DANNY LENNON: Kevin, welcome to the podcast. Thank you so much for taking the time to join me today.

KEVIN BOEHNKE: Yeah, thanks so much for having me. I'm delighted to be with you.

DANNY LENNON: As I'm sure you can probably tell from a bit of our conversation before we started recording, I have a lot of questions that I'm very eager to hear your input on. And before we get to any of that, can you maybe just introduce yourself to people in relation to the work you're currently doing, and maybe a bit how you got into that area and what your main focus is right now?

KEVIN BOEHNKE: Yeah, of course. So I'm Kevin Boehnke, I'm a research investigator, a junior faculty member at the University of Michigan, in the anesthesiology department and Chronic Pain & Fatigue Research Center. The work that I focus on is trying to figure out how to best use cannabis and its active components, namely THC and CBD to effectively manage chronic pain and related symptoms. And so, I think about this work in a few different ways, the first of which is really trying to understand what people are actually doing now – so why people with chronic pain are turning to medical cannabis, what the results of that more

naturalistic self-directed use are, especially when we think about use of opioids and other pain medications. And then what I've tried to do is look at those findings and translate those back into, okay, how do we do more rigorous study designs like clinical trials, to see how and when cannabis in these compounds are actually most effective, so doing things like applying to NIH for funding to better do those sorts of studies. I also do a bit of work in the psychedelic space trying to, as they say, cannabis is a gateway drug. I don't believe that in the use context, but institutionally, it certainly seems to be the case, in that, at UOM, there's now this body of cannabis research, and now we're moving into the psychedelic realm.

DANNY LENNON: Super interesting. I have a lot to get through, and I think before we start digging into some of your publications around its potential role in pain management, and then we can also maybe refer to the current body of literature around risks, I think maybe just to get everyone up to speed on the same level when we're talking about terminology, it might be useful to give some very quick definitions. You've just mentioned a couple of the cannabinoids like CBD and THC. We've mentioned cannabis, obviously. People will know terms like marijuana or hemp or all these different terms. What are some of the main definitions we can go with and kind of distinguish between some of those things just so people can get it clear in their head?

KEVIN BOEHNKE: Absolutely. I think that's a great place to begin. So Cannabis sativa is the Latin or scientific name for the plant that people think of as cannabis, marijuana, hemp, etc. I'm going to just use cannabis as that's the most, the broadest and most inclusive term, scientifically and otherwise. People also use marijuana, including some state laws, I tend to avoid this term, both because of its link with the war on drugs, as well as the fact that it was used in some of the initial prohibitionist campaigns against cannabis back in the 1930s in the

United States, and has some racist and xenophobic undertones that I'm really not fond of. Hemp refers to cannabis that has less than 0.3% THC in it, and THC delta-9-tetrahydrocannabinol is the primary psychoactive component in cannabis causing intoxication, makes people sleepy sometimes, produces euphoria, also has some pain relieving properties. CBD, which is then the typically predominant cannabinoid found in hemp, by contrast, is non-intoxicating. It has some anxiolytic effects, so it would be incorrect to call it not psychoactive, and the place that it has shown the most therapeutic promise at this point, is actually in treating seizures for orphan epileptic conditions like Gervais syndrome and Lennox-Gastaut. And, in fact, authorization by the FDA of Epidiolex, which is a plant based CBD product made by GW Pharmaceuticals, was for those orphan epileptic seizure conditions.

So we've now covered cannabis, marijuana, hemp, CBD, THC on the legal side of things, just so listeners know, hemp products in the United States, so those again with less than point 0.3% THC are pretty widely available. The 2018 farm bill made these products semi illegal under federal law, removed them from the Controlled Substances Act where CBD products had been previously, but they still exist in kind of a legal gray zone in which the FDA says they want to regulate them, but they're not doing, in my opinion, a very effective job of that. Products that contain more than point 3% THC, these still qualify as Schedule I drugs under the federal Controlled Substances Act, which means that they're criminalized at the federal level, and that Schedule I designation also currently states that that means they have no accepted therapeutic value and a high potential for abuse and misuse, which, of course, clashes with the state laws, which have legalized cannabis for medical and, in many cases, adult use purposes. So it's a really tricky and complex space, as you can tell.

DANNY LENNON: Yeah, for sure, and I definitely want to circle back to some of that complexity later in our discussion. For now, you've mentioned THC and CBD as these two primary cannabinoids of interest, and I'm sure we'll look at much of the literature related to those. But, of course, when we take cannabis broadly, there are many cannabinoids, probably hundreds of these cannabinoids. How certain are we that the primary effects we see from someone that is consuming cannabis is down to say a THC and – or why are those the things that we look at as these are the cannabinoids that we're going to isolate and work with, and how did we get to that point?

KEVIN BOEHNKE: Yeah, that's a great question. So some of it is that THC and CBD seem to be the two most dominant cannabinoids. So if you look at some of the cannabis plants, these are the ones that will show up most frequently. That doesn't mean that other ones are not present, and in some situations, present in large quantities. We focus the most on THC and CBD because their effects have been known for longest, and, as such, because they're so common, and there's sort of momentum that builds feeling like, okay, we'll continue looking at what we know the most about, there's been a lot of focus there, and from the point of having enough quantity of these other minor cannabinoids say, to do the sorts of studies that we're thinking about, that has been challenging both on its own, but also then in the context of the war on drugs that has made these compounds difficult to access, and, in many cases, illegal to access. But then to your point about what is the potential value of all these other things, there's probably quite a bit there, especially when we think about the combination of flavonoids and terpenes that also show up in the cannabis plant, some of which we know from studies of essential oils that they can have potentially, say, sleep inducing effects, that can help with anxiety, or be anti-microbial in nature and a topical product. So I think that there's just so

much more that could be done, that simply hasn't, much of which is due to this policy landscape.

DANNY LENNON: Yeah, that's super interesting to consider, and I wonder, then, we may get into this later on, but even more broadly, do we start to then see a disconnect in what might show up in either any observational research we have or even qualitative surveys of people who say habitually use cannabis. That seems to be a bit different from then when we do an isolated intervention on specifically just THC, and then we find conflicting findings. And if that is the case, could that potentially be one reason why?

