

Episode 66: CBD and Sleep - Clinical Evidence and Emerging Mechanisms

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Transcript

Hi everyone, welcome back to the Tox Lab. I'm Rebecca. I'm Rob. This week we're going to be taking a look at CBD or cannabidiol. I can't believe it's taken us this long to get to CBD to be honest.

It's certainly an area that I've been interested in for quite a few years and we'll come to that in a little bit. But what is CBD? Well CBD cannabidiol is a non-psychoactive cannabinoid found in cannabis. I use the term non-psychoactive fairly loosely actually because that definition is a little bit woolly.

It certainly doesn't make you high in the same way that THC does. And a few years ago CBD saw a real boom in its popularity. Suddenly it became a wellness trend out of nowhere and CBD products were available in all sorts of shops, in all sorts of strange forms. And I thought Rebecca we could start by having a little quiz about different CBD products.

Okay. And see whether you think they're real or whether I've made them up. Okay. Sounds good.

So to start with we'll start with an easy one. CBD oils, gummies, drinks. Yeah they're a thing. They're definitely a thing.

All right it's going to get harder. CBD beard oil. A thing? Definitely a thing.

Yeah that's a thing. CBD steering wheel cover to reduce road rage. That can't be a thing. That's not a thing.

Well done. CBD sports bra. Oh surely not a thing. Believe it or not that is actually a thing.

No. Apparently it's infused with small encapsulated beads of CBD that reduce inflammation whilst you're exercising. Interesting. No idea if it actually works but that's the claim.

No idea. We've got a few more. CBD pet treats. Surely not.

They are a thing. A very thing. To calm your dog. CBD condoms.

A thing. Bizarrely a thing. Yeah it doesn't surprise me as much as the CBD sports bra did. CBD judicial wigs.

Surely not a thing. Not a thing but a non horse hair wig made of hemp for vegans has been developed. Okay. So not specifically CBD infused but a hemp wig is a thing.

CBD gravy. Not a thing. Not a thing but recipes exist online. Excellent.

And finally CBD pillowcases. I'm gonna go out on a limb and say it's a thing. Yeah same as the CBD sports bra idea. So as you can see CBD products have entered virtually all markets and they were marketed as wellness trends marketed as something that could help reduce inflammation could help you feel better help with anxiety and help you sleep.

And so before we dive too hard into the science I'm actually going to start with a little story as to how I became interested in CBD when these products were all kicking off. We're going back a few years now actually. We're going back probably five six years. A thought crossed my mind and I had my forensic

toxicology hat on.

CBD products were occurring everywhere in the shops. Lots of people were buying CBD. Fairly quickly I had the concern well people are going to claim their cannabis test is positive because they've taken a CBD product. And so quite reasonably I thought we just need to validate our method and check that CBD doesn't cross react with the THC.

CBD is actually isobaric to THC. They've got the same molecular formula so it wouldn't be unreasonable actually that they may cross react. So I thought we just need to do a little bit of validation. And you could buy a CBD reference material so that was easy.

We were able to do that. But what you couldn't buy at the time was actually the CBD metabolite. And when you're testing for cannabis and urine you're often looking for the cannabis metabolite. And CBD breaks down in the same way and produces again this isobaric carboxy metabolite.

And I thought well we really need to validate that as well. So I approached some chemical suppliers. I sent them the structure and I said look any chance of a reference material. And they looked at it and they said oh it wouldn't be a cheap one.

You're looking at ten thousand pound for a custom synthesis. And I thought I don't have that sort of budget. So I had a brainwave. I went down the local health food shop.

I bought a bottle of CBD oil and I started putting my liver to work. I started taking the CBD oil to produce the metabolite within myself and was able to isolate it. Confirmed indeed that there was a peak that it didn't run in the same place. But there was a side effect that I didn't see coming.

And that was I slept like an absolute log. And it got to the point where I actually continued to take this stuff for quite a while. And I know that obviously this is just my experience, a single sample size. This proves nothing but it has always got me thinking: was that just placebo effect or does CBD genuinely help sleep?

