

Sleep Disorders in Rheumatic Diseases: A Wake-Up Call

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Patricia Katz, PhD (Guest): There's a good probability that it started even before their disease began.

Daniel Barone, MD (Guest): We, as a society, get 1 hour of sleep less than we did 100 years ago.

Meghna Rao (Host): Welcome back to season 3 of Rheum Advisor on Air, the official podcast of Rheumatology Advisor, one of the Haymarket Medical Network's digital publications that focuses on the latest news and research in rheumatology to inform clinical practices.

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I'm your host, Meghna Rao, the senior editor of Rheumatology Advisor. In this season, we will be continuing the conversation about topics in rheumatology, including practice management, data from conferences and scientific meetings, emerging diseases, patient care, and much more.

So, let's dive in!

Meghna: Before we jump into the thick of things today, I'm so excited to announce that my colleague, Liz Borreli, editor of *Neurology Advisor*, will be joining me again as a co-host on this episode. Liz, welcome to *Rheum Advisor on Air*, again!

Lizette Borreli (Guest): Thank you, Meghna. I'm happy to be here, again.

Today's conversation is centered on the prevalence of sleep disorders in patients with chronic diseases, such as rheumatoid arthritis [(RA)], which is common.

The current literature suggests there may be a link between sleep disorders and diseases, like rheumatoid arthritis; however, this relationship is still not well established.

To shed light on sleep disorders and patients with rheumatologic conditions and to identify what sleep disorders this population may be susceptible to, we're joined here with experts in the field to talk more about this relationship and raise awareness of how common and harmful sleep disorders can be for these patients.

Meghna: Let me introduce our guests. Dr Alfred Kim is an assistant professor

of medicine at Washington University School of Medicine in St Louis, Missouri, and the co-director of the Washington University Lupus Clinic. Dr Patricia Katz is a professor of medicine at University of California San Francisco [(UCSF)]. And Dr Daniel Barone is the associate medical director of the Weill Cornell Center for Sleep Medicine and an associate professor of clinical neurology at Weill Cornell Medical College. Dr Barone is also author of “Let’s Talk About Sleep” and “The Story of Sleep From A to Z.” Dr Barone was gracious enough to join us today in-person at the recording studio.

Hello, and welcome everyone!

Dr Barone: Thank you; glad to be here.

Dr Katz: Hi.

Dr Kim: Hello.

Meghna: Now, to get us started, I came across a study published last year led by you, Dr Katz, which showed that approximately two-thirds of patients with rheumatoid arthritis met the criteria for at least 1 sleep disorder. Would you briefly be able to go over these study findings, what did you and your team learn, and what the clinical implications are?

Dr Katz: Sure. So this was a study from a large cohort of people with rheumatoid arthritis (4200 people). We asked them, in addition to our questionnaire measuring sleep quality, we also administered some screening measures for obstructive sleep apnea and restless leg syndrome. What we found was that about 20% of the cohort, which was primarily women, met either criteria for obstructive sleep apnea or had had a diagnosis of sleep apnea. We had about 30% who responded positively to a screen for restless leg syndrome and both of those conditions were associated with poor sleep quality. We also found that 70% had reported sleeping an average of less than 7 hours and [more than] 40% reported sleeping less than 6 hours on average. So, that is also associated with poor health outcomes.

Lizette: So, Dr Barone, as a sleep medicine specialist, how often do you see patients with sleep disorders [who] also have a rheumatologic condition?

Dr Barone: I would say the most common thing that we see is either chronic fatigue syndrome or chronic fatigue associated with rheumatologic disorders or sleep disorders related to pain from, again, fibromyalgia, or things of that nature, or from rheumatoid arthritis, for example. Those can certainly be associated with restless leg syndrome, like Dr Katz, mentioned and it really becomes a bidirectional relationship where those conditions result in poor sleep, and poor sleep then results in more difficult time managing those conditions.

Lizette: On a similar note, in your clinical experience what are some of the most common sleep disorders that present in this patient population?