KEVIN BOEHNKE: Absolutely. And those sorts of studies have already been done, there's most of the ones that I have seen, there's not a huge amount of them, but some have been in the preclinical space where they say compare isolated CBD versus a full spectrum CBD product that has a bit of THC in it, and they see that the effects on pain and inflammation are quite different. And I believe there's been some work asking people using synthetic THC to compare it to inhaled cannabis, which again, has all those other compounds in it, and people tend to prefer the inhaled cannabis product. So I think some of this comes down to all those other components, and one of the reasons that it's complicated to talk about this – or maybe not complicated to talk about it, but just challenging to parse through because there's two camps within the cannabis space as I see it, one of which I think of just like the classic pharmacologist who say, let's isolate that active ingredient, and go with that, and you see this, you know, this is much of the basis of how we do medicine when it comes to medications in Western countries. We think of that dominant active ingredient, we give people that after figuring out what the dosage range is, and we go with it. And the other side is more the herbalist, or many people think of this as the entourage effect where the whole is greater than the sum of the parts. And it's possible that there's antagonistic

or synergistic, or other sorts of effects with all those components acting in concert that could be more effective than simply THC or CBD alone. From the human clinical trials side of things, I'd say, there's a lot to be done still, but it seems that everybody I talked to has a pretty strong opinion on it.

DANNY LENNON: Yeah, and we'll definitely maybe get to what that current evidence base looks like in a bit, and before I get to maybe some of the potential mechanisms of action, specifically around pain management, maybe the kind of final definition we can end talking about is the endocannabinoid system within humans. Can you maybe just explain briefly to people what that is, and its functions and how that might fit into this broader conversation we're going to have?

KEVIN BOEHNKE: Yeah, so the endocannabinoid system is one of the oldest, most conserved systems in animals. At this point, it's not been as well studied as, say, something like the endogenous opioid system or something like that. But there's two receptors that we absolutely know are there among many, many others that are thought to interact with it. So those two are cannabinoid receptors 1 and 2, very creatively named, and CB 1, cannabinoid receptor 1 is one of the most common receptors in the central nervous system. CB 2, on the other hand, is more found in the immune system, and some of the internal organs like the spleen, and seems to be more involved in immune function. So there's a lot of excitement about targeting these two systems, these two receptors for pain management, CB 2 more on the anti-inflammatory side of things, CB 1 for more central acting drugs. So, for example, THC, when it binds to the CB 1, produces some of that intoxicating effect, but also some of the analgesic or sleep promoting effects as well. So functions of the endocannabinoid system have been described as relax, eat, sleep, forget, protect. So things like memory, analgesia, immune function, stress, appetite, regulating

all of these things that are just essential for life and survival. Besides the CB 1 and 2 receptor, there are many others, as I mentioned, but then there's also the enzymes associated with breaking down the endogenous cannabinoids like 2-AG and anandamide, and one of the things that people are really excited about is maybe blocking – developing compounds that can block the action of these enzymes that break down the circulating endogenous cannabinoids. Because if you get up a higher volume of the circulating endogenous cannabinoids, then you might produce some of the same effects, say, as ingesting cannabis. So things like enhancing sleep or feeding behaviors or decrease in pain or decrease in anxiety. So there's a lot of excitement there on the pharmaceutical side of things. I will say that when it comes to new and novel cannabinoid compounds that are not found in the plant, but had been synthesized in the lab, there's some promise, but nothing that has really come to market yet in a mature way.

DANNY LENNON: Let's start digging through some of the current literature in this space, and obviously, we're going to focus maybe a bit on pain management, but we can talk health broadly, and I think from an outsider view, trying to do a bit of my amateur's research and look at what the current evidence looks like, one of the big things you see with cannabis and health broadly when you start piecing through that is that there is actually quite a lot of literature, but typically, with two things that are maybe separate from what we're actually talking about today, one is that most of it is on recreational use. And then second, the research questions are set up to specifically study negative effects it seems. So based on the current literature, and if we focus on the side that is showing risks of cannabis use, what are your conclusions from what the overall evidence tells us right now, and then, can you maybe place that in some context based on those couple of things maybe?

KEVIN BOEHNKE: Yeah, so as with any compound that you put into your body or any plant or any food that you put into your body, cannabis has risks, and I feel like this is something that we really need to be clear on, and that's also, as you mentioned, that's a space that a lot of the research has been focused on, especially since cannabis was designated Schedule I under the Controlled Substances Act, that's where a lot of the federal funding was going. So I've seen figures up to say like 30 to 1, in terms of funding of how that's gone towards looking at those sorts of research questions instead of the therapeutic side of things. But these risks are not insubstantial, when we say think about dependence and addiction, approximately 9% of people who use cannabis in their lifetime have some kind of dependence or addiction issue with it. This goes up higher, especially when people start using in adolescence, and goes higher still, if people are using it in chronic, daily way. Now, of course, we need to place this in the context of, okay, what about alcohol or opioids, the risk of dependence or addiction from cannabis is substantially lower than those, but it still does happen. There are also side effects of cannabis use, so people can get dizzy, sleepy, lightheaded, anxious less commonly, but it still happens, people may feel paranoid, some people can have seizures or it may trigger a psychotic episode; and people with underlying psychosis could be hallucinations. And then I'd say, one of the things that I have the most concern about for at least a subset of people who seem to show up with this set of symptoms is cannabinoid hyperemesis syndrome, which is kind of a cyclical vomiting that shows up among a subset of people, especially, it seems to be triggered by really heavy use of THC dominant products, but it results in a lot of visits to the emergency room, and really the only way at this point that we know how to treat it is to have that person stop using cannabis. But vomiting is very, very unpleasant. This is a difficult and often painful thing that people have, and because, again, cannabis is still in this legal gray space, it then

can make it somewhat difficult to have the kind of conversations with physicians about cannabinoid hyperemesis syndrome, so that people can deal with in a skillful way.

DANNY LENNON: Sorry to jump in, but that reminded me of something I was going to ask along those lines of given that there are these distinct risks, and that there are certain profiles where there's an increased risk in certain subsets of people that you've mentioned, but given maybe the problems with getting good information out to the right sources, where are we in relation to, let's say, a proper, comprehensive evidence based screening of people if they are going to be prescribed cannabis in a medical setting or otherwise that physicians can actually rely on now – are we anywhere close to that, do they have something similar? How do we go about an actual good quality screening of people that may be potentially using it?

KEVIN BOEHNKE: I wish we had one. I think what you're saying sounds completely common sense, and it'd be great if we had something like that, that people were using in a standardized way. But as we talked about beforehand, many physicians are concerned about engaging with their patients about cannabis, especially in this medical context, like, it's one thing to say, oh, don't use this, because it's Schedule I, and it has all these risks, it's another thing to say, let's optimize your use or think about harm reduction principles, and have a thoughtful chat about this, and a lot of people haven't received the training to do that, or might not feel comfortable doing it.

