Episode Introduction and Guest Preview

All right. It's time for another episode. So that means it's Time for Precals. Yes. Robert, what's going on today? And I'm telling you, we're in for a special treat today.

We have with us Dr. John Cronin. He is the current Senior Vice President of Clinical Development with ApnoMed. They are an early stage pharmaceutical company that is developing novel therapeutics for treating sleep apnea.

And he was previously the chief medical officer with Phillips, and then prior to that, he with better night as the president and chief Medical Officer.

So we've got one of the best in the business with us today and I know that he's going to share some significant insight into their current products that they have in development, and some of the other things that are happening on the Abnomad front.

All right. So for people that aren't as smart as you, like myself, when you say novel therapeutic options, do you mean like a pill for sleep apnea? Yes, the magic pill.

We'll find out if it's the Magic Pill. I think they're in phase three clinical trials right now, and I know they're fully enrolled and a lot of those patients have completed their part of the research.

It will be absolutely interesting to hear how that's going and what he anticipates from a future standpoint about the use of pharmaceuticals to treat sleep apnea and you know what patient populations may be best to see that type of treatment.

All right. I mean, you know, once again, it sounds like it's going to be very interesting. Obviously, the guest is going be amazing, but I think the conversation is gonna be interesting as well.

Well, we are definitely in for a treat today, and I'm telling you, We just have the best guest. We're very fortunate on this podcast to get some of the Best in the Business, And Dr.

Krulman certainly is one of those. Well, with that being said, let's go to the show. Now a word from our sponsor, MedBridge Healthcare. Medbridge Healthcare is a leading provider of sleep lab management services and home sleep apnea testing.

medbridge partners with hospitals, healthcare systems, and medical academic institutions to offer comprehensive, fully integrated services for sleep disorders.

Lights out.

Dr. Cronin's Career Path in Sleep Medicine

Welcome, everyone, once again, to another episode of Sleep Tech Talk, the Sleep Podcast with your hosts and friends, Emerson Kerr, Robert Miller, and me, Dr.

Gerald George-Moneycrode. Folks, thank you once for listening in and tuning in. It's been some fabulous episodes and it's all because of you. your listening, for your liking, and your sharing the shows with each and every one of your friends.

It's because of that we're able to bring in fantastic guests, amazing guests. We've got a very special guest today, but before that, we just want to say thank you, thank to you and thank the sponsors, because without all you folks

out there we can't do this, so we do it for you.

All right. With that being said, Robert, could you tell us what's going on today? Well, certainly. Thank you, Jerry. So today we have with us Dr. John Cronin.

He is the Senior Vice President of Clinical Development with ApnaMed, one of the most exciting oral medication for sleep apnea companies. They have lots of things in the development and pipeline stage, and we're gonna get to hear some things about that today.

But Dr. Cronin, thank you for joining us today, we would love to just jump right into the show today and let's learn a little bit about you, your history and the world of sleep medicine.

It's funny because all four of us actually have some history together at Phillips, you know we can talk a bit a that, but welcome to the Show and would just love for you to jump in and tell us a about yourself.

Yeah, well, thank you. And thank all of you actually for producing this show and providing our field with so much great content over the years. So it's really great to see you guys bring your collective wisdom and new things to the forefront.

Thanks for inviting me. I feel really honored to be here. Essentially, we're all here, I guess, accidentally. No one intentionally becomes a sleep medicine specialist, business person, etc.

In my particular case, my pathway to where I am now has been a delightful, happy accident, to use the words of Bob Ross. I became a young doctor and I was enamored of life in the ICU with major interventions to save lives and take care of patients and found myself in a little clinic room in VA hospital near Boston and started seeing these CPAP machines come through and really didn't know much about them.

Ultimately, what I did know and what saw at that time really is that patients came in and loved them, And patients often knew more about them than the doctors that I was working with.

In fact, the best person to learn from was the respiratory therapist that was in the clinic. He knew everything. So that transformation really caught me and made me very fascinated with this field.

because the other side of the pulmonary field that I was in was basically managing chronic illness like COPD and asthma, which are critically important, but you don't always get that transformative patient response.

That led to a life in sleep and sleep research. I very fortunate to have some very good sleep mentorship when I as at Harvard with Chuck Seisler and David White, who you guys know from Phillips Respironics.

As life happens, my wife, who is an academic, moved me from Boston to California. I had a 15-year career in what I call legacy healthcare, seeing patients every day, administering care for sleep disorders, really exploring that field.