And so this week we thought we would dive into that a bit more and have a look at that topic and see whether we could maybe answer that question or maybe even possibly ask another question. Before we jump into today's episode if you want to stay up to date with our content you can find us on Instagram at @the_tox_lab. We also have a page on LinkedIn and we're fairly active on there. And for those of you who don't use social media but still want to get in touch with episode suggestions or comments about episodes you can email us at thetoxlab@gmail.com.

So first a paper that looks at some surveys that were done looking at why people use CBD products and what impact it's perceived to have on their life. So the aim of the study was to understand users consumption patterns regarding dose, route of administration and reasons for using CBD. And they hypothesized that the top three reasons for using CBD would be for anxiety, sleep disturbances and stress. So the authors created an anonymous online questionnaire to collect CBD users self-reported characteristics, preferred methods of ingestion and reasons for using CBD.

And data was collected between the 10th of January 2020 and the 18th of March 2020 with 20 multiple choice questions. They used four different CBD brands and retailers based in the UK who sent the survey to 14,473 unique email addresses with 475 people clicking through to the survey with 430 people starting the survey and 387 people reporting using CBD themselves. The majority of users were female and the majority of respondents were from the UK.

When looking at other medications that people were taking 39.4% of respondents reported not to be taking any other medications, 14.7% stated they were taking painkillers and 14.7 reported other medications with 40% of these reporting anxiolytics and antidepressants. In terms of usage patterns

the majority of respondents were taking CBD sublingually for three to six months and the majority of individuals reported using less than 50 milligrams a day.

Individuals aged 35 and over were more likely to use CBD daily and those self-medicating for anxiety reported using CBD multiple times a day and the same pattern occurred in those self-medicating for stress. Individuals using CBD for sleep improvement had greater odds of using CBD in the evening whereas those who use CBD for anxiety had greater odds of using CBD in the morning. So quite a diverse range of respondents to this survey. We're capturing a few different routes of administration and things like that aren't we and quite a few different indications as well.

42.7% of respondents were using CBD for self-perceived anxiety, 37.5% were using for stress, 37% using for general health and well-being and 37% were using to improve sleep. More males were using CBD for general health and well-being than females with more females using CBD for self-perceived anxiety or self-perceived insomnia.

Those aged 35 and older had lower odds of using CBD for general health and well-being and had lower odds for using CBD for stress whereas those aged between 35 and 55 had greater odds of using CBD for chronic pain compared to those aged between 18 and 34 and those aged 55 or over had lower odds of using CBD for sleep improvement compared to 18 to 34 year olds. 43% of respondents cited sleep as a reason for use and improving sleep and self-perceived insomnia with the fourth and fifth highest ranking reasons for using CBD.

48.2% of individuals said CBD led them to fall asleep faster compared to 23.4% who said it did not make a difference and still struggled to fall asleep. 42.6% of respondents endorsed CBD for self-perceived anxiety and 87% said they felt less anxious although one person did report an increased feeling of anxiety. 59% stated that they thought about their problems less than before. 37.5% of individuals endorsed CBD for self-perceived stress and 92% reported feeling less stressed overall.

Other reported effects included feeling calm and decreased pain with 71% reporting no side effects and in those who reported side effects 11% reported dry mouth, 3% experienced headache, 3% experienced fatigue and other side effects included an increased heart rate, nausea, headache, dizziness, trouble concentrating etc but these were all reported in less than 2% of respondents. So quite a few of the people taking CBD did report some positive benefit to taking CBD.

Potentially all sorts of biases in this survey isn't there because they sent the survey out to people that were buying CBD oil and you're probably more likely to go and buy a bottle of CBD oil if you've bought one previously and so there might be a certain amount of self-perception if you think it's working and you're buying it more you're more likely to get picked up by the survey.

