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Updates in Major Depressive Disorder with Insomnia

Announcer:
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Chapter 1

Dr. Thase:
Are you familiar with recent data released at the Psych Congress 2025 on selective orexin-2 receptor antagonists to treat major depressive disorder with insomnia

This is CE on ReachMD, and I'm Dr. Michael Thase. And joining me today is Dr. Andrew Krystal

Dr. Krystal:
Hi. Great to be part of this.

Dr. Thase:
Thanks, Andrew. We're going to spend some time summarizing briefly 2 studies that are presented here. I know you were at one of the posters for one of these. I’ll be at both of these posters this afternoon. So let's talk about MDD with comorbid insomnia. I know this is a large part of your life's work. Do you want to just provide some kind of overview about the things that you are concerned about most and the current state of therapeutics?

Dr. Krystal:
Yes, thank you, Michael. The insomnia is very commonly comorbid with major depression. And people used to think about the insomnia as just a symptom of the depression, and the more time has passed, the more clear it's important to think of it as having its own independent importance, and that’s where the term comorbid came from. And it's because that insomnia has a lot of impacts on the course, the trajectory of depression in individuals.

First of all, it's extremely common. It's present in about 70% to 75% of people who have depression. And it negatively affects their quality of life. It decreases the likelihood of responding to treatment. And when there's insomnia left over after usual antidepressant therapy, it increases the risk of relapse. And the insomnia being left over after usual antidepressant therapy, to a very high degree, is one of the things that is a key indicator that we need to really think of it as comorbid and having its own importance, and direct treatment specifically to it

Current management of people who have depression, who have a comorbid insomnia, is to deliver first-line therapy for depression, and that is to use a serotonin reuptake inhibitor or a serotonin and norepinephrine reuptake inhibitor. And they do improve depression, as has been well established. And sometimes they improve the sleep, but many times, as I mentioned, they do not

And so, it's increasingly recommended to give an additional strategy or treatment for addressing that insomnia. And there are a number of ways this can be done. One is to give people FDA-approved agents for treating insomnia, such as benzodiazepines, drugs like zolpidem, sometimes referred to as non-benzodiazepines. Any of the FDA-approved drugs could be considered.

But it's also become a common practice to think about agents that are specifically used to enhance the sleep in this situation, which are not well established as treatments for insomnia based on large-scale, rigorous, double-blind, placebo-controlled trials. Some of these have been studied as add-on therapies, and this includes low-dose antipsychotics like quetiapine, a low dose of the FDA-approved antidepressant trazodone. And I think some of those strategies, while commonly used, have not been rigorously evaluated, and their risk-benefit remains somewhat unknown.

And then, the other approach that people recommend and is often used, or sometimes used, is cognitive behavioral therapy for insomnia. And cognitive behavioral therapy for insomnia, a number of societies and groups recommend it as the first-line treatment for insomnia in general. But the big challenge there is access. And so while a strategy of using an SSRI plus cognitive behavioral therapy has been studied in several randomized controlled trials and shown to improve sleep, it's not used that often clinically.

Dr. Thase:
Andrew, do you have any confidence in the website available, kind of, attenuated models of CBT-I

Dr. Krystal:
Yeah, so there are a number of other options to in-person cognitive behavioral therapy, or even web-based cognitive behavioral therapy by a therapist, which is the hard thing to access. And there is now evidence that web-based strategies for CBT-I that have high fidelity with in-person CBT-I actually work very well. Their main limitation is that people don't adhere to them as well as they do to in-person cognitive behavioral therapy, but they're showing increasing evidence for benefit

There are a number of apps and websites out there that are not really high-fidelity cognitive behavioral therapy; they are little pieces or they're sleep hygiene. And, Michael, as you know, people have been doing sleep hygiene to treat insomnia for many, many years. And while it helps, there's a limited number of people, those who are doing behaviors that are maladaptive to sleep and that's the extent of their issue, they can get improvement. But most people with insomnia have much more complicated situations. It's not just that they're drinking caffeine near bedtime or exercising too close to bedtime or that sort of thing. So a simple behavior fix like that can't usually address the problem for most people. And that's really what a lot of the websites focus on that are out there right now

Dr. Thase:
So, Andrew, it sounds like we've got a lot of options. Some of them, most of them, are helpful for some patients but we don't really have a treatment of choice, and we don't have one that gives us confidence that it will also improve the patient's depression as well as their insomnia

Dr. Krystal:
I think that's an excellent summary. The key need in the field, from my point of view, is a single strategy which delivers an antidepressant effect and robustly improves insomnia and has been demonstrated to do so in rigorous double-blind, randomized placebo-controlled trials.

