Welcome to the Cutting Edge Health Podcast with Jane Rogers, where we discuss science to help prevent cognitive decline.

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[00:00:00] Jane Rogers: Welcome to the *Cutting Edge Health: Preventing Cognitive Decline* Podcast. I'm Jane Rogers. Welcome back. Dr. Paolo Cassano is our guest today. He's an expert in photobiomodulation, a revolutionary intervention to treat and to prevent brain disorders like dementia. Dr. Cassano is the Director of Photobiomodulation at Massachusetts General Hospital, and he's also an Assistant Professor of Psychiatry at Harvard. I hope you enjoy this conversation. Paolo, thank you for joining us.

[00:00:33] Paolo Cassano: It's my pleasure.

[00:00:35] Jane: I'm so excited to talk to you because this audience badly wants to prevent cognitive decline, and who doesn't? There are many different ways to go about doing it, and your research that you've done with Harvard and Massachusetts General Hospital as Director of Photobiomodulation there is really exciting for the future. First of all, we're going to jump deep into it and do a deep dive into it, but first of all, I want to hear why. Why did you get involved in this? What's your backstory? You've got an MD and a PhD. You could have gone in many different directions.

[00:01:07] Paolo: Thank you, Jane. It's interesting you asked the question. Funny enough, I thought at some point I got in this story, in this path for serendipitous reasons. My interest was actually in international psychiatry. I was interested in cross-cultural issues. I worked for 10 years in the community. At some point, I knew that my patients didn't like what I had to offer.

It was medications and they really didn't like more pills. I was part of the depression program, and I am still to this day, and we were interested in brain metabolism. When you are depressed, your brain metabolism changes. When you are treated for depression, your brain metabolism improves. Talking with some coworkers, there was this new treatment that they were using for stroke, which was light, transcranial light.

I really didn't know anything about it, and we're talking about 15 years ago. It wasn't so popular back then. It was like, "Do you want to try it?" Well, it seems like this might be something that my patients might like better than the pills. They know they don't want that, so let's try this one. We embarked in this research, and before I knew it, that became the main topic of research.

At some point, it was so obvious that I was doing research on devices and that was the primary topic of my investigation that people said, "Okay, well, do you really belong here? Shouldn't you be in neuropsychiatry?" That's how. "Is that okay?" I was like, "Well, if you think so." I moved into neuropsychiatry and then all these other opportunities opened up. We became studying Down syndrome and language. We started studying Alzheimer's disease, whether it's in mild cognitive impairment or mild dementia. It kept growing.

[00:03:11] Jane: So exciting, it really is. I can tell you love to learn, don't you?

[00:03:17] Paolo: Yes.

[00:03:18] Jane: Yes, I can tell. That's the basis.

[00:03:21] Paolo: That's life.

[00:03:24] Jane: Tell me about transcranial photobiomodulation. That's what you're working on now with your latest research project. First of all, tell folks what that is.

[00:03:36] Paolo: Right. If you look at the semantics, it's really *transcranial.* It's across your head, across your skull. The good news is that for those who are already getting scared here, there's no surgery. It's not invasive. We're not putting anything physically. It's really the photon, the light, like in *photo*, that gets across. You're shedding the light over the head, it gets across the skull, the different layers, the meningeal layers, gets to the brain, and then it gets to the last part: *modulation*. It has an impact in stimulating brain function. In other ways, it is a modality to get the brain to jumpstart.

[00:04:27] Jane: You do this with a certain wavelength, right? You can't just shine a flashlight up there and have it work.

[00:04:33] Paolo: Right, exactly. Here is the point: that our tissues, as humans, as animals—let's face it, we're also animals—we absorb light. We make something out of light. We thought that plants were the ones that were supposed to make something out of light through the photosynthesis, get energy from the sun, and bring it to the earth, and then the chain started for the energy transfer.

It turns out that in a very elemental way, we also absorb light, and it's all sort of radiation, also visible light. However, we absorb more light that penetrates better. There is a specific wavelength, or a range of wavelengths, that are infrared. We're not talking about the heat waves we're all familiar with, with the infrared sauna. That's not what I'm talking about. There is some infrared light that is close to the visible, and that's why we call it near-infrared, just because it's so close to the visible wavelengths, that it’s really optimal for this type of modulation of brain function.