Every day was a treat. But I'll tell you, it came to a point where I felt like I was not doing a good enough job. The analogy I use is that essentially, I was like a master chef and I'm cooking meals for patients.

Every meal was a really gourmet meal, but the line out the door of the starving patients and the hungry patients was getting longer and longer. I really started to try to figure out how to innovate and get to that and scale and improve things for people that could benefit from sleep apnea care.

Which led me to a company called better night, where we built started to build at least I had some initial efforts in that a nationwide network of telehealth sleep providers to be able to get care quicker, sooner, higher quality.

Which then led to Phillips and I was very honored to join that team at Phillips, really a high high level team and spent some some good years there.

Why Oral Therapies for Sleep Apnea Matter

Obviously we had some unfortunate issues with a big CPAP recall that you guys know just about everything you need to know about that. But through that, that introduced me to what was going on at ApnoMed, where I am today.

And so I've been at apno med for about two and a half years, leading the clinical development program. Essentially, our mission is really straightforward, which is we are mission driven to develop the first oral novel therapeutic for obstructive sleep apnea.

Dr. Cronin, you and I got to work together at Phillips and we certainly got enjoy the excitement of that recall, but we'll put that behind us for this conversation.

When you think about the journey you've had, how sleep has changed and changed, and how you were able to make this gourmet meal, Now that you're at Apnea Med and you are looking at sleep through really a different lens, I would say, what do you see happening now from a pharmaceutical standpoint?

Because we had Dr. Farrell on just recently, and one of the comments that came out of it was, we went from this reverse vacuum cleaner to this incredible solution that has saved many lives.

But now we know so much more through endotyping, through really being able to know more about the person than we ever have before. How is that informing you and how is this leading to different care and pharmaceuticals?

Well, I think the pharmaceutical industry is just different than the device industry. But let's, as you know, ground truth, CPAP is an amazing therapy.

It works for so many people. And I Think when I reflect on the efforts that we've spent in the Pharmaceutical space, it's really undeniable that there's so Many patients that either can't use that treatment or won't Use that Treatment.

So even if we can all agree, and I think we cannot see pap is great for the right patients, there's still a lot of people that can't access the benefits of good sleep.

And so that's a founding principle, I of a patient-centered concept of, yeah, let's give the patients what they want and what I'll use and with the benefit from.

Then from that, you can say, well, what can we do? I think this work is so many scientists have built upon this, which is really whether you call it an endotype, but just really more precision as to how can you keep that airway open.

And so when we think about developing a drug around this, we've really focused in on sort of a neuromuscular pathway. So at least our main compound that we're working on right now, it's really focus on trying to activate the musculature of the upper airway to help keep that air way open at night in a way that is clinically sufficient to solve the problem or at lease mitigate the problems for the right patients.

And then you can sort of think of like, well, what's the next generation of that as well? Could you do that better, more precise, different side effects, or maybe different, there are different patient types, right?

So you have comissa, you standard obstructive sleep apnea.

How AD109 Works

You might have obstrative sleep Apnea with certain comorbidities. And those all might be a little different when you think about what drugs would be best for those people.

I know with the various drugs that you have in development currently that AD109 has certainly had the most

publicity and the information publicized about the medication.

Can you tell us a little bit about breakdown of the two different medications that make up AD 109 and how that works specifically to treat sleep apnea?

It's a completely interesting topic to me and I nerd out a little bit on how these things work specifically because it's interesting that you have two different medications that have been on the market for a long time treating different health issues and now to have this combination therapy that seems to be successful.

Yeah, thanks for that question. You know, it's interesting because a lot of people don't know about 8109 out there, but really there's been, I would say, you know over a decade of research of, people trying to get at this idea.

Can we use a drug to treat sleep apnea? And there have been numerous drug studies, smaller ones in the past, looking at different types of agents. nothing really that compelling.

Then it was roughly, I think it's around 2016, Luigi Toronto, our chief scientific officer together with Andrew Wellman at the Brigham and Women's Hospital.

Well, let's just say they had a theory and they put that theory into practice in terms of testing these two particular compounds together to see if they could affect the upper airway.

And sort of like that eureka moment, you know, they were really astonished with how impressive the results were for the first time, whereas in the past there really hadn't been any.

So the compound you're referring to, 8109, is a combination therapy, and it's basically one pill that combines two drugs within it. And these are at a fixed dose.

One is R-oxybutinin. R-oxybutyn is what we call a novel compound. It's an R enantiomer of oxy butynin. The class of medication is an anti-muscarinic, and this helps counter some of the muscarine signaling that occurs during sleep, particularly REM sleep around the upper airway.