Chapter 2

Dr. Thase:
So that's a perfect segue for what we're going to talk about in the next few minutes. And that is, we're going to take a look at 2 of the studies that were presented here at this year's US Psych Congress in San Diego. And as we discussed beforehand, I'll take the lead in summarizing these 2 studies' poster presentations, and then I'd like to, as I wrap up each one of them, I'd like to then just ask for your comments and thoughts about this

Now, I do want to disclose to our participants that Dr. Krystal and I are both authors of the first study I'm about to present, and I'm an author of the second study, so we're not the best people to give you an independent appraisal of this work, but we are knowledgeable about the work. So with that caveat in mind, the first one, the first study I'm going to talk about, it goes by the acronym MD-3001. And this is a phase 3 study of an orexin-2 selective receptor antagonist known as seltorexant. Seltorexant is the only drug right now in its class at this level of development.

Phase 3 means that there is sufficient evidence that it may work and that it is reasonably safe to move on to large-scale studies, of which are necessary for the FDA to review and make the final assessment about whether this is a treatment that can be approved with their indication.

So the 3001 study is a very large study. Nearly 500 patients are included in the analyses. It's a simple study in the sense that it's exactly about the issue at hand. These are people with major depression who have taken first-line antidepressants, but they have not remitted, and they have significant persistent insomnia. And the thing that makes the study beautifully simple is that it's simply 2 arms. What is thought to be the best dose of seltorexant, 20 mg a day, versus a double-blind placebo with independent evaluation of the benefit without knowledge of the treatment received and with the initial assessment done after 6 weeks of treatment. I think the actual assessment is on day 43, so 6 weeks and 1 day of treatment

I think the key take-homes here are that this includes both a 6-week double-blind trial as well as a 1-year extension of benefit in which all participants who remained in the study received seltorexant, whether they got it or got placebo in the first phase of the study. So we can talk about the benefit and tolerability in the initial phase and then talk about the long-term effects of the medication followed out for a year.

And so just to briefly summarize before turning it over to Andrew for commentary, the main findings from the acute phase were that the antidepressant effect and the insomnia effect were significantly greater for the seltorexant group than for the placebo group, and that's at the independent assessments and some self-report measures at day 43. That there was no significant tolerability burden for the seltorexant arm compared to the placebo arm. The dropout rates were comparable and so forth. So the benefit came at minimum cost in terms of tolerability issues

And then, in the longer-term portion of the study, patients in the placebo arm showed more rapid benefit when they began to receive active seltorexant at 20 mg, but patients in both arms continued to improve throughout most of the whole year. And at the end of the 1 year of continued treatment, they were an honest unit better off than they were at the start of the year.

So again, safety was good. In this case, there's no comparison group for safety because everybody who remained in the study was taking seltorexant now, but there were no new safety signals, including when the drug was discontinued at the end of the trial. No substantial evidence of discontinuation kinds of symptoms

So, Andrew, I hope you think I did a good enough job summarizing our work. And what else would you like to add about this trial

Dr. Krystal:
You did a great job. I think just to re-emphasize the high points, in the double-blind, placebo-controlled phase, there were significant effects both on the depression outcome, the Montgomery-Åsberg Depression Rating Scale, and on the sleep outcome, which was the PROMIS sleep disturbance scale. And that is, to me, quite impressive and important because of the need we talked about for an agent that can do both

And when you have an agent that can improve sleep and might have antidepressant effects, you have to go to extra lengths to prove it has antidepressant effects that are based on all the core symptoms of depression, not just by improving sleep because there is a sleep item on the Montgomery-Åsberg Depression Rating Scale for which you get points towards improvement just by improving sleep. And often when you improve sleep, you improve things like energy, which could lead to a false impression of an antidepressant effect.

But here, we saw a benefit when you remove the sleep item from the Montgomery-Åsberg Depression Rating Scale, and to me that really solidifies the evidence that this was an antidepressant effect, not just the sleep effect. So we really have 2 effects of this drug, both on sleep and on depression, and that's what excites me the most about this study

Dr. Thase:
For those of you just tuning in, you're listening to CE on ReachMD. I'm Dr. Michael Thase, and here with me today is Dr. Andrew Krystal. We're discussing the importance of insomnia for treatment of patients with MDD and discussing new clinical data on orexin-2 receptor antagonists for the treatment of depression with co-occurring insomnia

Thanks, Andrew. Why don't we go ahead now and talk about the second study, which is part of the Seltorexant Development Program. And this is a more clinically relevant study because instead of a placebo as the comparator here, it is adjunctive therapy with seltorexant versus double-blind adjunctive therapy with quetiapine extended release. And it's a large trial. And instead of simply having an acute phase, which is most commonly what happens in active-comparator studies, this study goes on for 26 weeks. So it is a half-year comparison of treatment with seltorexant versus treatment with quetiapine in patients who had an adequate benefit from first-line therapy with an SSRI or an SNRI and persistent insomnia.

