharmacologic perspective; I think I just learned that there's a variety of options, and a variety of newer options out there. And we have to balance the risks and benefits. And the other important thing is that we really need ongoing research, you know, to help us provide guidance on how to treat insomnia in people with Alzheimer's disease. Um, more phase 3 randomized controlled studies, um, are really necessary before we can make even stronger conclusions. But honestly, the take-home point for me is that there are options you can use.

Dr. Neubauer:
Yes, great take-home message there, and thanks for sharing that. And for me, what really stuck out in our discussion was this idea of bidirectionality, and really leading into, uh, the insights of, you know, recognizing how important sleep is, and how we can try to act early to help people, uh, prioritize sleep and to help create situations where people can optimize their sleep. And if – if there's some suspicion of sleep disorders, having those evaluated and treated, because all of that may help slow down, uh, the cognitive decline in this population. But unfortunately, that's all the time we have today. So I want to thank my colleague for helping us better understand insomnia in patients with Alzheimer's disease. Dr. Isaacson, it was a real pleasure speaking with you today.

Dr. Isaacson:
Thanks so much for having me today. I've really enjoyed the conversation.

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