DANNY LENNON: And for some of those implications of translating this to practice, I actually want to get back to that towards the end of this discussion. But for now, I do want to shift into discussing pain management specifically and certainly some of the work that you've done in this area. Before doing that when we talk about the concept of pain for people who are not from a pain science background, how should we

characterize that, what should we think of what is pain. It might be a very poignant question to just mention first.

KEVIN BOEHNKE: Well, that is a very philosophical question. It depends on what definition you're pulling from. I think oftentimes, in these studies, people are thinking of pain. For example, International Association for the Study of Pain says that the definition of pain is an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential tissue damage. But they go on to say that it is a very personal experience, it's influenced by many different factors both biologically, psychologically and socially, and I think this complexity is often simplified in these studies to a, what is your pain on a scale of 0 to 10. And then the outcome is to see, okay, does your pain change before like from the cannabis treatment. And in my mind, that's a somewhat crude way of trying to figure this out. That whole pain grading system got us into a lot of trouble with things like the opioid crisis. But does that mean that I've a better way of measuring it or thinking about it? Hmm, I'd say, I'm thinking more on the functional side of things, that's the place that I'm more interested in thinking about pain. So like the interference of pain with one's quality of life, preventing them to do the things that they find meaningful, important, impactful, both on a personal level and then a social community level. Pain can be both a physical sensation, it can be emotional, within the context of studies of clinical trials, it's typically physical in observational studies, it can be any number of those things.

DANNY LENNON: And has more of literature focused on people with chronic pain that has been unable to be helped through other means or has it also looked at maybe acute bouts of pain, where does most of that skew towards?

KEVIN BOEHNKE: The clinical trial literature at this point is more focused towards chronic pain. There are a few

studies that look at cannabinoids and acute pain, and then the observational literature is more focused in the chronic pain context.

DANNY LENNON: So if we think about some of the mechanisms of action here, what is the hypothesized mechanism by which a cannabis or any of those cannabinoids could potentially reduce pain?

KEVIN BOEHNKE: With THC, the fact that it influences sleep is likely quite important, so many people who have issues with chronic pain often had sleep disturbances, and because THC or THC analogues like nabilone can help with sleep in the context of chronic pain, that's one way that it can certainly help. Another way is that THC seems to reduce the unpleasantness of pain, likely through the activation of the CB 1 receptor in the central nervous system. So if people have distance from that pain, then they might be able to, say, function more effectively or do the things that they need to do a little bit more effectively. CBD on the other hand, again, non-intoxicating, but that anxiolytic effect may help with pain as many people with chronic pain often get stuck in ruminating catastrophizing sort of cycle, and that is in some ways driven by or it's related to anxiety, and so being able to soften that and break that cycle could potentially be valuable to CBD may be able to help with pain by reducing that anxiety again, which is linked to worsened pain through that sort of catastrophizing or ruminating thinking style. Also in preclinical studies, CBD does have a pretty strong anti-inflammatory effect, which has not yet been, unfortunately, not yet been translated to humans. But so with those combinations of effects and the fact that when people smoke cannabis or take THC, it's often a mood enhancer, all those things together could help with symptoms related to chronic pain.

DANNY LENNON: Cool. So we have clear potential mechanisms of action, we have some of these preclinical trials and mechanistic studies showing that they can impact all these various processes. So if we look

at the evidence based surrounding, its use on actual, as pain as an outcome, before we get to the clinical trials, maybe if we think of the epidemiology or any kind of self-report measures or surveys or so on, what do we see on that side of things of what is actually getting reported from people who are using cannabis?

KEVIN BOEHNKE: Yeah, that's a great question, and I think it's important to split those as you've done because the observational literature and the clinical trial literature diverge quite starkly. So on the observational side, I'd say, there's a couple of different trends that emerge, including work that I've done. On the one hand, you see that some people report adding cannabis to their treatment regimen, they notice an immediate, positive effect on pain, often within about three to six months. These people will often do things like reduce their use of other pain medications, including opioids, or we say that they do, and there's actually quite a few studies conducted in Israel and Canada and in the US that show that longitudinally. And so that group I would consider say they are responder group for people who seem to have a positive response, when they're using cannabis products, it seems to be a useful harm reduction treatment for them, and things are moving well. On the other side in the observational literature, there are certainly some people who seem to add cannabis into their treatment regimen, but their pain doesn't really get better. They often use it to, say, help manage mood issues, but then, if you are piling cannabis on top of benzodiazepines, on top of opioids and other pain medications, because there's often a lot of polypharmacy going on in chronic pain, then what's happened is you've just added another thing into the mix that may not actually be helping with symptoms, but is just adding potentially further dysregulation into this person's life. And so, there's quite a few studies that show that among some people who are using cannabis, that they have a higher rate of non-prescription opioid use, or that the use of their prescribed opioid medication is done in

more of a misuse context, rather than in a more medical context, or that they're more likely to drink alcohol or engage in other risky behaviors. So I think something that is really important to think about within this space is not everybody will respond to cannabis in the same way. I think, very likely, people who do respond quite well, as noted in that first group, there are some who respond negatively, where they use it in more misuse addiction dependence context, and then there are probably quite a few people who, they try it, it didn't work for them, and they stop it.

DANNY LENNON: So then if we think about the clinical trials, where are we right now in terms of just the amount that's been done up to this point, how have they typically been structured, what's a quick overview of the clinical trial data looking at chronic pain?

KEVIN BOEHNKE: Yeah, so there have been a few dozen clinical trials of cannabis and chronic pain at this point. At this point, there's probably been more reviews of these clinical trials than the clinical trials themselves. But what they typically say, especially the new ones, with the better methodologies and works with sophisticated techniques, and really well done and design studies, they typically say, we see a small and statistically significant benefit of cannabis and cannabinoids on chronic pain, typically, in the neuropathic pain context, so pain caused by nerve damage or inflammation, but we also see a significant side effect profile that means that for some people, the potential benefit from cannabis maybe outweighed by the potential harm. I'd say that's the big picture, 30-second summary. A couple of nuances that I feel like are really important to mention here are, these clinical trials were not done with the same products that are available in the medical cannabis market. So these are typically pharmaceutical grade cannabis products, you know, think of something like nabiximols, the brand name is Sativex through GW Pharmaceuticals, which is a one to one

sublingual CBD and THC spray, is not available in the US, but that's the product on which a large number of these clinical trials have been done. The other thing I'll say is that the trials themselves tend to be fairly short length, except in that chronic neuropathic pain space, especially with the Sativex studies and very few of these studies have also used CBD alone. So most of them are either that one to one CBD to THC or THC dominant products, be they synthetics or inhaled cannabis products.