Dr Barone: Well, I think it's similar to what we find in any patient population, which is sleep apnea and insomnia. Those are very, very common in the general population, as well, but certainly in this group. Also, like restless leg syndrome, periodic limb movements of sleep, which are the sleep correlate of restless leg syndrome, all those things will happen in somebody who is dealing with chronic pain or somebody who is not sleeping well to begin with. The body is in a more irritable state.

Meghna: I just wanted to get your thoughts, Dr Kim. As a practicing rheumatologist and with all this information about the prevalence of sleep disorders in rheumatology, how often do you screen for sleep disorders among your patients? Could you tell us about some of the screening methods that you use at your practice?

Dr Kim: Yeah, sure. Initially, we never used to screen for it because I think culturally, at least in the US, we really de-emphasized the importance of sleep quality, and as a result, I was never trained to even ask questions about it. We got interested largely because [of] a lot of our patients. I pretty much exclusively see patients [with lupus] where, at least based off of published data, both patients [with lupus] and [those with] Sjögren syndrome tend to have the highest rate of sleep disorders of all the autoimmune diseases that are out there.

So, we didn't know which instrument to use because there are so many that are available, particularly from a research perspective. We instituted several different ones, including one that's very powerful called the PSQI, the Pittsburgh Sleep Quality Index instrument. There we found that a little [more than] 80% of our patients hit the cutoff of greater than 5 of some sort of sleep disorder. We didn't know at the time what type of sleep disorder was associated with that.

But I think one of the emerging issues that Dr Katz here and I have been talking, prior to the podcast, about our own – each of us have our own data sets – suggesting that at least when you compare to a more objective assessment of both sleep quality and also circadian rhythm, which is actigraphy, we're not seeing very good relationships in both the RA population and in the lupus population between these patient-reported outcomes [(PROs)] of sleep quality vs the variables that we're seeing and collecting by actigraphy, which then kind of makes us wonder what we're doing with these patient-reported outcomes data. We wanted to move forward with a more stringent instrument that's going to need to be developed.

Dr Katz: I have a cohort, both a rheumatoid arthritis cohort and a lupus cohort, where I've done some objective measures of sleep. It's exactly what Dr Kim said. There's no relationship between the patient-reported measures of sleep quality and any of the sleep measures that we looked at. So, it's a challenge.

Meghna: I wanted to touch a little bit more on the topic of patient care and management itself. Feel free to weigh in. How often have you had patients seek advice for their sleep problems?

Dr Kim: It's almost 0% because, again, our patients have normalized bad sleep as just part of life. So, usually we have to solicit it from them. I think there have been some efforts by some of the other physicians that they've seen and they really focus on sleep length. But I think the one thing they're not really capturing through the questions is the quality of sleep.

The one thing we've seen a lot in our patients [with lupus] is chronic insomnia, kind of, the learned behavior of dissociating actual sleep with feeling fatigued and then the natural circadian rhythms that ensue as things get dark at night. This has been a huge threat for the majority of our patients. About 66% of our patients [with lupus] have chronic insomnia as part of the issues that they have with restorative sleep.

Dr Barone: In the last, probably, 10 years or so, the amount of research and the amount of time that clinicians and researchers have spent on sleep has gone up exponentially. So, hopefully, in the future, these kinds of things will become less prevalent.

Meghna: On that note, an ACR abstract I think that was published in 2019, again, in a study led by you Dr Katz, showed the effect of fatigue on patient sleep in RA. Now, although fatigue is known to be a common occurrence among these patients, why is this still an underaddressed issue?

Dr Katz: That's a good question, but again, if we look at the reports of fatigue in these groups that we've measured sleep, we're not seeing a relationship between fatigue and sleep problems. I get back to the issue that I think is so pervasive that we can't get good separation. I mean, just looking at the lupus group that we [assessed], sleep efficiency was below "normal" for almost three-quarters [of patients]. There's just such poor sleep, overall.

