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Insomnia and Comorbidity: High Risk with Poor Outcomes

Narrator Introduction:

This is ReachMD! This Prova Education activity is titled *Insomnia and Comorbidity: High Risk with Poor Outcomes*. It is supported by an independent medical educational grant from Merck.The following is a live lecture recorded at “From Guidelines to Practice: Managing Challenging Cases in Primary Care” in Pasadena, California.

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Your presenter is Dr. Larry Culpepper, professor of Medicine of Family Practice at Boston University.

Dr. Culpepper:

I really want to take you through an understanding of sleep, what it is, and I'm going to answer a question for you that, or at least partly answer a question, that has puzzled us for ages, which is why do we sleep? We're also going to look at three cases, particularly looking at the intersection of insomnia and comorbid medical sleep. So, I'm going to take three cases; one focused on cardiovascular, another on diabetes, and a third on depression, and really look at the interaction of insomnia and those chronic conditions.

So, if you've got a patient with a chronic medical condition sitting in front of you, what's the likelihood that they have insomnia? They often are complaining about musculoskeletal, but look at the frequency of cardiovascular disease which may be silent. The other, flipping that, if you have a patient with a medical condition in front of you, what's the likelihood that they have insomnia? The number of conditions, as we go up the four, it more than doubles from just one condition up to about 40%.

So, 40 to about 60% of patients with chronic insomnia have a considerable hereditable influence on that. When we look at mechanism, we find autonomic and CNS arousal. Hyperarousal is a very common final pathway. What we now understand is we have two systems in the brain. One basically increases the sleep drive throughout the day. The other is a drive to stay awake. The reticular activating system is a key component of that. What happens is that drive is on a circadian rhythm. That can be out of balance, it can be uncoordinated, and it may be that it is a failure of the wake-promoting drive to decrease in the evening.

It was only about the late 1990s that orexin was identified, first time in the brain, and it turns out to be a key component, a key driver, of the arousal system. In what we find is that arousal system involves a number of brain areas, I'm not going to go through them, but they keep the cortex aroused and alert. The best approach is to think of insomnia as having a significant component of dysfunction in the arousal system. Now, when we evaluate a patient, is the duration of sleep important? Well, it actually turns out to be quite important. When you have objective short sleep, that is a real marker for genetic predisposition, it tends to be unremitting and chronic and it goes along very much with basal brain activity we see; glucose, cortisol, and ACTH levels altered.

When I approach a patient, I want to diagnosis insomnia, but I also want to keep in mind my assessment. So, I want to know is it acute or is it chronic? Were there any precipitating events? Is it nightly, intermittently? Is it only during the work week? Is it only on the weekends? When you're in the night, is it onset problems that just can't turn the mind off and go to sleep or is it early morning awakening? I wake up too early and just can't stay asleep and I don't feel rested. How severe is it? We don't have a sleep lab to put them in, but certainly we can get a sense of severity in terms of self-report and then, importantly, what's the impact on function? Other

things we want to think about are expectations, preferences, what medical comorbidities and medications might be an influence? A patient that gets up to urinate and then stays awake for an hour, that is insomnia. When we approach treatment, certainly the base that we start from is sleep hygiene, education, CBT-I which we may not be able to get formally but we can certainly use some of its principles in terms of helping a patient approach their sleep problem, and exercise which is a critical component. The key with exercise is moderate exercise but four to five hours before they go to bed at least and the reason for that is you want core body temperature to come back down because a cool environment and a cool core body temperature is very helpful in getting a patient to sleep. We then have a number of nonspecific treatments; the benzos, the non-benzodiazepines, they tend to act on GABA which is throughout the CNS and is a suppressant. We also have specific agents, melatonin, histamine antagonists, and orexin antagonist that target that awakening system and are the specific brain centers involved in regulating sleep.