DANNY LENNON: If we were to split out those of the one to one THC and CBD versus mainly THC alone, do we see any differences in results in those studies, or, is it fairly consistent regardless of the kind of CBD content?

KEVIN BOEHNKE: Yeah, this is an ongoing point of contention. There are some studies that are continuing to come out looking at this, but the question of whether CBD is co-administration with CBD is beneficial, I think the evidence is leaning in that direction. So it seems that giving people CBD with THC may reduce some of the side effects of THC, especially on the anxiety side of things. So some people when they take too much THC, they can get quite an anxious feeling that is then potentially helped mitigated by CBD, and then there's also some suggestion that people can take a higher quantity of the combination than of THC alone. So if they need to take that higher dose, especially if you think you can say in an inflammation context or a neuroprotective context, might be potentially helpful to be able to take a higher dose without having as potentially significant of a side effect profile. But I will say within, you know, there's a lot of individual, inter-individual differences, so 5 milligrams of THC might affect you much different than it would affect me. And so, all of these pieces become really important, especially, again, when we're considering the divergence between the clinical trial and observational literature where people on the observational side can very frequently take the amount that they wish to, which might be even

a very tiny amount, but at the same time, they may way overdo it as well.

DANNY LENNON: So with the current evidence base we have, and particularly around the clinical trials, and if we were maybe to know some potential shortcomings you might see in how some of those are done or better ways that they could be constructed, or even just unanswered questions that haven't been got to there yet, what do you see as the most important research questions that those upcoming trials should focus on over the next couple of years, and what is the kind of really best way to answer some of those outstanding questions?

KEVIN BOEHNKE: Oh that is a good question. I think some of it depends on what your lens is. So for me, I have a public health background, sorry, I guess, I dodged your question about that, initially, I did do a PhD in public health in environmental biology. And so, I bring that with me into all these questions, and, I think really population level, what do we need to see to improve outcomes of people using cannabis for your medicine. And so, I think not of do we need a specific ratio or anything like that, and do we need to test every combination of those and every pain state, that would be ideal, but it's also not that practical at this point in time, like, we're talking about dozens or hundreds of trials. What I would like to see is empirical evaluation of kind of the best in class evidence synthesis that is then put into clinical practice. So we know the effects of, largely the effects of THC and CBD, how can we design an intervention that helps people optimize their use given the current medical cannabis climate. So I think that would be, if I were to put together a holy grail of if, if there's only one study, and that's all I could put together, that's what it would be. If we're going a little smaller scale than that, I think, another really important question is who responds to CBD alone. CBD is known to be non-intoxicating Epidiolex, that product that is approved by the FDA is descheduled. It has little or no abuse

potential. CBD is known to be quite safe even in fairly high doses, and if we were able to figure out who could respond to CBD alone, without adding in THC or other cannabinoids, I think that'd be really valuable, because at this point, when we think of a harm reduction strategy, that would be one. If you can get positive analgesic response with CBD without THC, then why would you take it, why would you take THC? Unless you want those effects. But many people who are using medical cannabis they want to take it like they would any other medication and go back to spending time with their family or friends or whatever brings them meaning, and they are pursuing their hobbies, or whatever is giving them meaning in their life. So I think that's one of the big, unanswered questions in this space right now for sure.

DANNY LENNON: One of the interesting things you said to me before we were recording is about how the, I suppose, the policy in this area has kind of out sped the potential research or the ability to keep up with it, given the timeframes. It requires to do a lot of research in this area, and so, now we're in a situation where medical professionals, in jurisdictions where it is illegal to prescribe this, are in a position where they can be using medical cannabis with patients with certain indications, but as you've noted, may be hesitant either for particularly with maybe a lack of being comfortable with what current evidence we have, what actually is an evidence based guideline here. So based on the, and with the caveat that there are still a lot of unanswered questions and very difficult to give hard recommendations, in lieu of that, if you were to talk about what evidence based guidelines might be possible now in translating some of this to practice, what do we actually know about dosage or the type of administration, the frequency of use that someone may able to tolerate the different kind of risk profiles of that, like, where would you even start a conversation with someone about what an evidence based guideline is?

KEVIN BOEHNKE: Yeah, so I'd say it started out in a patient centric way, this is really going to be critical here, so many of these people who are using cannabis, they probably want to be able to talk to their doctor about it, because they want to know about medication interactions, or when they should use it, or how to use it most effectively, because at this point, they may have learned about this from their own personal experiences or from a budtender, or anybody who's not their physician, and I think that physicians are uniquely, or other healthcare professionals for that matter, are uniquely placed to be able to work with their patients in this sort of shared decision making way that optimizes all the things like the placebo effect of seeing a healthcare provider. I feel like that's kind of a flippant way of putting it, but when people see a healthcare provider, they often feel better just from being listened to, and talking to that person who knows about them and their health. So I think leveraging that in combination with education and knowledge about how to do this is really important. In terms of how to actually start, say, putting that into place, I'd say, the principles of cannabis use and thoughtful cannabis use typically revolves around the routes of administration, the dosing, and the cannabinoid content.

So with regards to routes of administration, we do know how quickly they typically work. Smoking or vaporizing usually takes effect in a few minutes, peak effect maybe in 10 minutes, 15 minutes for some people, and then lasts for two to four hours. But quick spike and effect, quick taper, because it's smoking and smoking is not good for the lungs, and vaporizing, same way, although not quite as bad, I think it's typically better for people to seek out things like tinctures or edibles. Tinctures, the sublingual products that, when held under the tongue for one or two minutes, can take a faster effect than an edible. So an edible takes about one to three hours for peak effect. For somebody who's new, they should definitely

wait that full three hours, so they don't take too much. But a tincture, 15 to 45 minutes, if held under the tongue is typically how long it will take to get an effect. And those are quite easy to titrate, if, once you have education, and making sure you're doing the math appropriately there, topical products are just the last one I'd want to mention, because these are widely used, and people typically grab them on like superficial joints like the fingers, the knuckles, the knees, the elbow, etc. We don't know as much about how well they work, because it's unclear how much they penetrate the skin, but typically, they don't cause intoxication, unless they have something that really helps them get through the skin, enter the bloodstream and have THC in them.