[00:05:50] Jane: Tell me about your aha moment when you realized, "Oh my gosh, this is going to work. If we use this near-infrared light and we shine it, whereabouts on the brain." Then you saw things happening, like the mitochondria perked up for people who had the cytochrome oxidase mitochondrial deficiency, you saw it helping. What was your aha moment?

[00:06:09] Paolo: Yes. It's interesting, again, what you're asking here, because, at the very root, I am a clinician. I am a clinician, and my research has been very much clinical research. In fact, my very first studies where we looked at photobiomodulation for depression or photobiomodulation for anxiety were primarily clinical studies. Then we realized, "Wait a minute, we just need to understand more because, yes, we know all the biology here. We know what's happening at the culture level. We know what's happening at the animal models. Is that the same when you shed it in the brain?"

There's a little bit of a difference in size in between your average mouse brain and your average human brain, so we can't really make a lot of assumptions here. My aha moment was actually very much clinical. In that depression study, we had people coming back after a couple of weeks, and they were feeling much better. It was fast, it was quick, pretty substantial, and also, they were feeling better in ways that we didn't quite expect, based on our experience with antidepressants.

For instance, their sexual dysfunction was gone. With antidepressants, that's something that you rarely improve and sometimes you worsen. It was like, "Oh, this is real. Something is happening."

[00:07:44] Jane: There's so much I want to unpack in this. You put the wavelengths on the brain for someone struggling with cognitive decline, and you are seeing mitochondria better enabled by this light therapy, you're thinking, right?

[00:07:58] Paolo: Right. This is complicated. I'll do my best to make it—

[00:08:03] Jane: Thank you.

[00:08:03] Paolo: —simple. As a group of scientists, clinicians, we're also trying to wrap our head around this because, for a long time, the primary mechanism that has been postulated and then found in animal models and in culture was, in fact, the engagement of mitochondria. To make it short, mitochondria are the energy powerhouse of the cell. Within the mitochondria, you have these final steps of the metabolism of all energy products, which is the respiratory chain that happens on the membrane of the mitochondria.

It turns out that the light shunts and gets to the very end step of this respiratory chain and brings energy there. In a sense, you don't need to get all your food across that metabolic chain. You can energize the final step and get this high-energy molecule ready to be used by the cell, which are called ATP.

[00:09:10] Jane: It's very exciting because I've been told that my family's problem, both my parents passed with Alzheimer's, I've been told my family's problem is mitochondrial insufficiency. What you're saying is that there is a chance that light can help that problem area in there.

[00:09:26] Paolo: Yes. Yes. There's no question about that. That has been demonstrated in animal models, in cultures. Interestingly, even in humans, the studies that have been done by the University of Texas have shown that you can change that photoacceptor, which is called cytochrome C oxidase. That's the last step of the respiratory chain. You change the redox state. You can actually activate or change the status of that photoacceptor, even in humans, so that's very telling.

We are now conducting a study at MGH looking specifically with MRS or Magnetic Resonance Spectroscopy, based on phosphorus, specifically to look at mitochondria after a course of treatment of eight weeks, and that's, in fact, our Alzheimer's study, to see if, in fact, mitochondria are boosted in terms of her own metabolism. That will really answer your question.

[00:10:38] Jane: That study at Massachusetts General Hospital involves using photobiomodulation for three times a week for eight weeks, right?

[00:10:47] Paolo: That is correct.

[00:10:48] Jane: Okay, when are you going to have those results?

[00:10:54] Paolo: That's a question that our participants always ask. "When am I going to know if I got the sham or I got the real thing, and when is this going to be available?" Well, in terms of the results, it will take another two to three years, probably two years to conclude recruitment and finish up, wrap up with all our participants, and then one more year to claim the data, analyze, and present.

[00:11:22] Jane: Is there anything, Paolo, that we can do now? I know that you've taken a device, and you've changed it for this study. Did you change it a lot? Can people get that device today and maybe start working with this? Alzheimer's can come on so quickly. Well, no, it doesn't. It works over years, but all of a sudden, these changes happen, and

some people get motivated, and they're going to sit here and say, "Oh, we don't want to wait three or four years for this result." Is there anything we can do today?