CBT works and it works well and it has a lasting influence. CBT takes a while often for it to kick in, whereas pharmacotherapy will often take effect early but then you get rebound insomnia, which is not rebound from the medication, it's just the insomnia that comes back if you've only treated it with pharmacotherapy. So, oftentimes we may use both. When we look at the hypnotics of the benzos and non-benzos, they use GABA which is an inhibitory agent. That is a broad, broad effect on the brain; it's taking a sledgehammer to the entire brain, but it works, and patients know it. Melatonin works. It is not used very often, but what we find is after three to four weeks it really kicks in for some patients, and particularly if patients have circadian problems it may be useful. It certainly is benign in terms of side effects. The antidepressants; we really have two in this class, trazodone, which we often use off-label, and one that I'll show you in a minute that actually has an FDA indication but there are other ways to get it. So, trazodone certainly, H1 antihistamine at the low dose is key and also has the Alpha-1 antagonist effect; that might be useful for nightmares and PTSD. It does have six to eight hours of half-life so it does last through the night. The problem is we don't have studies on this that go beyond about two weeks, so we're not real certain if this preparation really has a long-term effect on sleep. Doxepin low dose is a pure H1 antihistamine. We think of it as an SSRI and, in 1982, it was one of the major branded antidepressants but it was very sedating. What we find is at 3 to 6 mg it is very effective for insomnia, particularly for sleep maintenance and insomnia and keeping people asleep throughout the night and into the next morning. There is also no head-to-head comparison in the literature between the 3 to 6 mg branded approach and the 10 mg dose, so I will leave that for your consideration. Orexin antagonists are fairly new and there is one on the market now. There are a number of these in development that you are going to see coming out over the next few years I expect. What they do is very specifically affect the sleep mechanisms. These are really the most directly affected at targeting the sleep control mechanism. So suvorexin suppresses, inhibits orexin and, in doing so, it inhibits the alerting system in the brain. It's very specific to the sleep system. It doesn't change your sleep profile, so if we look at REM sleep and we look at different stages of sleep, they all increase as patients improve their insomnia.

Let's look at the first patient, a cardiovascular patient. This is a 39-year-old accountant. Think about it, he is doing your taxes, okay? Approach it from that perspective. He comes in for a hypertension follow-up, he has been on benazepril with good control in the past, but recently it's not been keeping his blood pressure in shape. He's got some stressors in his life and, in reviewing it, he also reports that, yes, he's having more difficulty sleeping. He goes to bed at 11:00 and gets up at 6:30, that's seven-and-a-half hours potential sleep. It takes him an hour to get to sleep, that's down to six-and-a-half hours and now he is often waking up at 5:00 a.m. He's not able to stay asleep throughout the night and he doesn't feel good the next day, it's really having an effect. He's having difficulty focusing and concentrating. But it has only been going on for a few months and that's key. This is acute onset. There are stressors involved. If you look at family history, yeah, he's got some red flags in terms of cardiovascular. He does have some arterial narrowing and he is borderline overweight/obese. So, how is insomnia associated with hypertension?

What they found is that those that developed insomnia over time were twice as likely to go on and develop hypertension. Let's go beyond hypertension. How about cardiovascular risk? These are all national registry studies. Taiwan, Sweden, Norway; they all have national registries, so they can track their entire population over years and these are prospected follow-up studies that are done that way. What we find is that acute MIs go up by 70%, stroke goes up by 80 to 90%, first cardiovascular events under that is men and women (both genders) go up 30 to 40%. When we look at congestive heart failure, the number of insomnia symptoms increases your likelihood of then going on later to develop congestive heart failure.

How about contributing mortality, cardiovascular mortality? There are a number of studies here, large, federally-funded study, was reported in circulation a couple of years ago. Those with difficulty initiating and reporting nonrestorative sleep had a 55% increase in total mortality per year over the follow-up and, specifically, cardiovascular mortality increased by about 30%.

Moving to treatment. The first thing is do no harm and what we find is that a big impact on whether beta blockers get into the brain. When we get down to the beta selective and then to atenolol and bisoprolol, which do not cross the blood brain barriers because they're low lipidicity as well, they have marked decrease likelihood of contributing to new insomnia. If we treat insomnia, is it going to help blood pressure? A hypnotic actually does decrease both diastolic and systolic blood pressure and it's particularly impactful when the insomnia improves.