So think of by blocking that signal, we might stabilize the upper airway. And then second, the medicine is adamoxetine. Adamoxetin is a norepinephrine reuptake inhibitor, and this drug increases the presynaptic presence of noraepinephrin.

in the hypoglossal motor neuron, which is responsible for controlling the upper airway muscle tone. Those two things in combination seem to work, at least in complementary, if not synergistically, to improve the airways caliber and airflow.

The ROxybutinin also helps mitigate some of the alerting side effects that can come with atomoxetine. So together we see, and we saw in our phase two studies, a very consistent, we're seeing this through our entire development program, that we are seeing the impact of the airway in positive ways.

Is there any issue with sleep fragmentation with this combination of medications? Well, if you look at a phase two study called Mariposa, which was published last year, we looked at all the different components from atom-oxetine to R-Oxybutyn and the combination.

Sleep Architecture and Trial Eligibility

Really, what we see with the combinations is that, and this is somewhat predictable, that you preserve sleep time, but you get a slight reduction in REM sleep, about a 10 percent reduction REM-sleep after taking the medicine for four weeks.

That usually comes at the, well not the expense, but what you see is a little bit increased stage two sleep as a result. The correlate here would really be, I guess, in general, the class of medicines like antidepressants that are

classically known to have a slight reduction in REM sleep, something that's understood, incorporated into practice, not of known clinical significance, but an observational finding.

We're attentive to that and we're going to see in our phase three study that comes out later this year, the full picture of sleep architecture and efficacy, things like that.

Before we go, we would like to thank our sponsor, MedBridge Healthcare. MedBridge Healthcare is developing innovative inpatient, post-discharge and population health programs to screen comorbid conditions, diagnose and treat sleep disorders.

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Dr. Cronin, are you beginning to see any kind of breakout here where certain patients are not candidates for this type of medication? Have we gotten to that place yet to understand the patients that would fall out and wouldn't be candidates this combination drug?

Well, you'd have to look at our clinical trials. As you know, every clinical study has inclusion and exclusion criteria. In our phase 3 study, which is currently underway, we've enrolled patients with mild to severe sleep apnea across a big range of BMI from as low as 18 all the way up to 42. Really casting a wide net.

We do know with the component compounds, the R-oxybutynin and atomoxetine, there are different medications, for instance, that probably you shouldn't be on at the same time.

And so there's some exclusions around those specific medicines, specific drugs that are metabolized through the pathway and things like that. Then ultimately, we also enroll patients that we believe have your very typical type of sleep apnea, meaning it's not clearly an anatomical issue related to massive tonsils or a small jaw, large tongue, where we can say, okay, this is really in that range of you've got somewhat standard airway crowding and you have a neuromuscular sort of deficiency that's letting that airway collapse.

And then I'll say, you know, we'll find out from the phase three, hopefully what will come with some learnings is to, maybe some people respond better to the medication or maybe people will respond poorly and we will be able to better understand that such that if this becomes a reality for doctors and patients in the field that they will better fine tune what they do for their patients.

I think this is all exciting. I, I thinks it's great for patients. Uh, we probably all agree with that, that it, uh, it is great to have another solution and another tool in our tool belt to help treat these patients with sleep apnea.

But just shifting gears just a little bit, because one of the things that ApneMed has also produced recently, and I would say fairly recently is, has been the SHINE study.

And can you talk a bit about that and maybe what some of learnings were from that particular report? Yeah, certainly I'd love to. A real honor. I mean, the SHINE survey is a survey that was conducted here at APNMED.

Really got to give credit to Alyssa Mendoza and Kate Schneider and our team that put this together, which essentially is the largest survey study of people who are living with obstructive sleep apnea.

And what is their experience as kind of the ground truth of sleep Apnea? Shine stands for sleep health inquiries on needs and emotion of people with OSA.

We're able to provide a questionnaire to about 1,500 patients with obstructive sleep apnea across all different types of severities and demographics and age range to really to explore in their own words what are they seeing and what do they feel with their sleep Apnea.

And on a personal level, for me, I feel like, well, like I know a lot of this because I've been seeing sleep patients for

20 years and we've all heard the different stories, the common symptoms, and the uncommon symptoms.

Patient Experience and the SHINE Survey

But this really, to me took it to another level in terms of really understanding what happens beyond the initial symptoms. Fatigue, check mark, sleepiness, those are common symptoms that I think most of us can understand whether they're present or not.