Dr Barone: Yeah, I'd like to go one step further with that. The relationship between chronic pain or rheumatologic diseases and fatigue is so nebulous. Fatigue that we see in the sleep disorders clinic is so hard to pin down. Hypersomnia or sleepiness, there are really only a few major causes of that. If somebody comes in, they're objectively sleepy, and we do polysomnogram followed by an [multiple sleep latency test] (MSLT), which is a nap test, if we do that, we can confirm that they are sleepy and that's usually because of narcolepsy or insufficient sleep or things like idiopathic hypersomnia, which may or may not coexist with rheumatic conditions. But the process of fatigue, it sounds like it's the same thing, but it's not.

Dr Katz: I think, too, that we focused on fatigue as being part of the disease process, so that it might have a link to immunologic factors or other behavioral factors; inactivity, probably, being the primary behavioral factor. Daytime napping affects sleep, but fatigue does have multiple causes in this

group.

But I'll tell you the thing that actually troubled me the most when I looked at my results was that [more than] 50% of the people with RA that we measured with the home-monitoring for obstructive sleep apnea [had] measurable moderate to severe sleep apnea. Some of it was really quite severe, so I think that's a big take-home for practicing rheumatologists to really consider that.

Lizette: I am curious, Dr Barone and our rheumatologists here on this call, do you think there might be a genetic component involved?

Dr Barone: There very well could be. I mean I'll let the rheumatologic colleagues discuss that as far as rheumatology goes, but in terms of sleep disorders, like I was saying before, everything is so multifactorial. Many patients with sleep apnea will have a first-degree relative who also has it, or if somebody has narcolepsy, they'll have a first-degree relative [who] has it. It's nature vs nurture.

Dr Kim: I think to piggyback on that, the risk factors for insomnia/poor sleep [are] so diverse. If we think about the genetics, it might be important for some etiologies vs others. I was really struck by some of the observations about 10 years about narcolepsy potentially being an autoimmune disease, which I think, probably, some portions of it are. The original observation was actually after H1N1 vaccination, where a certain protein that activates the immune system, something called human leukocyte antigens (HLAs) that is found normally in 25% of the human population was enriched by 98% in the narcolepsy group that got vaccinated. It was that particular protein that allowed for the immune system then to attack a certain neuron that expressed this protein called hypocretin.

That entire story I think is a very specific example that may represent a very small fraction, though, of what's going on in potentially the general population, but it's also certainly within the rheumatic disease population.

Dr Katz: There is this hypothesized link between [interleukin] (IL)-6 and the circadian rhythm being pushed forward for people with RA, which corresponds to the peak times of symptoms.

Dr Kim: Dr Barone can also comment about this, but we've known for a very long time that assuming you have normal central circadian rhythms - assuming that's true - we tend to be proinflammatory at night. There is a wide variety of [i]mmune proteins that we call cytokines; these IL-6 levels tend to peak maybe around 3 to 5 am in the morning, depending on the person, and then we become very anti-inflammatory during the daytime.

For reasons that I think are unclear, we do see an earlier kind of peak of IL-6 in patients with rheumatoid arthritis. It's interesting to note that because we tend to associate more inflammatory joint symptoms in the morning with rheumatoid arthritis, so again, is that link the reason why we end up what we call experiencing "morning stiffness" in the RA patient population?

I think there [are] a lot of good data with acute insomnia and immune responses. I think what ends up happening with a lot of our rheumatic disease patients is that this is not just acute insomnia; it's not technically chronic insomnia, but it's long-term likely circadian dysfunction; and we actually still don't fully know how that influences the immune system.

Dr Katz: You know, we did find differences in IL-6 levels in our RA cohort for people who had no or mild obstructive sleep apnea compared [with] those who had moderate to severe [disease].

Meghna: I think that's very interesting. We've been talking about RA and lupus, but would you say that there are any differences between the different disease states in rheumatology with regard to sleep disturbances?

Dr Katz: Yeah, in the ones that I've measured, lupus was worse. [For] the people with lupus, [i]t was more common for them to have a sleep disturbance.

Dr Kim: Yeah, I think that's also true. We haven't looked at RA, but certainly, like I said, 80% of our patients have some sort of sleep disorder if you use that PSQI instrument.