Let's come back to this 39-year-old. We assess him, he's got a recent onset, it's frequent, he's having onset and early morning awakening and he's got some recent stressors. He is down in a pretty significant range; severity is five to six hours subjectively and he would like medication. That's a preference; he just doesn't have time for the CBT. So, if we approach him in terms of treatment, it's new insomnia to him so sleep hygiene is going to be pretty important to think through. Getting him to exercise can be very helpful, it's very augmenting in terms of sleep, moderate use of alcohol and calories, particularly later in the evening is critical. The old idea of "hey, I'll have a glass of wine and it'll put me to sleep," it will put you to sleep but three or four hours later it's going to wake you up and that's the problem, particularly when he has early onset. So, that's certainly something to emphasize. Explain catastrophizing, "oh my god I'm not asleep, I'm going to mess up tomorrow, I just gotta get to sleep." That type of catastrophizing sets in for a lot of patients and is one of the foci of CBT, so explaining to him that, yes, you're going to feel drowsy, but, objectively, your performance doesn't decrease that much with just one night of lost sleep, it's really the chronic cumulative effect that is critical. Epworth Sleepiness Scale, you may not have seen it, but Google it; it's a simple chart, few questions that really helps you gauge the severity of a sleep problem. It's things like how long does it take you to fall asleep if you're just sitting in a quiet room reading or do you fall asleep watching TV, or do you fall asleep at the red light as you drive home? That's kind of a red flag for severe insomnia. So, it's useful. A sleep diary may be helpful. I use these both to find out more about it myself but also to get patients involved in thinking about their sleep. In terms of treatment, I want something short-term so this might be a place where I might use a short-term benzodiazepine. I also might use doxepin since it does have a good impact in terms of the early awakening which the non-benzodiapines is problematic in terms of half-life having something that stays effective six to eight hours into the night but doesn't wipe out the next morning in terms of alertness.

Let's move to diabetes. A 34-year-old, sixth grade teacher comes in with a family history of diabetes that is a little worrisome, overweight, and finds herself irritable. She wants to lose weight. She is concerned about the diabetes. She is tired all the time. Getting a further sleep history, she goes to bed a little bit before 11:00 and alarm is set at 6:00, seven hours and change in terms of possible sleep, but she takes an hour to get to sleep, so that's down to six hours or so and then she wakes and stays awake for at least an hour. We're down into that five hour range and it's been chronic since college. She has just sort of accepted this, it's just her lot in life, but it really is dragging her down at this point. On the weekends, she does compensate but that by itself is not adequate. There's no report of snoring or apneic events by bed partners, so we're thinking of another potential diagnosis. So, again, is it associated? Objective sleep markedly increases, a threefold increase, in your likelihood of having diabetes. This is cross-sectional not cause and effect. We don't sleep well, we don't eat well. Lifestyle intervention advice is helpful, but this just is the impact that we worsen our diets is just behavioral. That active duty military study showed more than twofold increase, it doesn't matter if you look by age, insomnia, chronic insomnia precedes and leads to the development of diabetes. When we look at mechanisms, well, insulin resistance is altered for the worst in those with insomnia, particularly if they have daytime sleepiness which is a good indicator of severity. When a Japanese company looked at their annual checkup data, what they found was the difficulty maintaining asleep and early morning awakening markedly increased diabetes, in the range of two, four, almost a sevenfold increase in diabetes.

Back to our 34-year-old school teacher. She's got chronic insomnia that's been part of her life since college. She complains of being tired but not "I can't sleep." Most nights onset is in the middle of the night so she needs something to start, to keep her asleep. She is not exercising so that's something we're going to kick in. Just start out five minutes more walking, let's move it up to ten minutes, 15 minutes can be very helpful. Education, again, it's catastrophizing. Sleepiness scale or sleep diary may be helpful in terms of letting her monitor her sleep as well as you. Here's a patient with chronic insomnia. I don't want to put her on a benzo. She has tried the OTCs and has already encountered the side effects. Diphenhydramine; the problem with it is it's still in your brain 16 hours later knocking you out the next day when you're trying to be alert and active. So, it's a big downfall. It also has a number of side effects.

I would be looking at something that is going to be targeting specific sleep mechanisms. We've got the sense she wakes up, she keeps alert, and she keeps thinking. She is not turning her brain off at night. So, she needs something to dampen the awakening drive and that's where suvorexant, doxepin, as FDA-indicated treatments may be effective. Trazodone, if you look at the American College of Physicians recommendations, they certainly don't use it first line. Suvorexant here is probably the most specific again, and I definitely would want to get her in to a CBT-like intervention if possible.

Let's move on to the third case. This 55-year-old house painter says "my life's turning gray again." He's had multiple episodes of depression, and it's back. No real new stressors and that's very frequent. But, insomnia and sleep problems may be interactive with onset. So, he's been on escitalopram maintenance therapy and he is noticing his flags for depression; that's why he is in your office, which is decreased innervation, energy, he is a-motivated, has trouble concentrating and focusing, and he's having difficulty sleeping again. He has found that's a real concern because that often is part of the problem. He is really getting down in that five to six-hour range of sleep and it's persistent.

Further assessment is chronic recurrent with depressive episodes. Most nights five hours of sleep, middle of the night and early awakening. That's often a very common pattern with depression. He's tried his wife's alprazolam, it worked, and he liked it. He wants

some for himself. He is willing to take your advice and he's got really no nocturnal concerns and doesn't exercise regularly.