But the Shine Survey really gave color and life to this idea, well, what happened after that? For me, the aha moments were really that really this is a condition, a disease that carries a lot of stigma with it.

It has the ability to really isolate people, dislocate them from their loved ones, from friends, their family, socially getting to a point where you don't really want to spend time with other people because you feel fatigued, feeling judged by other because your sleepy.

We've all seen almost like the humorous ads of CPAP out there that this is not really aspirational and that puts people in a box and I think it creates a degree of a type of emotional suffering that I don't know that really plumbed as a physician deeply as maybe as I should have.

For me, it's a great exploration of this issue. Then the other thing is that it has been really great to see the patient community and the advocacy groups come together around this type So this work was done in partnership with the Alliance of Sleep Apnea Partners, Project Sleep, the Academy, other really important stakeholders in this issue.

And so it's nice to see that component of our field get stronger and impress upon us all how important it is to put the patient at the center of what we do.

And I think, I know our leadership and our whole company has really taken that to heart and we're trying to make that evident in everything that we do in this effort.

So, Doc, you talked about several very interesting points and kind of to put them together at the time of diagnosis or diagnosis of, okay, patient has obstructive sleep apnea.

Where would the medication fit in in the treatment plan versus CPAP or any other things that are out there right now? Well, that's a great question. And I guess I hesitate to speculate because we're still talking about an investigational drug.

And we really need our 2 phase 3 registrational studies to report out later this year to help really inform that. And I think our field is coming to grips with what does it mean to have successful therapy?

When you have the standard bear being CPAP, which is. it can be 100% effective in the right patients, to 0% percent effective to patients who don't come in or who reject it.

Where do we rest and what is enough therapy, right? And so I can say from our phase two studies, we see a range of different types of responses. Some people have a complete response.

Their HI goes less than zero and their symptoms improve. Other patients may have 50% improvement or a 30% improve, I don't think we have sufficient understanding as a field to know what does it mean to get a 30 percent reduction in your AHI or maybe stated another way, a thirty percent improvement in oxygenation.

Is that enough and for what type of patient? If you're a patient who can't tolerate CPAP and essentially has no options, Is 30, 40, 60, 70% improvement worth it to you?

Those are the types of questions I think the field needs to be asking. And fortunately, with what was reported out this past year with Terzepatide and Eli Lilly, we're starting to have those conversations a little bit more robustly.

Measuring Success Beyond AHI

It's interesting you say that. Among the conversations we have a lot on the show is about women in sleep. and the criteria that we have right now to decide what sleep apnea is or isn't is really built around men and their rule set there.

And when you look at how you're trying to design what success looks like, it even kind of folds back into how we decide, what the criterion is for what Sleep Disorder breathing is.

If we this movement away from AHI, then what are the metrics that we begin to look at? Because with women, that may be a different set of metrics in the future.

When you look it from that standpoint, and what we're learning about endotypes, how does that change what you begin to consider as success? If we take AHA off the table and think of how a medication could begin impacting these different variables, what does it change for you?

How do you began to assess success when the rules could potentially change in the future as we learn more about the airway and breathing? Well, yeah, there's a lot there.

Very important questions. I mean, I think clearly AHI is our main biomarker. We've all lived and died that. And there are always robust discussions about, is there a better biomARKer?

How can we better risk adjust? And I the field is progressing there nicely, whether it's hypoxic burden or heart rate response. and this intersects with Diagnostics 2, and I'll come back to that.

But ultimately, it's really hard to unseat the AHAI. It's understood, basically a frequency metric. Most of us can get our minds around it. Certainly, its on every sleep study, so it is hard displace that, but you can see that being informed also by some of these other things, whether it's gender, BMI, indication of cardiometabolic risk, the heart rate response to an apnea or hypoxic burden.

But that adds complexity and work. I'll just call it the connective tissues of the field that we've all built and worked around are hard to change. even simple things like getting hypoxic burden into the diagnostic report of a sleep study is difficult to do.

I think that the smart scientists out there will continue to have to help us really understand that and say, okay, well, what does it mean if I take someone with a hypoxic burden of X and I improve that by two X?

Does that mean that my job is done? I don't need to reduce the HI less? Things like that. It's an exciting time. There's a lot to be discovered, I think.

I there's whole podcast episode on just that topic, by the way, because that's really interesting. Yeah, no doubt. And I think we're all trying to get there.

Um, and, you know, we've got some, I don't think maybe a little inertia in our field because the H I is so it's so usable and readily assessable. But, even the simple things that be in my bonnet about even how we call sleep apnea mild moderate severe.

