Cannabis Use Disorder - Khan

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This presentation is entitled Cannabis Use Disorder: Science, Trends, and Clinical Implications. I will now turn it over to Dr. Mashal Khan to begin our presentation.

00:10

Hello, everyone. Welcome to the ASAM review course. Today's topic will- that I'll be reviewing is a cannabis use disorder. I'm Mashal Khan. I'm an attending here at Weill Cornell. I serve as the Associate Program Director for our Addiction Psychiatry Fellowship. I do not have any financial disclosures to report.

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But today's talk, by the end of today's talk, you should be very aware of the epidemiological trends in relation to cannabis use in United States and be able to name different formulations of cannabis that impact individuals today. And we'll be reviewing some of the medications that have an evidence base for treating cannabis withdrawal and cannabis use disorder.

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Our talk is going to be structured in a way that we're going to be covering initially epidemiology. getting into cannabis, its different formulations, its effect- the effects of cannabis, its impact on different special populations, then getting into the treatment available and its role as a therapeutic agent.

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Let's start with the most exciting topic- epidemiology. So cannabis has been on the rise over the past- cannabis use has been on the rise over the past few decades. And just to give you an idea of how much the use has increased- back in 2021, based on the National Survey of Drug Use and Health and Monitoring the Future, what we saw was that 27% of people over the age of 12, that took the surveys,

reported use in the past month. Data from the same surveys showed back in 2015, that the numbers were close to 8.9% people reporting past-month use, that's roughly a 38% increase in use- reported use in the past month from individuals that are 12 years and older in just a six-year span.

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The trends between different age demographics is that the cannabis use tends to peak around late teens to early 20s. And then tends to decline over the following years. What we also note is that marijuana use is also more common amongst men: roughly 24% men versus women who are only 19.7%.

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And the increase of use has been attributed to a number of factors. But the most obvious ones are legalization of marijuana in many states, growing popularity of the things like vaping, and the perception of marijuana increasingly as a safe drug. With increased use, what we all, you know, we see that, at baseline, individuals using... 9% of them will will develop some form of cannabis use disorder. And that risk tends to double when... if- if the users start early in their adolescent years. And if the use pattern is almost daily, the the the likelihood of developing a use disorder tends to compound from there. So if you're starting in adolescence, it's almost 17% versus 9% from... in comparison to the adults that start using. And then if you're using daily, it goes up to 25-50%.

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So let's start by understanding cannabis. What is it? What are- what are its components and... So cannabis plant has over 104 cannabinoids in it and for our purposes, for the purposes of your board, you only need to be familiar with two of those components: THC, tetrahydrocannabinol, and CBD, cannabidiol. THC is the- the most psychoactive component. It can be inhaled and ingested, whereas cannabidiol is- which is not psychoactive- is considered to be... its mechanism of actions are considered to be more through anti-inflammatory analgesic pathways.

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Here's a picture of the cannabis plant. It is a subspecies of the hemp plant. And often the two strains that are the most popular are sativa and indica, and at times are- these two strains are hybridized for a mix of their properties.

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So for with regards to formulations of preparations that are available. The most common ones are the marijuana bud itself, the- the flower as it's shown in the picture. And then there are... then there's hashish which is a slightly more processed version of the mari- marijuana psychoactive components and, and hash oil which is also extracted from the hashish preparation. And THC concentration over time has been on the rise mostly because of the different sort of strategies used in enhancing THC concentration within plants through different sort of botanical techniques of growing, but also by way

of different- by different techniques of extraction. And the most concentrated forms are noted to be through what we call extraction techniques using butane, also referred to as dabs. And the concentration in these dabs is close to 90%.

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And then there is synthetic cannabinoids. These are THC molecules synthetically made in a lab. These molecules are- have a very high affinity for the cannabinoid receptor. The active metabolites can have a very prolonged effect. Synthetic cannabinoids are not as popular as they were in the 20-teens. You know, that's when we all saw a spike in, you know, synthetic cannabinoid toxicity presenting to the emergency rooms with prolonged agitation and psychosis. And we'll get into the toxidrome in a second. But it's- because of its affinity for the receptor and its action on the receptor, its potent actions, it has an increased potential for toxicity.

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And it was often referred to as spice or K2. And... they didn't call it synthetic cannabinoids, but they were marketed as spice and K2. And the packaging, as you can see in the bottom picture was meant was targeting an audience, targeting a consumer base that was attracted to such graphics. So the unfortunate... and another unfortunate thing about this was that it was the synthetic cannabinoids were not detected on your typical urine drug screens. And there are a variety of reasons for that. Not only were these molecules- there was not one molecule that was being used. There... And you know, whenever we would identify a molecule and the- the government would have some kind of action against it, those molecules would be slightly tweaked and

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and re, you know, resold, it was basically a lot of vegetable matter ground up and the synthetic synthetic cannabinoids would be sprayed on top and it would look a little bit like this in the picture here. It would appear like ground-up marijuana. But it wasn't, it would smell differently as well. But it was- it was easily available and we saw a lot of toxic presentations.

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So let's look at the cannabinoid receptor neurobiology next. The cannabinoid system includes CB1 and CB2 receptors. These are- these- the CB1 receptors are very much found in the brain are mostly highly dense in the brain and are noted in areas such as the cerebellum, the basal ganglia, hippocampus, the cerebra-l cerebral cortex, and operate through G protein-mediated systems. And there's somewhat of a lower density in the brainstem, therefore, you know, there's less risk of respiratory depression upon activation.