I think the other aspect here too is this multifactorial impact of a wide variety of what appears to be disparate variables impacting sleep – mood disorders, depression, anxiety, stress, so many things, things that contribute to health disparities, for example, housing insecurity, [and] financial insecurity. All of these will pitch in in some way to each person's summation of sleep quality.

I think this is where I was nodding my head when you asked the question about differences between diseases because I certainly perceive that patients [with lupus] probably may have a higher proportion and potentially more severe mood disorder issues. At least in our cohort about 60% of our patients either have severe depression or anxiety, and this has been very persistent over a 3- to 5-year period.

Dr Katz: Well, and a lot of those factors you just mentioned are also going to affect disease activity. We have pretty good evidence that stress affects disease activity in both lupus and RA, for example.

Dr Barone: I call it a tridirectional relationship, instead of a bidirectional, because you have the condition itself, whether it be lupus, whether it be RA, whatever it is that they have, along with a sleep disorder, along with mood disorder, and they usually all come together.

I'd be curious to know from my rheumatologic colleagues, medications like prednisone – I don't know how often you use them – they will definitely disrupt sleep. Where does that fit into this whole picture?

Dr Katz: Well, [w]e do. I totally would have expected the glucocorticoids to

have an effect. In my larger cohort study, when I threw everything into the regression model – disease activity, obesity, comorbidities, other medications – the effects of steroids on these other conditions washed out. I think, though, that's because I was primarily accounting for disease activity, which is going to be associated with these steroids. And it was rheumatoid arthritis.

Dr Kim: Yeah, we also found no statistically significant differences and the effect sizes were actually relatively modest. We dichotomized prednisone utilization based off of what we would consider physiologic dosing, any positive integer up to 7.5 mg, and then above 7.5 mg being supraphysiologic, where we would have expected an effect.

Again, it was surprising when we saw those results, similar to what you guys saw at UCSF, but I think the other aspect here – we may get into some deep weeds here, so I'm going to need Dr Barone to provide additional comments – we haven't really discussed this [d]iscordance between central and peripheral circadian rhythms, which have been associated at the broad population level with increasing cardiovascular events/death. It's potentially one of the explanations why when we have transitions from standard to daylight and vice versa, we have maybe a spike of [myocardial infarction] (MI) and stroke.

I think one of the fascinating things about prednisone is that it can reset peripheral circadian rhythms, but it doesn't reset central circadian rhythms.

And, I've always wondered maybe we need to be trying to measure central circadian rhythms in order to better dose when we're giving steroids because the leading cause of death in both RA and in lupus is cardiovascular disease. Again, the inflammation, probably certainly makes the endothelium much more sensitive. I just wonder given how much glucocorticoids we do use in our patients, whether or not we may be making it a little bit worse just because we aren't timing it. We're making an assumption that their central circadian rhythm is actually normal.

Dr Barone: Well, to kind of piggyback on that, if you look at the general population, the literature is actually very clear on this. When you look at people who do not have obstructive sleep apnea, the risk for an MI or stroke or any kind of cardiovascular event is usually in the window from 6 am to 12 pm, when they're first waking up and the body is kind of getting going. People who have obstructive sleep apnea, they oftentimes have their cardiovascular event from 12 am to 6 am, so in the middle of the night, as all these pressure changes are happening, the inflammation is probably even higher than it should be.

So, you have that, plus the thing that we, as a society, get 1 hour of sleep less than we did 100 years ago, which doesn't sound like much, but if we're looking at, again, broad strokes, that's a major, major problem.

Dr Katz: Wasn't there some research done about nighttime dosing of

prednisone? Are you familiar with that?

Dr Kim: Yeah, so there's that Rayos drug; I can't remember which company makes it. But basically they have that delayed-release prednisone. There's basically a 6-hour coating around it. You take it at 10 pm and then it basically starts to activate at 4 am, again, this makes the assumption that [patients'] central circadian rhythm is actually what we think it is.