This is looking at the study. Three-and-a-half year follow-up, no psychiatric disorder at baseline, insomnia at baseline, and what we see is from those that continued not to have insomnia only 5% of them became depressed and that bumps up to a sixfold increase up to 31%. Who develops insomnia, in relation to their mental health history? This was a study of New Zealanders, about 1,000 New Zealanders born in '72, '73, and they're still being followed. So, this is a long-term follow-up starting at birth. When we look at insomnia at age 35 and then look back at psychiatric histories that have been assessed repeatedly in this population over time starting at age five, what we find is that patients that develop insomnia, had family histories of depression and anxiety and had lifelong episodes of depression and anxiety, particularly beginning in childhood. Depression and anxiety tends to lead to chronic insomnia. Overall, as we look over the lifespan is anxiety disorders, which tend to be fairly chronic, often precede the insomnia. They very likely contribute to the insomnia, but they precede the insomnia. Does insomnia alter the course of depression? What we find is that those with persistent insomnia, those that continue to have sleep difficulty were much more likely to remain depressed.

Depressed patients or anxious patients that also had insomnia, you're going to see them in the office a lot more commonly; two to three times more visits to us and the insomnia may still be hidden or we may just consider it part of the depression, but it's a comorbid condition. It needs to be focused on separately in addition to the depression, and it certainly has its impairment in terms of work and activity. The key here is that you need to treat both. There have been a number of studies now that show that if you start, if you have a depressed patient, and they have insomnia, and that should be part of the baseline assessment, if you treat both of them from the get go, so you start treatment for both, at the same time, and you look down the line, in terms of the depression status, three months later, six months later, they're more likely to be in remission from depression than if you take a consecutive approach. The latest DSM-5 and the latest insomnia guidelines around diagnosis and treatment categories, eliminate primary insomnia from their vocabulary and secondary insomnia. They're comorbid conditions, and they need to be treated at the same time.

When we look at choice of antidepressant, we certainly do know that there are sedating antidepressants and certainly paroxetine will cause daytime somnolence and mirtazapine at low doses will cause daytime somnolence. Sometimes we use that to help patients get sleep, but overall, there's no systematic effect on insomnia as opposed to daytime somnolence. Zolpidem certainly improves the insomnia but it really doesn't augment the antidepressant effect.

When we look at suicidality, patients with sedative hypnotic use have a significant increase after adjusting for our insomnia. This is certainly an issue to consider in terms of hypnotics and non-benzodiazepine use in depressed patients. Let's go back to our 55-year-old house painter. He's got chronic insomnia and it's a co-traveler with his depression. It's onset, it's the middle of the night, there's early morning awakening, he does have the impact in at five hours; now, his depression is already doubling his likelihood of diabetes and cardiovascular disease and other chronic conditions. Throw insomnia on top of that and he is at marked risk for increase in those chronic conditions. He has tried OTCs, tossed them out; he likes his wife's alprazolam. He is not exercising regularly, and so, again, encourage exercise. This is, again, a patient I would stay away from benzos on. So, he wants a benzo, I don't want him on a benzo. Again, suvorexant, doxepin; they're both going to help with the early morning awakening. They are both very helpful at that range. They don't have the marked knockout effect that the benzos have, which he really liked, in terms of onset, but they are effective at onset. I find that the antihistaminics tend to decrease, particularly their onset effect, with time. There is an accommodation to that to development of tolerance in terms of putting the patients to sleep at the beginning of the night, but the early morning awakening effect does continue long-term. Doxepin certainly would be a reasonable recommendation for him. Suvorexant, again, because of the chronic nature of his condition and the specific targeting would be very useful, and, again, I would emphasize it has a much more gentle, totally different effect in terms of putting people to sleep. They can take a half-hour or so before bedtime and it does significantly cut down on onset insomnia. It doesn't have the psychic knockout effect that the benzos have.

In summary, chronic condition is not a wastebasket diagnosis. Particularly important is significant insomnia, particularly if it's objective and you can often see that just with the hours that they report being in bed and not being awake. Treating it is something to think about doing coterminous with the treatment of those conditions. It's a comorbidity; it's not a primary or secondary thing. Pharmacotherapy, you need to select pharmacotherapy in keeping with the chronicity and pattern of insomnia and the expected duration of treatment. If you're using it like in our very first case, for a short-term insomnia problem, hopefully we can quickly get that patient back to sleeping well, that's where a non-benzo hypnotic might be valuable. Other than that, I would tend to stay away from those.

Narrator Close

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