So those are groups of administration. I typically think in the chronic pain context of, if you can take a capsule or edible as like a long term baseline pain control, and then you can use a tincture for breakthrough pain, that can be a useful way to conceptualize it, or somebody could just use a tincture all day, if they want that faster effect onset. Then we go to titration, and the rule here, start low, go slow. Everybody's body is different, and we want to make sure that you don't overshoot. There does seem to be this sort of sweet spot in which people are taking enough cannabis, that they're getting symptom relief, but not too much, that they're getting negative side effects. So you can only really determine that on an individual basis, so moving methodically with the same product slowly increasing until you hit that point can be a really useful way to go especially when done in concert with symptom tracking. And just for a couple of limits that have been proposed in the literature, people typically say, if somebody's had about 50 milligrams of CBD and they don't get response, they are potentially not a responder to that, and same with up to 30 milligrams of THC, although many people will not get up that high with THC.

And then the last thing is THC versus CBD. So THC, you don't want to use it while driving or operating a vehicle because it is intoxicating, but it can be a good thing to take, especially if you're trying to use it to help asleep. CBD on the other hand because it's non-intoxicating, much better for daytime use and also, as we talked about before, for co-administration with THC to potentially help with some of those anxiolytic effects. So then putting all those things together, the context of, okay, this is to say somebody who has chronic pain, the pain is really negatively affecting the sleep cycle and they get a little bit anxious, well, perhaps that's somebody who is good to take CBD during the day that could potentially help with some of the pain during the day without causing intoxication, and then not causing the kind of anxiety spikes if they're taking too much THC. And then, they could take one to one product at night, to help with sleep as they're then transitioning into bedtime routines, and they could consider taking something, right before bed, that's faster acting, as well as taking, say, a small dose of an edible so that they stay asleep longer.

DANNY LENNON: I do have one final question, and apologies, because it's probably a relatively large one that we could probably spend an hour talking about alone, but we can just give a very quick overview on it, and the reason is, because I know you have talked about this before and actually has huge implications for the work you're doing in the chronic pain space, given that we've talked about some of the impacts for individuals, but there's a potentially incredibly huge societal impact, and I think particularly in the United States, where the opioid epidemic is particularly concentrated. It's obviously far worse than it is, say here in the UK, I think you guys have a, just the problem can't be understated or overstated, I should say. And some of your work has looked at this idea that if we can potentially get some pain management through the use of CBD, THC or other cannabinoid products, then if that allows

someone to not have to be using opioids and use in place of them, we can potentially have this huge effect. Can you maybe just give a very quick synopsis of that?

KEVIN BOEHNKE: So that's a great question, that's actually the research question that got me into this space with some of my survey work. I think you actually framed it really nicely. A lot of pain medications, especially opioids, are typically not that effective for chronic pain, and they cause all kinds of societal damage and harm through things like overdose, addiction, diversion, etc. And I think, in fact, this is one of the reasons that cannabis has been thrust into the limelight, especially in the past year, because there's a lot of dissatisfaction with current pain medications, including opioids, and cannabis has this potential to act as an alternative, an adjuvant or a substitute. And I think that's where some, again, where some of my first work really centered on is a lot of people were specifically saying, so in one of my studies, I think it was somewhere around 75% of people said, yes, I substituted cannabis for pain medications, I did it because I got better symptom management, I had fewer negative side effects, and I don't want to take these other pills anymore, if it's not going to help me. That's one of the reasons, for example, that NIH is putting a lot of funding towards that very question. It's definitely a fruitful and exciting research space. There's plenty of mechanistic plausibility both on the side of THC and CBD seem to have analgesic properties, so they could be used in place of some of those other compounds, but also, that there seems to be some synergy. So there's a really nice clinical trial conducted by Ziva Cooper and her group where she showed that giving a small amount of inhaled cannabis with a very small amount of Oxycontin – Oxycodone, I should say, resulted in a similar amount of pain relief as a higher dose of oxycodone alone. And so, that suggests, okay, maybe this is a way that you could actually just reduce that dose and help some of these people

who are taking higher doses of opioids start to taper off.

DANNY LENNON: I've really enjoyed this discussion, so thank you so much for your input here. It's been incredibly informative for me, and I'm sure for listeners.

KEVIN BOEHNKE: Absolutely, and thanks so much for your kind words as well as for hosting me today. It's been really nice chatting with you.

[00:49:26]

[00:50:22]

DANNY LENNON: Welcome to the podcast, Dr. Carrie Cuttler, thank you so much for taking the time to join me today.

CARRIE CUTTLER: Thanks for having me, I appreciate it.

DANNY LENNON: Maybe you can give listeners some context on you and your background of work, so can you maybe introduce where you're currently working in academia, where your research focus is, and, I suppose, a bit of your background that got you to that point?

CARRIE CUTTLER: I am an assistant professor in the Department of Psychology at Washington State University, and my research focuses on better understanding the potentially beneficial as well as detrimental effects of both chronic cannabis use and acute cannabis intoxication.

DANNY LENNON: At least from someone on the outside who's kind of looked at this, there's a kind of an interesting thing that you're hit with when you first look at this area of literature, in that, there is actually quite a lot of literature published relative to what maybe people think, but overwhelmingly, that tends to be investigating risks that come with cannabis use, and there's obviously a good reason for that, but there's also maybe other reasons there too. And so, in more recent years, I suppose, there's been a turn towards maybe looking at some of the therapeutic effects. Can you maybe just give us an overview picture of maybe that trajectory of research in cannabis more generally, and where that has kind of moved us to this current, I suppose, place where there's a lot of interest and external interest in this area?

CARRIE CUTTLER: Yeah, I think you're right that in the US, particularly, there's been this whole war on drugs, that's been happening for quite a long time, and the sort of demonization of cannabis, which had very racist origins actually, was part

of this war on drugs. And because of that, I think that things shifted into harms based focus. First of all, it's very difficult to study cannabis at all, because it's classified as a Schedule I drug in the United States, and that comes with all sorts of restrictions you need, licenses from the DEA, Department of Health, and whatnot, and these things can just take years. And because of that we have, historically, not had nearly as much research on cannabis as we should. And again, like you said, it did start out or it was a lot more harms based research, and this is probably because of the federal government's perceptions of cannabis as being the most dangerous, one of the most dangerous drugs out there, then it's easier to get funding from the federal government to do harms based research. But it seems that things are starting to shift and change and cannabis is becoming recognized as having more therapeutic potential, and some of the laws are starting to relax, at least, at the state level, allowing people to better able to access cannabis, but we're still a long way. Schedule I drugs basically are drugs that are perceived as having a high risk of abuse and no therapeutic effects. So it really has no business being scheduled in this manner, because we do know that there are therapeutic effects and medical cannabis is legal in many states, the majority of states, so it's very paradoxical.