Lizette: So, now that we've talked about treatments that are available for patients with rheumatologic conditions and how that can potentially interfere with sleep medications, I'm curious; we have a neurologist here and rheumatologists on this call, how do you guys envision working together to help address sleep disorders in this patient population? [T]his question is more geared for Dr Barone, but the rheumatologists on this call can also weigh in, of course: how often do rheumatologists refer patients for sleep disorders? How does that work?

Dr Barone: I think the first step is just knowing that there is this connection between our fields. Something like chronic fatigue syndrome or something where neither one of us really owns it, I think that happens where the patients are not really sure where to go and that causes a lot of confusion. I think that there just has to be more education, such as this podcast, where rheumatologists, neurologists, other sleep specialists, kind of talk and discuss things. Honestly, I probably only get a handful of referrals from rheumatologists over the course of my year at Cornell, but certainly [hope] that increases after this.

Dr Kim: I think between [Dr Katz] and me, [w]e have influenced the people around us. We have definitely a selection bias. I mean I refer almost all of our patients [with lupus] to our sleep group.

But, I think, on the sleep treatment side, the group has to be both diverse and have deep expertise, because especially with our patients with this chronic insomnia, there's really no medicine; there's no [continuous positive airway pressure] (CPAP) for that. You actually have to retrain them somehow and I just don't fully understand how it works; retrain them how to sleep. So, that process of cognitive behavioral therapy for insomnia or CBT-I is not commonplace.

But if the majority of our patients have that problem, that means 99.9% of the sleep centers that are out there can't treat them and really you are stuck to people like Dr Barone, too, being able to help not only identify that root cause, but also then to most effectively treat them. Because the treatment could also include things like hypnomeditation therapy depending on that person.

Dr Barone: That's a good point. Unfortunately, a lot of times what happens is sleep specialists may be very well versed in treating sleep apnea, but if they don't have that other, sort of, side of things, a lot of times patients will [say],

“All right, I have sleep apnea. I have that treated, but I have these other problems that need to be addressed as well,” and that sometimes falls through the cracks.

Dr Katz: Yeah, behavioral issues are almost always the hardest ones to treat.

Dr Barone: Right.

Dr Katz: I think if you’re talking about retraining someone and using CBT for insomnia, then that’s a behavioral issue. Also, I bet for many practitioners it may not be reimbursed, so it’s, sort of, a big kettle of fish.

Dr Barone: That’s right.

Dr Kim: Just to finalize this thought, you have to think that a lot of our patients have had poor sleep not for months, we’re talking years – 5, 10, [or] 20 years, right? So, with that lack of restorative capability, CBT-I, like [Dr Katz] had mentioned, requires this effort.

Dr Katz: When you say that they’ve had this problem for years, [t]here’s a good probability that it started even before their disease began. Because there [are] good data that show very short sleep is associated with incident RA and with incident lupus.

Dr Kim: Yeah, I guess we’re hoping that we’re scaring some of the audience into really thinking about this, not only for themselves, but for their patients. [W]hat I tell our patients is there are 3 things that you do every day without thinking about that you shouldn’t have to think about it: eating, hydrating yourself, and sleeping. Yet, at the same time, sleeping is the part that we completely ignore.

Anyway, like Dr Barone said, we really have to do a better job of making people more aware. Culturally, we definitely need a substantial mindset shift in order to recognize the threat.

Dr Barone: For sure. I think going back to what you said, Dr Kim, you really didn’t have any sleep training. I had a couple of lectures when I was in residency; that was enough to light the fire inside of me that this is something I wanted to do.

Meghna: I think this conversation is going to be so valuable to our listeners, especially for clinical practice management. I only hope the dialogue continues and is not limited to conversations like [these]. But on behalf of Liz and myself, I want to thank you all for joining us today.

Dr Barone: Thank you very much.

Dr Kim: Thank you for the invite.

Dr Katz: Thank you.

Meghna: For more information on *Rheumatology Advisor* and this podcast, you can reach out to us at editor@rheumatologyadvisor.com.

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