Talk about something that's really insulting. Tell a patient with mild sleep apnea that it's mild when they're falling asleep at the wheel or they are undergoing a divorce because their wife is fed up with them or whatever it is.

It's not mild for them. This balance between cardiovascular long-term outcomes and health versus your current symptoms, things like that, there's probably a whole lot of diversity there.

Doc, we're getting close to time and actually we've gone past time, but it's been really interesting. But before we close, wanted to know what's the future look like?

What do you see on the horizon and what can you tell us in terms of oral medications for sleep apnea? Because it is the magic pill, right? Right. Yeah, I think I'm really optimistic and enthusiastic.

There's a lot to anticipate. I mean, clearly, we'll see how our current program, the ApnoMed, goes. And I can also speak to the fact that we do have pipeline activities, looking at different ways to approach this problem through an oral medication.

Some of that will deal with endotypes, which in my mind is still in the R&D realm of what we're doing. But I think we're really sort of breaking the ice on what's possible and exploring for the very first time what else we could do.

The analogy I've used a little bit and like any analogy, it has its limitations, is really like the diabetes world.

Future of Oral Medications for Sleep Apnea

We used to just have insulin. Yes, insulin will drive your glucose down. However, and now we have this rich tapestry of different ways to put together a result for a patient based on their unique considerations, circumstances, demographics, needs and wants.

And I think there's plenty of space. So we estimate there is about 80 million people in the US with obstructive sleep apnea. The far majority aren't even diagnosed.

We all need to come together as a field to solve this problem in whatever way we can find, essentially. Well, Doc, the conversation has been amazing. Before we go, anything else you want to add and work and get people get more information about the work that's being done at Abnomad.

Well, I guess I'd point people obviously to our website, www.apnomed.com. We have our trials listed in clinicaltrials.gov. Our two phase three studies are currently fully enrolled, so patients are now exiting that study and we hope to have a big announcement later this year for the results of those studies, which we don't know because all the data is blinded.

And we'll take the next step in the journey together. I really appreciate this conversation with you guys and all of the work that you do and how you help us all stay current and informed.

Well, thank you so much for joining us, Doc. We sincerely appreciate it. Thank you guys. And thank you all out there for listening. We can't thank enough for being there, for us and continuing your support.

What we also thank our sponsors for their support as well. It's been a fantastic ride and we just continue to grow all because of you. And be sure once again to hit the like button, continue to subscribe and most importantly share with all your sleep friends, everybody in the sleep field and all those who are sleep curious.

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back to the show. All right. Now that was quite a show, it's time for some post cows. Robert, what did you think, man? Oh my gosh, Jerry. I mean, I could listen to Dr.

Cronin talk for most of the day. We have so many topics that we could sort of unpack from what he was talking about. the chance to tell my story. So I'll do it really, really quickly now that I did have the opportunity to hear from some of the research folks who are involved in their program.

And this is a real life patient story, so I think it's important to add this to the show today that, you know, one of that the patients who was involved with the clinical trial had previously been on CPAP, but it was on the medication and

that she reported back to researchers that It was the first time in 20 years that she was able to go on vacation and sleep next to her husband without her CPAP machine.

And she didn't snore after taking the medication. So just, you know, that's amazing. Yeah, it's phenomenal.

Closing Remarks and Sponsor Outro

Yes. Restoring marriages. You know, that's another thing that we do in the world of sleep medicine these days. But man, what a great show. What great content, you know to hear all the things that Aptimid and you now I want everyone who's involved in world treating patients for sleep apnea to keep up to date on these new therapies and things on the horizon.

And you what better I guess method for them to do that than to listen to sleep tech talk. Hey, Sleep Tech Talk. You hear it here first and you get all the latest news on the technology regarding to sleep health, right?

Yes, absolutely. But we've got to have Dr. Cronen back. He's phenomenal. I was just going to say the same thing. We need to him back and not just an update, but he touched on several points that would have, each of those points would've been a separate episode on its own.

So I'd love to having back on. It's just amazing to talk to. Absolutely. All right, you ready to close? Let's close it up. We miss Emerson. He can only join us for the show today.

Sorry, Emerson, we didn't get to have you for pre-cows or post- cows today? Yeah, that would have been fun. But hey, fingers crossed that we got him there for next one.

That's right. Well, folks out there, thank you so much. And until next time, say cheers. Sleep Tech Talk is sponsored by React Health. Within our LUNA PAP device line, each offering is FDA approved, encompassing CPAP, APAP by-level and by level ST models.

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