DANNY LENNON: There's also an interesting thing now where the therapeutic effects are being acknowledged to some degree or at least investigated, but there are undoubtedly, as with anything that shows a degree of promise within the literature, there are people that maybe take that too far, or the hype gets ahead of the actual evidence. And so, hopefully, we're going to see where that exactly lies. I wanted to start in terms of actual health outcomes with depression, and from seeing some of the work that you've published in this area and some of the lectures you've given on this, one of the overview things that seem to emerge, and you can correct me if I'm wrong, is that with some of the acute interventions, there

seems to be a potential for improvement in some symptoms. But when we look at some of the long term data, there seems to be this association with exacerbation of symptoms. How do we go about reconciling these two things?

CARRIE CUTTLER: Yeah, depression is a particularly interesting one, because we do see these different short term versus long term potential effects of cannabis on depression. So I conducted one of the largest studies of its kind using back data from this Canadian medical cannabis app called Strainprint, and Strainprint allows users to put in their symptoms immediately before using cannabis, and then shortly after using Cannabis. And, as a scientist, I'm able to get those back data and look at symptom reduction as a function of cannabis use, and also map it on to sort of THC and CBD concentrations, dose and whatnot. And what we found was very consistent with what we found for other conditions, which is like roughly 50% reductions, I think it was 58% or 60% reduction in depression ratings from immediately before to immediately after using cannabis. So we see that when people are under the immediate acute intoxicating effects of cannabis, that they do experience the typical euphoria and elevation in mood that cannabis is known to produce. The problem is that it's kind of a, what I've been calling, a band aid approach, and I don't mean anything negative by that. But and then, it's just sort of temporarily masking the problem, and it's not addressing the root core issues underlying and maintaining the depression. So it's a quick fix, a quick way to alleviate symptoms, but the symptoms are going to return when the cannabis wears off, which might just offer only an hour or two of reprieve. And what we also did was this is an app that people use repeatedly so that they can find the best strains and doses that are reducing their personal symptoms. And so, we were able to track their sort of baseline depression symptoms as a function of time over almost the course of a

year, and what we found was that those baseline, those before cannabis use symptom ratings were actually increasing over time so that the depression looked like it was getting worse as a function of the repeated use of cannabis to manage that depression. And it goes hand in hand with meta analyses of longitudinal studies, which also support this idea that using cannabis chronically can represent a risk factor for depression and can exacerbate depression over time.

DANNY LENNON: Do we know anything about what mechanistically could explain why symptoms could get worse over time, yet, in an acute setting, they're having a potential benefit for the number of hours someone may be under the influence of it?

CARRIE CUTTLER: Yeah, so it has to do with the desensitization and downregulation of cannabinoid receptor, CB1 receptor. So basically our endocannabinoid system, so we have our own endogenous system, we have our own versions of THC within us called anandamide and 2-AG, and those bind to these receptors, and they help protect us against negative mood states like depression, and the endocannabinoid system is implicated in protecting us against depression. And so, what happens when you repeatedly use the drug as you can desensitize and downregulate that system, so that you're kind of tampering with your natural defense system and affecting that. Therefore, you might need the drug now to help alleviate depression because your endocannabinoid system has been dysregulated, and it's not able to do that anymore.

DANNY LENNON: So this is clearly a situation where there's some preexisting depression, and we can get a worsening of symptoms with an ongoing chronic cannabis use. And indeed, there's this association, it seems with depression and cannabis use disorder, but with that specifically for their direction of causality, how do we tend to summarize that typically?

CARRIE CUTTLER: Sure. Historically, it's been interpreted that cannabis is causing the depression, which is unfortunate, because those conclusions should not be made on the basis of the types of research that can be done in humans. And we did a survey several years ago, we did a very large scale survey of medical cannabis users just trying to better understand and characterize their use of cannabis, what they're using it for, what products they're using and whatnot; and we actually found that the top three reasons that these medical cannabis users were reporting using were pain was number one, but then anxiety and depression were numbers two and three. And so, what that tells me is that a lot of the relationship between cannabis use frequency and whatnot and depression symptoms may actually be the exact opposite direction that people have historically interpreted. It is because a lot of people are actually self-medicating with cannabis for their depression. So the depression is predicting the cannabis use. But, like I said, there's a bidirectional relationship such that regular use of it can then exacerbate the underlying condition. And we don't necessarily see that exacerbate with other mental health conditions, it really seems to be fairly unique to depression from what we've been able to tell.

DANNY LENNON: Yeah, one of the things I remember you referencing in the depression piece was quite interesting, you relayed the story of Rimonabant, which was originally developed as a potential anti-obesity drug. Can you maybe just briefly explain how that kind of fits into the picture?

CARRIE CUTTLER: As you may know, when people use THC, they often experience the munchies. It makes people – it increases appetite basically. So some clever people thought, well, maybe if we block the endocannabinoid system, then people won't feel hungry. And yes, they did have reduced appetite. The problem was a lot of them became suicidal and very depressed. And so,

what we were seeing again, is that blocking this natural endocannabinoid system was producing depression and suicidal ideation. And again, this just goes along with this idea that this endocannabinoid system is protecting us and tampering with it by repeatedly using cannabis and again desensitizing that system can put people in a similar vulnerable position, and not to the same extent as this drug that was very much blasting the system and blocking it, but that drug was a good illustration of the role of the endocannabinoid system in depression.

DANNY LENNON: With some of those acute interventions where there was a reduction in symptoms in depression with cannabis use, do we have any analogous interventions that use, say, CBD alone, because if we're saying that potentially the effect is when people are taking cannabis, and whilst under the influence of that, that's where we get this alleviation of symptoms – could that indicate that maybe it's the THC component more than CBD, or do we actually have that figured out yet?