[00:11:48] Paolo: Yes. First of all, I would say that science moves slowly. There's no question about that. However, industry moves fast, and a lot of these devices, because they are considered non-significant risk by the FDA and some also receive some specific designations that are not necessarily approval,…approval by the FDA means that there is an indication that the FDA recognizes that this device can be prescribed legitimately for a certain disorder or condition.

Even though this threshold has not been achieved, the FDA has given, to some of these devices, a wellness categorization and have considered these devices as breakthroughs, so what we call breakthrough designations. They've seen potential on these devices. What that means is that the industry is putting out these devices for wellness that can be considered as an adjunct to what is standard treatment or also could be used by people and could actually be bought over the counter if people wanted to try them out. Now, I'm not suggesting that. I'm saying that that's possible.

[00:13:18] Jane: Possible.

[00:13:19] Paolo: What you should be doing, it's a bigger discussion, and we can certainly go into that.

[00:13:24] Jane: The downside of jumping into this technology before your results are ready…pretty low, minimal downside. You don't want to hurt yourself by jumping in too early to this technology, but you're not seeing that it is causing that problem.

[00:13:37] Paolo: Right. This technology is extremely safe. The only aspect that we really need to be mindful about is that if you're using a laser device, that requires specific protections because you don't want to risk an injury of the retina of your eyes. That is obtained by simply using goggles or glasses that have specific lenses that filter out that light. Those come with the device, and the manufacturer would provide those.

The devices that are actually available over the counter are typically LED devices, and they're typically low power, which means that they typically don't have that type of risk. If you are going to buy a device, you should know whether you need to protect your eyes or not, so that's a clear and very important aspect. Beyond that, the only risks that you can encounter that we have seen are risks related to overexposure to light.

When you go in the summer, you don't put your sunscreen, you can get sunburn. With a device, you feel excessive warming, you take it off. In most of the cases, what we really

see is a little redness, a little gentle warming, and those are pleasant. They stay there for 10, 15, 20 minutes, maybe after the treatment, and then they go away. That's all that we're noticing. In rare cases, people might have, that night of the first treatment, some difficulty falling asleep. In rare cases, people might feel a little irritable after the first treatment. Sometimes that might be a sign to lower the dose.

[00:15:30] Jane: Does it concern you that the devices that we can get now are LED and not laser? Are LEDs going to get through the cranium like a laser device?

[00:15:40] Paolo: Right. Again, that's very much debated in the field as well. What really matters is the wavelength and the light intensity. If you reach a certain light intensity and overall power, you should have similar penetration with laser and LED. However, we're not quite sure in terms of efficacy if having a laser light, so basically, you're having all your photons oscillating, if you imagine all these little waves, in sync if that really makes a difference, as opposed to scatter photons that are not organized if you wish.

[00:16:28] Jane: The LEDs are the not organized ones.

[00:16:30] Paolo: That is correct.

[00:16:30] Jane: They're a little more scattered. Okay. The specific wavelength that you've seen efficacy, is it 800 to 1,200 nanometers of near-infrared?

[00:16:40] Paolo: Yes. This is also a bit complicated. When I say a bit complicated, I'm not saying for our audience, but it's complicated for us.

[00:16:52] Jane: Then it will be for us, too.

[00:16:53] Paolo: We find ourselves having a lot of firm beliefs, and then all of a sudden, it's like, "Oh, okay, that probably wasn't quite true." For instance, we know that from a cellular level, red light is the type of light that is more effective in inducing cellular changes. We're talking about 630 to 670. That wavelength is very promising, but we also knew that red light doesn't really penetrate much, right?

I was just saying that we would rather be in infrared below the red in order to have better penetration. We were thinking, "Okay, well, of course, it's not going to work as well because it doesn't penetrate as well." However, we have groups in Australia and China that actually have looked at the effect—in Australia, specifically, the effect of red light for Parkinson's; in China for cognition in general—and they have found that they could in fact obtain a similar precognitive effect with red light to near-infrared light and sometimes even better.

That's really puzzling. So far, because the assumption was that the infrared light was going to be better, penetrating better, most of the research has actually been done in that range, around 808, 810 nanometers. That's also a magic spot because not only do we know that there is more penetration, and when I talk about penetration, the issue here is that we have a lot of the so-called chromophores.