So there could well be some self-fulfilling prophecy in this study design but nonetheless particularly looking at the sleep quite a lot of people do claim that it helps them with their sleep and then there's the other indications as well the anxiety, feeling calmer and possibly they all do play a little role in sleep as well don't they? So the next question then is what's the mechanism? If CBD can help with sleep what's the pharmacological mechanism? And CBD has a few different proposed pharmacological actions.

The main one that we're not going to focus very much on today although could well be the subject of a future episode is how it interacts with in particular the CB1 receptor. That's the receptor that THC binds to and leads to the psychoactive effects of THC.

CBD seems to have some modulatory effect at this receptor it can actually to a degree counteract some of the effects of THC when present with THC and cannabis but on its own it doesn't really do very much at the CB1 receptor and instead a lot of the mechanisms are proposed to be through other

pathways and there's some talk of it affecting some 5-HT receptors some serotonin receptor subtypes there's some other mechanisms involving some orphan receptors that aren't really very well characterized but the one I really want to focus on and it's the subject of our next paper is actually CBD's effect on adenosine.

Adenosine is a compound that is responsible quite a bit for sleep. When you're awake adenosine builds up and sleep reduces that adenosine and it acts a bit like your clock how tired you are. Caffeine works by blocking adenosine receptors and as many of us know caffeine helps us feel more awake and it's by that adenosine blockade and so I thought we could have a look at CBD's effect on adenosine. So this next paper is actually focused on the mechanisms of cannabinoid immunosuppression and it looks at the potential for THC and CBD to decrease proliferation in immune cells.

The release of adenosine is an endogenous mechanism of immunosuppression that occurs during cellular stress and inflammation and uptake of adenosine is a primary mechanism for stopping adenosine signaling and therefore adenosine uptake inhibitors enhance endogenous activity at adenosine receptors. So they looked at radioactive adenosine incorporation in mouse microglial cells, specifically the cell line EOC20, as a marker of proliferation and showed that both THC and CBD inhibited this radioactive adenosine incorporation and this occurred at similar potencies.

They also assessed radioactive adenosine transport and THC and CBD both inhibited this transport resulting in decreased incorporation into DNA and the effective adenosine uptake was also examined in an alternative macrophage cell line raw 264.7 and CBD inhibited both adenosine and thymidine uptake and this was also seen with THC but to a lesser extent with THC compared to CBD.

Because in the study they looked at both adenosine and thymidine transport uptake and CBD inhibits both of these with similar efficacy it was thought this was due to the inhibition of a common nucleoside transporter and they looked at the transporter ENT and found the CBD competitively inhibited this transporter.

Adenosine transport inhibitors decreased TNF alpha in LPS treated mice by increasing the amount of endogenous adenosine available to bind the A2A receptor and they hypothesize that the A2A receptor mediates the decrease in TNF alpha as seen with CBD treatment and CBD was given before an LPS injection significantly decreased TNF alpha but this decrease remained unchanged after co-administration of the A1 adenosine receptor antagonist. Co-administration with an A2A receptor antagonist reversed the effects of CBD on TNF alpha. So the premise of this study was nothing to do with sleep. No.

One of the other proposed benefits of CBD is a reduction in inflammation and this study really looked to try and identify mechanisms by which CBD might improve inflammation but what it revealed was quite interesting: CBD acts to reduce adenosine reuptake into cells and therefore lead to an increase in extracellular adenosine. So these A2A receptors mediate sleep-promoting signals in the brain particularly in the basal forebrain and ventrolateral preoptic area. A2A receptor activation induces rapid eye movement sleep by activating sleep regulatory neurons and inhibiting arousal-promoting neurons in the brain.

So in other words it's possible then that CBD might actually have an impact on sleep via this mechanism. That wasn't what the study set out to show but actually could be an additional interpretation on top of what they identified in terms of the inflammation pathways. So we've got a compound that's really widely used and reported to help with sleep. We've got populations of people that claim it helps with sleep but also other people that claim it doesn't have an effect on sleep.