CARRIE CUTTLER: Yeah, cannabis that was lower in THC and higher in CBD was predicting the largest change in depression symptoms. I would personally still like to see that replicated. It is based on a very large sample, and it's good, because ideally, we'd like medical cannabis users to be selecting products that are a bit higher in CBD than THC. I just don't know that there's a huge literature to support that finding at this stage of the game, and I think that they need to do more and better controlled studies where the researchers are really manipulating those concentrations, instead of it being what participants were choosing to use, which was the case in my study, and that we're just looking at people's natural use of the cannabis that they naturally use, and I wasn't manipulating anything. So we see these associations, but we can't infer this causality, so it could be something about people that are choosing those strains, but some indication

that, yes, lower THC and higher CBD might be optimal.

DANNY LENNON: So if we move to anxiety, and this is also really interesting, and I think, if we look at, again, start maybe with the acute effects, if I remember some of the, I suppose, an overview of the literature seems to be a fair amount of heterogeneity in those findings, and you can tell me if that's accurate, and so, we're seeing some show positive effects, some showing no effect at all, some showing negative, if that is correct, what do we put that down to, is that a function of dose is it a population type, is it study methodology, how do we kind of piece apart this kind of discrepancy in some of these findings?

CARRIE CUTTLER: So acute cannabis use can relieve anxiety, and a lot of medical cannabis users say that it does. A lot of recreational users say that's the number one reason why they're using the drug is to decrease stress and tension, and so, it's very, very commonly used and reported to decrease anxiety. But as a lot of people know, a lot of people also end up in the emergency room experiencing panic attacks under the influence of cannabis, and so, it can actually produce anxiety in some individuals. And we're still trying to understand that, but one thing we do know is exactly what you mentioned was dose. So lower doses and probably lower THC is more likely to be anxiolytic to reduce anxiety, whereas higher doses, and again, potentially higher THC concentrations are believed to be more anxiogenic. And there's good research and several studies that have found this, that there's sort of this biphasic effect, such that it's dose dependent. I think experience also plays a role though personally, and I don't necessarily have a scientific literature to back that up, but I think that more experienced users are less likely to experience anxiety, and they're more likely to experience reductions in anxiety, whereas less experienced users might not know how to self-titrate properly or just are less familiar with the drug, and maybe even a little

anxious in taking the drug, and are therefore more likely to have those experiences. And then we know too that edibles might be more likely to trigger like panic attacks and whatnot, because it is so hard to titrate the dose, people tend to just take too much of the edible products.

DANNY LENNON: That's really interesting. So if we think about that discrepancy, and the anecdotal evidence you mentioned around someone's experience with it, could that be functioning both physiologically and psychologically, as in, is there a physiological tolerance that experienced users have or is it also that they are kind of like comfortable when things feel a bit more out of control, that they just cope with it better?

CARRIE CUTTLER: Probably both. They're more used to the sensations that cannabis can produce, and might be less likely to attribute those sensations to anxiety. So just as an example, cannabis is known to elevate heart rate. So when you're under the influence, heart rate's going to be elevated. And an experienced cannabis user might just know that's just part of the feeling of cannabis, right – it increases my heart rate a little bit, but I'm still relaxed, and I'm still fine. Whereas someone who's less experienced with it might not understand it, and might misattribute the elevated heart rate to anxiety, and then, sort of spiral into anxiety symptoms, because they start worrying about that. So the tolerance issue is true, yes. So chronic cannabis users who are using regular do start to demonstrate tolerance to the effects of the drug, so it no longer has as many detrimental or potentially positive effects as well an experienced user. And again, it just has to do with this downregulation and this desensitization of the endocannabinoid system. So that's our body basically trying to maintain homeostasis is, well, where this system is getting blasted, we need to make this system less effective, because it's repeatedly being blasted by the use of THC. And so, yes, absolutely, they develop tolerance, and that

tolerance can be to both the detrimental and the beneficial effects and anxiety reducing effects.

DANNY LENNON: So clearly, there's differences between people in how they may respond and how they will respond in terms of say, anxiety symptoms is just one example. And now we're in a situation where cannabis can be used medically, and there may be practitioners that can prescribe it in certain jurisdictions and so on, but it probably seems that we're still a bit away from having real good validated screening tools for saying, here's how we can screen people to know who will respond well or not. It seems to be more down to practitioner judgment and experience right now.

CARRIE CUTTLER: Absolutely. Absolutely. And I've tried to do this research to where we were assessing adverse reactions to cannabis, and just sort of self-reported side effects and adverse effects, and we were trying to map those on to all sorts of things like frequency of use, age of onset of use, personality characteristics, demographic characteristics, anything we could think of. And we really didn't find anything, we couldn't come up with anything that would predict these adverse reactions that people were reporting and experiencing. And so, it's something that we need to do more research on to try to better understand, but I think it's a very complicated issue, and I think that some of it is also just sort of set and setting, people talk about set and setting with drug use, right? That a person's mindset and their environment also have an effect on, and this is not something that we studied in that article, but people's mindset and their expectations of the effects of cannabis are also going to play a role. So if somebody is worried going in, and they're worried about doing it, and they're worried that they're going to feel anxious, well, yeah, they're probably more likely to feel anxious. Whereas another person is very relaxed or doing it and is expecting to feel relaxed and better and a little bit euphoric might be more likely to experience

it. So placebo effect is enormously powerful and plays a role in the effects of cannabis, I very much believe that.

DANNY LENNON: One of the other areas I've seen you publish on is related to Post Traumatic Stress Disorder or PTSD. Where are we with that general literature base overall?

CARRIE CUTTLER: So we found, so a lot of people obviously with PTSD use cannabis and they subjectively report and say that it helps them with things like sleep and just general wellbeing and reduces some of their symptoms, and we did another one of these Strainprint studies where we were looking at people's use of products in their own home, what products they were choosing, and we looked at ratings before and after, for various dimensions of PTSD like flashbacks and anxiety and whatnot. And we found again, very similar roughly 50% reductions in symptoms from before to after, but those reductions are not really sustained. And so, we did not see the issue with, like we saw with depression such that PTSD was not exacerbated by the repeated use of cannabis, but it also wasn't ameliorated, it was just maintained, it'd just stay. So again, this band aid idea of like they – and my studies are all inhalation, so they inhale cannabis, the symptoms are reduced temporarily, but then they come back at the same level that they were previously, and that's the problem. And then, I believe we found with PTSD that people were using higher doses over time, and in some cases, reporting less of a reduction in symptoms over time, again suggesting that there might be this tolerance that starts to develop over time, unfortunately. What I think is most exciting about the PTSD literature though, and some of the studies that are kind of happening now are they're looking at things like FAAH inhibitors basically, and so, this is a drug that basically helps to prevent the breakdown of our endogenous cannabinoids, so that we have more of those endogenous cannabinoids. It's not introducing this

exogenous cannabinoids like THC, but actually just functioning off of our own internal cannabinoid system and preventing a breakdown of these endocannabinoids. And this is showing a little bit of promise, and there's trials going on right now at other universities where they're giving these thought inhibitors, or Marinol which is a synthetic THC during treatment, and seeing what the effects of these products have on people during actual treatment exposure therapy, because it seems to help with extinction memory, so it seems to help them extinguish the memories better. And so they're doing these trials to better understand that, but I think that's a very exciting avenue.

