HEALTH LAB
by ZANA MEDICAL

Interview Transcript: Nick Jikomes, PhD

Jeremy: How does the long-term safety profile of cannabis compare to other drugs?

Nick: Cannabis does have some habit-forming potential. There's a lot of people who I think romanticize things a little bit too much and say that it's not addictive. That's not true. I don't like to think about drugs as being addictive or not addictive in a binary way like that. I think you need to think about their habit-forming potential on a spectrum that goes from really high for something like an opioid or nicotine down to relatively low or to zero. Some things are completely non-habit-forming, but those are typically less interesting substances.

Something like cannabis is low on the habit-forming potential spectrum. Much less habit-forming than certainly an opioid or something like cocaine or nicotine. Much less than alcohol even. Possibly even less than things like caffeine, but substances like this do have some habit-forming potential, things like cannabis, things like caffeine, but it's lower than some of these nastier substances, and it's just important, I think important to think about things on a spectrum like that. Whether or not we want to tolerate something with low, but non-zero abuse potential, if it does have other benefits.

Jeremy: What is it about cannabis that makes it have less addictive potential than, let's say, nicotine, or alcohol, or opioids?

Nick: There's a number of reasons. There's two things I would basically say there. One, the mechanism of action. That's the first thing to always think about. Opioid receptors ... I mean, they're named after the fact that they're bound by opioids. Both drugs like Percocet, and Fentanyl, and all of these things, but also the endogenous opioids like endorphins and those things. When you dig down into the nitty-gritty of their biology, those things are just hooked up to the reward system of the brain in a way that just makes them highly habit-forming because it feels so damn good to tickle those receptors.

© 2017 Zana Medical

Things like THC are hooked up and do affect what you would call the reward of the pleasure centers of the brain, but not in the same way as these things or not quite as much more basically, so that's part of why there is some abuse potential, but it's much lower than for something like opioids. They're tickling the pleasure centers, but just not quite as much would be the shortest, simplest way to think about it.

The other thing to think about is that when people take opioids, they're taking a pill, which is a pure form of that compound. It's a single type of molecule, and that is basically the only thing present in that pill, and you're putting that into your body. When you consume cannabis, typically, you're consuming some sort of flower product, and that's not just THC. That's basically an entire cocktail of substances that are going into your body and your nervous system.

Now, what's interesting there is something like THC, as I mentioned, does tickle some of the pleasure centers of the brain, and so it does have some abuse potential even though it's much lower than for something like opioids, but you've got other molecules there that can modulate that effect, and that's where we'd start talking about something like CBD, Cannabidiol.

CBD itself, we know from a lot of animal work and actually some human work as well. CBD specifically seems to actually have what you would just call "anti-addiction properties," and there are few different ones to think about. One, CBD is and anxiolytic. Meaning, it has anti-anxiety properties. Two, it seems to specifically help with diminishing withdrawal symptoms in opioid-addicted animals.

If you take a rat that's been experimentally induced to be addicted to opioids, and then you would take away those opioids, it will have withdrawal symptoms. It will shake, and it will act funny for a time. If you give it CBD, those withdrawal symptoms are diminished by a fair amount, and you get similar results actually in humans.

They've done experiments where they take people who are heroin addicts, and they're no long on heroin, so they're still addicted, but they've recently started to abstain from heroin, and the basic experiment they do goes like this. You show those addicts videos of cues associated with heroin, so not heroin itself, but other types of things, right, that your brain has associated with heroin.

© 2017 Zana Medical

I don't remember specifically what they were. It could be needles or instrumentation, a paraphernalia, things like that. What that does in a normal addict is it induces anxiety and cravings. It makes them anxious because they don't have this thing that they're addicted to, and because of that, they start to crave that substance.

If you pre-treat people with CBD systemically before showing them these drug-associated cues while they're addicted, but abstaining from the drug, the anxiety and the cravings are diminished, and so that's probably something to do with why cannabis also has much lower habit-forming potential than some of these other substances because you have these interactive effects between multiple molecules, some of which have habit-forming potential on their own and some of which actually have anti-habit-forming potential on their own.

Jeremy: That underscores the importance of CBD?

Nick: I think the thing that's really nailed down super tightly about CBD in both animals and humans is it does have good anti-anxiety properties. It's not going to be … It's analogous to what we were talking about before, the opioids versus cannabis in pain. Is it going to knockout your anxiety as strongly and potently as Xanax? No, but it's also not going to be addictive like Xanax is either.

In fact, as I just mentioned, it seems to have properties that make it useful for treating addiction, but because it's such a good anti-anxiety medication … One of the side effects of THC consumption, especially at high concentrations, is anxiety and paranoia, and so as you increase the amount of CBD you have relative to THC, you decrease the probability that you're going to have that type of reaction.

Jeremy: Interesting. Have they looked at CBD for … I haven't seen much, but to treat CUD?

Nick: To treat what?

Jeremy: Cannabis Use Disorder.

© 2017 Zana Medical

Nick: Oh, no. I haven't seen anything on that specifically, but it's interesting, right?

Jeremy: Yeah.

Nick: It could be ironic. There could be people who do develop Cannabis Use Disorder, and you might actually be able to help treat them by using this one compound, CBD, that actually comes from cannabis. The open question is and one thing that would be interesting to look at, but it would be really difficult to do is a lot of people are still getting their cannabis from the black market, so they don't know what's in it. It would be interesting to speculate on whether people are more likely to develop Cannabis Use Disorder with high THC, low CBD strains. That would be my prediction based on what we know about the habit-forming potential of THC and the properties of CBD.

Jeremy: Now, what about the risk of long-term administration of THC affecting down regulation?