There are molecules, proteins that absorb light in our skin, in our blood, in our muscles. Those are melanin, hemoglobin, myoglobin, so those shield the light. That's why we're trying to get through those wavelengths that are less likely to be affected. That spot has magic because it is very good in terms of penetration, and it's also an ideal wavelength for the absorption by the cytochrome C oxidase.

That's why a lot of research has been conducted around that wavelength with encouraging results. Also, our laser is around 808, 810 nanometers for our research study in Alzheimer's. This being said, some research, especially in healthy subjects, actually, and some also in Alzheimer's, has been conducted around 1,050 nanometer and 1,064. You might wonder why this kind of bump, in between the water starts absorbing much light.

As you might know, we're mostly made of water. That could be a problem. Some people think it's a good thing, actually, that water absorbs light, and that might have something to do with also the mechanisms of and the benefits of light. Beyond that, that's why 1,050, 1,064 has been also chosen. Very promising, at least in healthy subjects, for the pro-cognitive effect. You might say for brain hacking, for performance. Those are also very studied and good wavelengths.

[00:20:33] Jane: I know you don't want to recommend a device that we can buy now because that would put you out on a limb that maybe you don't want to go. Could you talk about some of the different brands that you are aware of? I know that, is it Vielight? Vielight is one of them.

[00:20:48] Paolo: Yes, Vielight is one.

[00:20:49] Jane: That's one that I have. It's interesting because there was concern about that light getting through the cranium, but they have a nose piece that is used. What's the efficacy of the nosepiece?

[00:20:58] Paolo: I love this question. This is something we have been working quite a bit on. At some point, we're thinking, "Okay, well, can we stick something into the nose deep enough to get really close to the base of the skull?" It's so exciting because right at

the base of the skull, on the ceiling of the nose, there is the olfactory bulb. The olfactory bulb is connected to our most primitive sense.

When we smell things, that has a lot of emotional impact. It's connected to our amygdala. It's connected to our hippocampus. Can we go really close? Then we realized we can't. The reason we can't is that because the space in our nose is like a millimeter thin. It's really hard to go that in-depth. The other problem is that in our nose, there's a lot of blood in our nose. It's really hard to pass that, just because of all of those chromophores. Bottom line, at the end, when you shed light in your nose, you're really shedding light in your nose. It's not getting to your brain.

[00:22:23] Jane: That's not what I need.

[00:22:23] Paolo: However, it could still be effective. The reason why is because we're more and more aware of the so-called systemic effects of shedding the light. The mitochondria are filling our bloodstream. As a matter of fact, mitochondria are also free-floating in the blood and circulating. It's very much possible that you are energizing your bloodstream, and that has systemic effects that might also benefit the brain.

[00:22:57] Jane: Oh, good, encouraging. What's a device that I can turn to if I don't want to wait until the end of your study? What are several that I might consider, especially if they're laser, not LED?

[00:23:08] Paolo: Okay, well, I will say that the field is changing really rapidly. In less than a year, my expectation is that there would be clinics, med spa, or at your average physical therapy shop, possibly, I believe, within nursing homes or independent living, devices that are meant to help with improving performance and offsetting some mild cognitive impairment will be available, and providers that are trained, skilled, and have a support system with consultation will be available.

That's from my perception of the field, also working with industry and understanding how these companies that so far have just put their devices in the market as wellness devices, I see how the field and these companies are transitioning, creating a support system, and really, a structure out there for people to access safely. I know this is a big introduction here. What I want to say to you and to all our listeners is that I believe that within one year, you're not going to be alone searching for these solutions.

In my little experience, I have experienced how that feels. I am a researcher. I'm a clinician. I know all this because it's my field of studies, yet when it came to helping my father, who is suffering from mild cognitive impairment from Alzheimer's disease, and helping him to access this treatment, I did face some of the questions you're asking me.

What's going to be the device? How are we going to use it? Who is going to help him? It's a tough spot to be in because, unfortunately, the medical establishment has not yet adopted these treatments, and for good reasons because they have not reached approval. It is a tough spot.

[00:25:42] Jane: Paolo, I'm sorry that you're struggling with this with your dad. What a hard situation you're in because you can see something that will help him. Am I right in saying you don't have access to it to say, "Dad, come on over three times a week to my living room, and we're going to do this."?