So I think critically, the study's key findings were that both treatments were effective. They were comparably effective. There was no meaningful difference in symptom reduction or the probability of benefit. In both arms, more than 50% of the patients randomized got better. But there were differences in tolerability. And these differences were seen, for example, in the proportion of people who experienced somnolence as a side effect. They were observed in the proportion of people who experienced weight gain as a side effect. And ultimately, the dropout rate due to intolerable side effects was more than twice as high on the quetiapine extended-release arm compared to the seltorexant arm.

So I think this study, providing kind of a real-world comparison, suggests that this approach, adjunctive seltorexant, can have a magnitude of benefit comparable to one of our most widely used newer-generation antipsychotics, and it can deliver that benefit with a more favorable tolerability profile.

So, Andrew, I know you got to see this report when it first came out, and were you surprised by the results

Dr. Krystal:
I wasn't surprised by it, but I'm really glad you and your colleagues did this study, because I see a lot of people using a medication like quetiapine as an augmentation strategy for depression, and there are obviously good data that support that use from the point of view of depression. And I have worried, though, because of the risk-benefit ratio and the concern about side effects and the hope that we could establish treatments that had a better risk-benefit profile than quetiapine. And I think what you've shown here is that seltorexant promises a better risk-benefit profile. It's got the same therapeutic effects with less side effects, particularly in the areas where we know that quetiapine are as likely to be problematic: daytime sedation and weight gain.

Dr. Thase:
Thank you, Andrew. Daytime sedation is a gift that keeps on giving in a bad way, right? You have trouble staying awake at work, you may fall asleep while you're driving, and you just aren't as present in your day-to-day life when you're taking a medication that makes you sleepy. So I think you've really hit on important kind of key real-world aspects of this clinical trial

Chapter 3

Dr. Thase:
Now, I know there have been other medications recently studied, including some here at this meeting, and I have the good fortune of asking you to talk about some of the other things that you've been involved with, or have a chance to comment here

Dr. Krystal:
Yeah, I would like to talk a little bit about the use of the medication mirtazapine, because it's also something that's done commonly, and particularly in people who have not already been treated with another antidepressant. And the reason is that it's an antidepressant medication, FDA-approved for depression, that tends to have sedating effects, tends to improve sleep. And I think that's been established in its clinical trials for depression

But there are also a couple of trials that have actually looked at its sleep effects in insomnia populations, which is a cleaner way to assess the degree to which there might be therapeutic effects on sleep. But like quetiapine, mirtazapine brings with it a well-established history of daytime sedation and weight gain, and so we really haven't known what the risk-benefit is when you look at it from the point of

view of comparison with other kinds of medications that might be used for sleep. And I think, because mirtazapine has FDA approval for depression and has sleep-enhancing effects, it could be a candidate for what we'd like to have, which is a single agent that improves both depression and sleep

I'm going to just summarize the couple of studies that we have looking at its sleep effects. And the bottom line here is that we don't actually have any data showing that mirtazapine at a dose where it is FDA-approved to treat depression and used to treat depression also has sleep effects with an acceptable risk-benefit ratio, because both of the studies we're talking about are not at the antidepressant dosages

So the first study, which was called the MIRAGE Study, was a study of 7.5 mg of mirtazapine in a group of 60 older adults, age 65 and older. A small percentage of them had depression to a limited degree. The dosing issue here is that 7.5 mg is not a recommended dose for treating depression. That's a range of 15 to 45 mg. So this might give us some hints about the likelihood of therapeutic effects on sleep in the antidepressant range, but it doesn't actually test that. And what was found here is that people reported that their ability to stay asleep was improved and their total sleep time was enhanced. They did not note that they fell asleep faster, but in the older adult population, difficulties staying asleep are quite common and of high clinical significance, and that can still be of great value for many people

Interestingly, they did polysomnography, an in-lab sleep studies, but they didn't show effects on any of the sleep lab variables, which is likely because this was not a study that had an inclusion criteria that you had to demonstrate an effect or dysfunction on sleep using the sleep study. And so there was a variable degree of abnormality on the sleep study to start with, and I think that decreased the effect size, because we typically do that. We use an inclusion criteria to select for a population that's appropriate to look for effects on the sleep study