Nick: Yeah. The general rule, and it doesn't matter if we're talking about THC, and cannabinoids, or any other type of neurotransmitter or signaling molecule. The general rule again comes back to this homeostatic regulation. This is literally the core concept of all of biology, and you can think about it at the level of behavior of the entire organism, and you can think about it at the level of individual cells and molecular mechanisms.

Basically, the cells, based on their genetics, know where they want to be. They know what they want to do. When you go too far in one direction or the other, they have adaptive responses that compensate for that, and I'm actually … I'm writing an article for Leafly right now about endocannabinoid system, and I'm using the analogy of Goldilocks and the three bears. You don't want things to be too hot or too cold. In the case of animals, right, you literally don't. Our body temperature is a great example of homeostatic regulation.

Now, if you get too hot, you're going to sweat or you're going to pant if you're a dog. You're going to seek cooler air … You're going to behave so that you get out of the heat, so that you can lower your body temperature until it gets the right level, and then those mechanisms shut off. Similarly if you're cold, right? You might seek a

© 2017 Zana Medical

warm area. You might start shivering. That's your body's way of raising temperature because you want it in that sweet spot.

Signaling molecules and the firing of neurons, you can think of by analogy. Neurons don't want to get too many inputs or too few inputs, and they don't want to have too much of any type of signaling going on, so what does that mean? If you have a molecule like THC, for example, and it finds … THC activates CB1 receptors on neurons. If you crank up the amount of THC you have or you have chronic THC use, that means you're going to have a lot of THC stick into a lot of CB1 receptors that respond to that from a lot of neurons. It's going to be to reduce the levels of that receptor on the neuron to compensate for the fact that you're getting more signaling through it, right?

That's a general phenomenon with any type of molecule. If you increase the levels of some drug or some molecule that signal through serotonin receptors, those serotonin receptors would be homeostatically down regulated to compensate for that increased in signaling and vice versa.

Jeremy: The risk of the body adapting to any sort of drug, it's not unique cannabis?

Nick: Yup.

Jeremy: Does that mean it's unsafe to be on any of these drugs long-term because your body is going to adapt and it's no longer going to be effective?

Nick: I would say that that's always something you should think about. I don't want to say that any drug is going to be unsafe or harmful with long-term use, but it's definitely something you should think seriously about. It's definitely something if you were taking a medication that was prescribed that you should talk to your doctor about, but long-term chronic use of anything is going to cause these adaptive changes in your body.

If you then stop taking whatever substance you are, there's going to be a rebound, so similar to the way that we talked about the REM rebound before, there's going to be a rebound at the molecular level in terms of receptors and things like that. That probably actually has a lot to do with why certain things come with withdrawal

© 2017 Zana Medical

symptoms when you stop using them. Your body is reacting to that, right? There are some chronic long-term response that your cells had to your chronic use of the substance that was acting through whatever receptors it was acting through, and now there's going to be a rebound afterwards, right, and it all comes back to this idea of homeostasis.

With some drugs that rebound, it probably underlies part of withdrawal symptoms, and they just happen to … We call them "withdrawal symptoms" because you feel shitty when this happens. Your receptors are basically being recalibrated or however you want to think about it, and that might come with some unpleasant symptoms. Other things? I don't know. You might not notice, but it really depends.

Jeremy: THC is an agonist and it does this, but do other cannabinoids … They don't seem to alter the ECS in the same way now …

Nick: Again, it depends. CBD is not an agonist of the CB1 receptor like THC is, but it is an agonist of other types of receptors. I actually wrote an article for Leafly in October that touches on this, and it's all about the fact that CBD … CBD has what you might call a promiscuous pharmacology or pharmacological profile. It interacts with all sorts of different receptors in all sorts of different ways, so even though it doesn't stimulate or activate the CB1 receptor like THC does, it does stimulate other receptors, including things like serotonin receptors, so perhaps, it would have that sort of effect on that type of a structure.

The short and unsatisfying answer is that it's really complicated, and it depends on the dose, and how long you're using it, and the pharmacological properties of that molecule.

Jeremy: There's a lot of folklore out there about different cannabinoids and terpenes. Maybe you can discuss the differences between, let's say, CBD, CBN, and these different terpenes.

Nick: Yeah. I think the main ingredient for sleep based on the huge number of anecdotes that come from humans and also some of what we know experimentally is higher doses of THC will eventually tend to knock you up. THC seems to have something to do with insomnia. Obviously, the dose, the concentration that you're taking in is going to matter. CBD in experimental animals.

© 2017 Zana Medical

I know that there's evidence that goes both ways. People have observed inactivating effects from CBD. People have observed a more sedative effect. I think the jury is still out there. It quite depends on …

Jeremy: I've heard this. Yeah, and there's dose dependency and also maybe done some experiments with lights on versus lights off.

Nick: Exactly.

Jeremy: Yeah.

Nick: Conditions matter, external conditions. Dose matters of that one molecule, but then obviously, when you're consuming cannabis, if you're consuming flower at least, you're really consuming a cocktail of molecules that probably have many different interactive effects with each other, so the ratio of all those things together is going to matter. THC and CBD is the shining example of that because THC, as we said, activates CB1 receptors, but CBD … It basically gets in the way of THC, so CBD doesn't activate CB1 receptors like THC does, but it does prevent THC at least partially from activating CB1 receptors, so the exact amount of CBD you have according to THC is going to really influence the effects you experience.

Then, of course, those aren't the only two things. We've got a bunch of other cannabinoids. Basically, all of them are even less studied than these two, and then you've got the terpenes, which we know give cannabis its aroma and flavors because they're volatile molecules that have those properties, but I think we know very little about the terpenes when it comes to psychoactivity and effects on behavior.

© 2017 Zana Medical