[00:25:57] Paolo: Right. You're correct. We actually have tried to have him access a laser treatment. He's in Italy over there. However, as I was just saying, the medical field, the medical community is not ready. It's not ready yet for this. In the positive side, the LED devices are already available to the community of people that want to prevent and want to improve their performance or maybe treat their first signs. That's the good news. Again, the other good news is that the industry is now organizing itself to bring that support and really train providers, licensed providers, in the States for this purpose.

[00:26:55] Jane: What are some companies that we should watch for in the next year? Who's surging ahead and getting excited about what you're doing?

[00:27:00] Paolo: That's really a hard question. I don't know if I can name names. What I will say is that generally speaking, I can give some guidelines here. Watch out because it doesn't cost too much to produce these devices. However, a reputable company will market these devices for a certain price range, which most likely will be in the $1,000 ballpark, give or take, and probably more if there are additional features, if there are many LEDs or if there are many options in terms of treatment and variation of parameters.

You want a company that markets their device in that price range. I'll tell you why. Because ensuring that your product is, in fact, delivering the light that you want is not trivial. It takes a lot of quality assurance, and it takes a lot of intermediate steps, a lot of rigor. A company that has a track record, has been in the field, a company that is not just putting out devices there and trying to win the price battle is a company that will eventually give you a "treatment" device, treatment in quotes, because as there's no indication yet, as opposed to a sham or feel-good device.

[00:28:39] Jane: Good advice. You're excited about the future of this, aren't you?

[00:28:43] Paolo: I am very excited. I am very excited. I think we are at a pivotal time. There was a time in neuropsychiatry when medications became available that were easily accessible, well-tolerated, safe. All of a sudden, because of those medications like the

SSRIs, primary care felt comfortable and started prescribing them for depression, for anxiety disorders, for agitation, or even insomnia, or many conditions.

All of a sudden, we saw these interventions out there, and people started feeling better, yet when you consider many of these neuropsychiatric disorders, only one-quarter of people that have the conditions actually receive the treatment, the medication. We know that psychotherapy is great, is demonstrated, effective, but it's quite expensive. It's time-consuming. It's difficult to find providers, many times, that are really skilled and trained in evidence-based psychotherapies.

Now, with device-based interventions, we're getting an entirely new field opening up where people can get this treatment at home. It's huge. For me, it's another shift that will bring much excitement and much help. I will say also that what is very exciting, and I alluded to that before, is that devices can produce effects that medications have not been so helpful with. The pro-cognitive effects, very few medications, like stimulants can have some pro-cognitive effects, and most don't. There is, there, a lot of opportunity altogether.

[00:30:49] Jane: You're talking right to me because I have a son, an adult son, who's really struggling with depression, and he needs help. The medications aren't really the answer for him. He's tried that for many years. What you're proposing, what's out there, as another way with a device to help a whole group of people in this country, especially after COVID and all who were struggling with after-COVID mentally, this is very exciting. Thank you for sharing that. Thank you.

[00:31:15] Paolo: Yes. No, absolutely. You're not alone. In my family, there's been quite a history of depression as well. I know that medications have been very helpful, and I don't want people to be discouraged. They should still look at readily available treatments that are FDA-approved. We cannot stop there. We need to find other treatments because people cannot receive treatment and feel better in terms of depression but then have a bunch of side effects that will also affect their life. We need to do more.

[00:32:00] Jane: Paolo Cassano, thank you. Thank you so much for the time that you've spent and the energy you're putting into this to help people be better as we move forward. Thank you.

[00:32:12] Paolo: Thank you, Jane. It was a pleasure. Thank you for having me.

[00:32:15] Jane: Thank you. The feeling's mutual. Have a great day.

[00:32:17] Paolo: Thank you.

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[00:32:20] Jane: You've been listening to the *Cutting Edge Health: Preventing Cognitive Decline* Podcast. Any information shared here is for educational purposes only. Guest opinions are their own. This podcast is not responsible for the veracity of their statements. Do not use any of this information without first talking to your doctor. Cutting Edge Health, LLC, is not responsible for what may happen to you if you use their information in place of official advice from a medical professional. Thanks for listening. Be well.

[00:32:55] [END OF AUDIO]

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