Why don't we look at a clinical trial to see whether this could help unravel this mystery? So this randomized controlled trial looked at the nightly supplementation of 150 milligrams of CBD and then looked at the objective and self-reported sleep effects in adults with moderate to severe primary insomnia and it also aimed to assess CBD effects on well-being and trait anxiety. So this study looked at individuals aged between 18 and 45 with an ongoing moderate to severe insomnia symptom severity score and they were invited to participate and were pre-screened.

Those who self-reported medical conditions or took medications that can affect sleep such as benzodiazepines, antidepressants and opioids and those who participated in shift work and those who consumed more than 400 milligrams of caffeine were excluded from the study. Individuals with severe depressive symptoms, severe anxiety symptoms or moderate to severe risk of obstructive sleep apnea were also excluded.

They started off with a one-week single blind placebo run-in trial where individuals were given a placebo and asked to fill in a provider's sleep diary and treatment compliance log and they also wore a gene active actigraphy watch which was used to monitor sleep and this helped to confirm participant eligibility and allowed the identification and exclusion of those who responded to placebo and those who didn't comply with treatment.

Those who made it to the next phase participated in a two-week randomized double blind placebo controlled trial and were given two weeks worth of active or placebo treatments and have scheduled in laboratory visits one week and two weeks after daily dosing. Participants were instructed to take 1.5 mL of the treatment they were given which would equate to 150 milligrams of CBD if they were given the active treatment 60 minutes before bed.

Insomnia severity symptomology data was collected which included daily self-reported sleep onset latency in minutes, wake after sleep onset and sleep efficiency which the total reported hours of sleep divided by the total time spent in bed as a percentage. Sleep diary derived daily sleep quality, total sleep time and number of nightly awakenings in addition to actigraphy derived sleep onset latency, sleep efficiency, wake after sleep onset and total sleep time were also collected and they were also given questionnaires to measure changes in well-being, sleep quality and sleep effort.

810 potential participants were identified between February 2021 and September 2022 with 88 passing the pre-screening criteria and 44 were started on the placebo run-in period. Eight were identified as placebo responsive and two with Drew so 34 were randomized to receive either CBD or the placebo. Two patients went from each group with Drew leaving 32 who attended the final visit and 15 in each group performed part of the final analysis. The study population included 15 males and 15 females with a mean age of 31.6 years and a mean weight of 72.2 kilograms and a mean height of 174.8 centimeters.

63% of individuals who completed a tertiary degree and 53.7% were in full-time employment. Looking at primary outcomes the insomnia severity index scores were comparable at the pre-screening visit and there were no differences between the two groups after the two week dosing study. Sleep diary derived sleep onset latency, sleep efficiency and wake after sleep onset did not differ between the two groups. When looking at secondary outcomes those in the CBD group reported improved sleep quality after one week of dosing which was statistically significant but this was not shown after two weeks of dosing.

Participants receiving CBD shed fewer awakenings than placebo and presented with less wake after sleep onset compared to placebo at the end of the placebo run-in period but no difference was noted at any other time point. Sleep efficiency was greater in those taking CBD after one week of dosing and at the conclusion of the study. From the questionnaires data showed that behavior following

wakefulness showed an increased total score after one week of dosing with CBD but this was not significant. There was an increase in the WHO wellbeing scores with those receiving CBD and these were consistently higher than the placebo.

So all in all actually not too much success. Some self-reported improvements in wellbeing which was statistically significant which was interesting. So it possibly is doing something and this was where I was a bit woolly about it being non-psychoactive. It's clearly doing something.

What it's doing and to what magnitude I think is a lot harder to quantify. It didn't seem to have a significant impact on sleep and there's a few points really with this study that I do want to sort of drill in a little bit. Firstly we were looking here at primary insomnia so people who have got a clinical diagnosis of insomnia and that is quite a complex disorder. I'm definitely not a sleep scientist but I suspect that has got a lot of underlying potential causes.