A notable finding here, like with your quetiapine study, Michael, is that there was a 70% rate of daytime sedation in this study. It was elevated over placebo. That, dizziness, and also weight gain was also noted with mirtazapine compared to the placebo. So overall, there was a sense of a therapeutic effect here in terms of people's experiencing improvement in their sleep time and in their ability to stay asleep, but there was a very high rate of daytime sedation. And like the quetiapine, it speaks for a risk-benefit ratio that I believe will be better if, instead of using this drug, one would use seltorexant as a single-agent approach

Also, this was, again, at a dose below the antidepressant dose, so you can imagine that the rate of daytime sedation and weight gain might be even higher in the 15 and higher group

And then, the other study was a study of the S-isomer of mirtazapine. So people may not be aware that mirtazapine is a racemic mixture of an S-isomer and an R-isomer. And both are active, interestingly. And this was a study of the S-isomer at a low dose, around 3 mg. There are actually 2 doses studied, 3 and 4.5. And again, well below the antidepressant dosages.

And here, the usual methodology was employed looking at polysomnography as a way to screen subjects and then using it as an outcome. And here, benefit was shown on every polysomnographic outcome measure; the time to fall asleep, the ability to stay asleep, total sleep time, and as well as the self-reported measures of ability to fall asleep and stay asleep. So it showed very robust improvement on sleep in this population

And none of these people had depression. In this study, they were selected for having primary insomnia

And there was robust therapeutic effects. There was an elevated rate of daytime sedation and a limited increase in weight gain. And so those signals are there. So I think the bottom line for both studies is, these are lower dosages than are used to treat depression. They show promise for therapeutic effects, but they also show that tendency of this medication to lead to daytime sedation and weight gain, which I believe in higher dosages is going to be even more significant, and suggests a risk-benefit ratio that for some people may not make it a great choice. For others, it will be fine, and it is one of the options out there for treating people who have depression and insomnia together

Chapter 4

Dr. Thase:

Thank you, Andrew, for that wonderful summary. So when you think about everything we've looked at and talked about today, what would you say your major take-home messages are for our audience today

Dr. Krystal:
I think I want to first emphasize that it's important when people treat people who have depression and co-occurring insomnia that they think about the insomnia, and they think about how they're addressing it because of the impact it has on people. And we talked about several options, and the fact that I think there's been a need for something that has antidepressant effects and sleep-improving effects at the same dosage. And people have been using some strategies for a long time, quetiapine and mirtazapine, and we now have some data on some of those key strategies that suggest to me that seltorexant would be a better risk-benefit choice, either as an add-on or as single-agent therapy, potentially, than some of those things we've traditionally used. Particularly from the point of view of the side effects.

Dr. Thase:
Andrew, do you think if we went back and restudied trazodone—one of our favorite off-label, low-dose options—if we went back and restudied it and used modern methods of looking at daytime sedation, driving performance, vigilance task, and so forth, do you think even at 25 or 50 mg, trazodone might have a signal to worry about

Dr. Krystal:
Yeah, there was one double-blind, randomized, placebo-controlled trial of trazodone in primary insomnia patients. That is, they didn't have any comorbid conditions, no depression. And it was at 50 mg. And it was a decent-sized population, I think at least 200, perhaps more. And there was a signal for daytime sedation there over placebo.

One of the things I believe and find clinically with trazodone is it's a drug that you need to titrate carefully in individuals. I think if you give everybody 50 mg, you're going to see things like daytime sedation. Some people need less; some people need more because there are polymorphisms in its metabolism that are common in the population. So the data out there do not provide us with a clear guide to how to use it in a way that has optimal risk-benefit yet, so we really don't know. But my guess is we need studies with flexible dosing for that drug

But overall, my guess is that seltorexant would be a better risk-benefit therapy than trazodone in this setting.

Dr. Thase:
So, Andrew, for our colleagues who weren't able to be with us at the Psych Congress 2025, what would your kind of 1-sentence key take-home message be about what we learned about depression and sleep here at this year's meeting

Dr. Krystal:
I think we have some reason for optimism that we may have, in seltorexant, a medication which could be a single-agent therapy that could address both depression and insomnia. And particularly, we see that for those people who have not had an adequate response to usual first-line therapy for depression and have insomnia, it could really be an ideal choice for many people. And I look forward to seeing more about this medication as additional studies become available and are presented

Dr. Thase:
Well, I certainly can't do more for that other than second your take-home message. And that's important because that is about all the time we have today. So I want to thank our audience for listening in and thank you, Andrew, for joining me and sharing all of your valuable insights. It was really great speaking with you today. And thank you all for tuning in to listen to this, I think, important continuing education presentation

Dr. Krystal:
Thanks for having me.

Closing
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