DANNY LENNON: Yeah, and that actually kind of touches on something you've mentioned a couple of times now in relation to these various outcomes and endpoints; and that there may be potential roles here, but it's still, to some degree, a kind of band aid solution, I think was the phrase that you're using. And that's really useful to think about in terms of not only cannabis, but we're seeing this in other areas where there's a lot of hype behind something and a lot of interest, and for good reason, but maybe sometimes people can elevate that to a panacea that's going to take care of a whole range of problems without any side effects or additional work. And I think one can make the case people are doing that in relation to other drugs, for example, even with PTSD that we mentioned, there's the data around MDMA. But again, it seems that that in combination with adjunct therapies is probably the way to go as opposed to I'll take this drug, and then it's going to fix everything. And can you maybe just talk a bit more and elaborate on this idea of this band aid solution and how you see it fitting into how we should just, from a meta level, consider cannabis and its role in health going forward?

CARRIE CUTTLER: Yeah, I really do believe that it’s temporarily masking symptoms, it's giving people a

reprieve, and that's nice for people to have, and I completely support that, and I think that that's fine. I just think that people really need to understand that they're not doing anything to address the root core issues that are underlying the problem; and that's less of an issue with something like pain, which every medication is a band aid approach for basically, right? It's just sort of masking the pain and dulling the pain, it's not fixing the systemic problem causing the pain. But we do have cognitive behavioral therapy, and we do have therapies that will address the root core issue underlying the problem, and will dramatically reduce relapse rates in the future. So for a lot of these issues like anxiety and depression, cognitive behavioral therapy produces comparable outcomes to SSRIs and other medications, but the benefit of it is that even after it's stopped, people continue to reap the benefits, because cognitive behavioral therapy is about teaching people a skill, which is how to identify these sort of automatic negative thoughts that run through people's heads and challenge them, and learn to replace them, and that's a skill they take with them, and they have with them forever. And so, it really does address the root core issue, which is believing these negative thoughts to be fact and true, and having them continue to wear down the individual. And then with PTSD, there's exposure therapy, which shows good efficacy as well and again, longer term efficacy. So I don't have a major problem, I don't view cannabis as the most dangerous drug out there at all. I think that it should be descheduled entirely. I view it better than alcohol, I'll go ahead and say, which is not scheduled at all. So I have no problem with people using cannabis to get this reprieve. I just think that they need to understand that they're not working on the problem, they're getting a break from the problem, and the issue is going to come back. And if they want to stop the issues then therapy is the best approach.

DANNY LENNON: I agree with you, and I think most people would agree with that position that cannabis is certainly, from a health standpoint, not as detrimental as alcohol, and I think that's not even controversial in the least, so we're just in a strange position here of this disconnect between policy and evidence. But it's interesting around this idea of how it can be potentially used in kind of combination with something like therapy of, for some people, perhaps just getting enough alleviation of symptoms, to be able to even get into the therapy process may be really useful, and that's their kind of gateway in, so they can start doing it. I suppose at a population wide level, one of the things that maybe is more appealing about cannabis or cannabis related products now is that there's much more ease of access to them in most places, versus there's clear problems for a lot of people getting access to appropriate things like therapy and so on, which is a whole other issue we could talk about for a long time.

CARRIE CUTTLER: And stigma is a huge one – a lot of people don't want to go to therapy because of stigma. And weirdly, the stigma surrounding cannabis might actually be less than the stigma surrounding going for therapy, and that's just a really unfortunate set of circumstances.

DANNY LENNON: Where do we go from here in terms of research, in terms of over the next few years, what would you ideally like to see what big research questions we'd like to see answered either your group or others that we need to get answers for in the coming years?

CARRIE CUTTLER: Yeah, I mean, really along lines of what we've been talking about, which is like combining cannabinoids with therapy, but also just looking at whether cannabis users compared to non-users have differences in therapeutic outcomes, and that's something we've been collecting data on for some time, just in our own health psychology clinic, we're collecting data on who's a cannabis user, who's not a cannabis user, and just how many sessions it

takes them, and how much their scores drop over time and that type of thing. And I think that that will be very informative to, again, see whether using cannabis and being a chronic cannabis user is somehow facilitating the therapeutic process or hindering the therapeutic process, and then again, exploring this idea of how they're doing the psychedelic research as well. There's microdosing, and they're having people microdose, and then they're doing therapy with them while they're under the influence. And so attempting some of that, I think, would be very interesting and cutting edge and potentially enlightening. The other direction that we need research to go in is we need to look at like proper double blind placebo controlled trials of cannabis as effects on these mental health conditions. So my research does not include a placebo controlled group, which is problematic because we can't tease apart placebo effects from actual therapeutic effects of cannabis in those circumstances. So what we really need is more people doing these good double blind placebo controlled trials. The problem with that, again, is that people need to have these Schedule I licenses, which take a long time and a lot of effort to get, and I'm just about to start this process myself.

DANNY LENNON: I'm sure that will not be a fun process for a long time.

CARRIE CUTTLER: I'm not looking forward to it, but it'll be great at the end of the process.

DANNY LENNON: So before I let you go, for people listening, who maybe want to find out more about the work you're doing or get access to any of the publications you've had, where on the internet would you like to send our attention, social media, links otherwise, where's best place for them to go?

CARRIE CUTTLER: Maybe my website, which is carriecuttler.com.

DANNY LENNON: And that will be linked in the show notes to this episode for everyone listening, and we'll also link to some relevant papers related to what we've discussed tonight. So check those out. Carrie, thank you so much for taking the time to talk to me. I really, really appreciate it, and I appreciate learning from the work you've published as well, so really thank you for doing this.

CARRIE CUTTLER: Thank you. I appreciate you having me.

[01:19:09]