You've probably got quite a mixed population. Yeah for definitely because it's not one condition and there are different presentations of insomnia it might be helping some individuals but not others. It's quite hard to unpick that. And at the end there was actually only relatively small sample size wasn't there?

15 participants in both groups. The other point here was that they used a massive dose of CBD and whilst you would probably expect that to have a bigger impact. I mean how many milligrams were they dosing with? It was really high.

150. 150. So if you think a typical CBD drink might be 20 or 30 actually dosing 150 milligrams a night becomes quite an expensive habit. Oh for sure yeah.

So interestingly CBD does seem to have an inverted u-shape dose response curve so it has an effect at low doses and at high doses but there's that middle zone where it's not as effective so maybe this dose of CBD in patients with insomnia for treating their insomnia is just hitting in that middle of that u-shaped dose response curve and it isn't doing anything. It's certainly possible. I mean 150 milligrams is a lot for somebody who self doses with CBD but if you compare it to the doses that are used to treat epilepsy isn't that like 400 milligrams or something? Higher than that yeah yeah yeah yeah.

So maybe that's what we're seeing here then it's falling into that u-shaped curve. Again another area of further research needed. Yeah for sure. So let's bring this all together then so we have got CBD which is definitely a thing and it's reported to be a thing that may help sleep seems to possibly work in some people maybe we're not sure.

Clinical trial happened that didn't seem to show much of an effect. We've discussed possible reasons as to why that might be and crucially there is at the very least a pharmacologically plausible mechanism for why CBD might help sleep. So Rebecca I have a hypothesis. Okay go on.

What if we are missing some nuance in these studies? I mentioned earlier about how caffeine actually works by blocking adenosine and in chronic caffeine users of which I am 100% a chronic caffeine user. 100% you see adenosine receptor upregulation. There is an increase in expression of adenosine receptors and that's one of the reasons why when I don't have coffee I am in such a foul mood.

If CBD is increasing the amount of adenosine by reducing the clearance or reducing the re-uptake and an individual is a chronic caffeine user who expresses more adenosine receptors, is CBD going to help sleep in those people more than people who don't regularly use caffeine because their system's already primed? Is this why when I did my experiment all those years ago I slept like a log but quite a few people say CBD doesn't really affect my sleep. I mean it's a good theory.

Purely a speculative hypothesis but could it be that actually chronic caffeine consumption combined with CBD has more of an effect on sleep than in caffeine naive individuals? It'd be interesting to test that because it seems like a lot of the studies looking at CBD and sleep exclude people who frequently use caffeine because they don't want to skew their results but maybe that's exactly the population we need to be looking at. Exactly. So let's tie it all together then.

What is the dream study? What would put this all to bed? How long have you been planning that joke? I came up with it this morning.

Solid. So I think we need to take a study design where we stratify two groups of people, those who regularly use lots of coffee a day, 500 mgs plus, coffee, caffeine, any form of caffeine, 500 mgs of caffeine a day and those who don't and then within that we could have randomisation between placebo and CBD and see whether there are improvements in sleep outcomes more so in the caffeine group. That'd be good and I think based on that inverted U-shaped dose response curve it'd be really good to look at different doses of CBD and see where or if that affect lessons as you increase the dose of CBD that you give them. It's getting complicated.

I know. But you're right. That is another consideration, isn't it? Those U-shaped dose curves.

So all in all then CBD is a thing. It's much less of a thing than it was five years ago. There's still a lot of it around. You can still buy CBD drinks and CBD oils.

Certainly I think perhaps the era of the CBD sports bra might be behind us. But I think there's an awful lot still to learn about CBD. I think it's a really really fascinating compound and we've only really scratched the surface haven't we looking at the adenosine data. There is other data showing it acts at other receptors and maybe we could come back to CBD and have a look at that in a very different way.

But I do hope you've enjoyed listening to us this week. I hope it's given you something to think about. If you're a sleep scientist and you want to collaborate on this study do get in touch. That would be amazing.

Hope you have an amazing week and we'll see you next time. Bye!