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And CB2 receptors are mostly found in the rest of the body. It's not like that they're absent in the brain. They're very, very low density in the brain. So, but it- CB2 primarily is everywhere else in the spleen, hematopoietic cells and mast cells. And their respective functions are, with CB1 it's involved

spleen, hematopoietic cells and mast cells. And their respective functions are, with CB1 it's involved in memory, learning, problem-solving, coordination, and its endogenously, endogenous cannabinoids, such as anandamide tend to act on and influence such functions and can modulate different neurotransmitters.

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Whereas CB2 density outside of the canna- the central nervous system primarily and then is present on these immune cells and has more of an anti-inflammatory effect. With cannabinoids, there are over 400 molecules that fall under that, chemicals that fall under that umbrella term. And in general, they tend to reduce neurotransmitter release with the exception of GABA and dopamine. Natural cannabinoids, as opposed to synthetic cannabinoids, include anandamide, which we just talked about in the previous slide and also 2-arachidonoylglycerol. It's a bit of a mouthful so just call it 2-AG. The exogenous cannabinoid cannabinoids include the the THC and CBD that is that that we derive from sativa and indica plants or the marijuana plant.

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Now, when we look at the THC molecule closely its structure is very similar to anandamide, the endogenous cannabinoid, and similar to anandamide, it also dials down your neuron activity. However, it's worth mentioning here that it's a weak agonist. And it's you know, at its maximal potency, it tends to have up to 20%, around 20% activation of the CB1 receptor. In comparison, however, in comparison to the synthetic cannabinoids, which fully activate that receptor and can get up to 100% activation, that's when we start seeing the toxic effects.

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Here these two pictures and diagrams tend to show us how the CB1 receptors are spread out in the brain and their corresponding functions that they influence such as the movement, sensation, judgment, reward, memory coordination, and vision. And at a neurotransmitter not modulation level, we see that when CB1 receptors are activated, they can indirectly influence release of dopamine and which leads to euphoria reward and pleasure. They indirectly activ- enhance GABA action, which results in the muscle relaxation and sleepiness. They also cause suppression of glutamate, which in the short term results in or acutely leads to relaxation, however, with- can in long term impacts memory formation.

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And so the desired effects with cannabis intoxication for most people are the relaxation and the euphoria. The slowed time perception, the altered sensory perception and the increased appetite at times. However, the undesired effects that one does not control but can occur are the impaired concentration, the ante- anterograde amnesia, the it can cause anxiety, panic attacks, paranoia, derealization, also depersonalization and psychosis. And there's psycho, the interesting thing about the psychosis is that it's often reported as being more visual than auditory. In terms of the hallucinations.

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When it comes to synthetic cannabinoids, the undesired effects are somewhat magnified. So, and that goes back to how THC which only maximally in you know activates the receptor up to 20%. Synthetic cannabinoids can, you know, activate that same receptor up to 100% and have that enhanced toxicity profile. And, you know, there are a lot of case reports that you know, mention seizures, agitation, confusion, paranoia, and, you know, cardiovascular impacts, autonomic dysregulation, and metabolic dysregulation.

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So, when it comes to routes of administration, what we see is that the common method of use is inhaled, which can be either smoked or vaped. And when it's inhaled, the- it reaches the brain in minutes. The- it's pretty rapid in its onset, so you know, it reaches the brain in minutes, but the onset of the actual desired effects are within like five to six minutes or to 10 minutes. And then the effects last up to one to three hours.

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And in comparison to the edible form- formulations, whether it's the- whether you eat it or drink the marijuana formulation, it's a, it takes half an hour to an hour for the effect to take- to have an onset. And then, as you can imagine, if someone is a little bit impatient, a lot of people have been reported to take extra doses, and that, unfortunately, sometimes leads to the undesired effects being elicited. And the effects last up to four hours and sometimes longer.

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And it's important to point out here that THC gets metabolized as it goes to the liver to 11-hydroxy-THC, which is a far more lipophilic, potent, and longer-acting form. And why is that important to mention here, it's because when we either inhale or ingest THC, the initially you know, has peak effect in the blood, but then over time, it just, as time goes on, it sort of tapers off the- but it doesn't go... It gets redistributed in the body and you know, tends to accumulate. Because of its lipophilic nature it tends to get stored in the fat. And that point is important to bring up here. Because when it comes to testing for THC we see is that casual users can test positive for up to seven to 10 days. And with heavy users that are you know, almost like daily or every other day users can test a test positive for up to 30 days.

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It is important when you're testing not only to just use your regular urine drug screen, but also to get a quantitative so that it can allow you to see how how, how the overall THC is reducing over time in and it's also important to be mindful of the fact that as one loses weight, and there's a breakdown of fat and any adipose tissue in the fat in the body. It can result in a spike in in THC. And if anyone is using dronabinol which also known as marinol, they can also test positive.

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And then another question that often comes up on the topic of testing is, you know, someone or patients would ask you, you know, "I was in the presence of others smoking and I may have inhaled something passively. And will I test positive as a result?" The answer is most likely not.

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So cannabis withdrawal is a phenomenon that has was that most people that use frequently or I shouldn't say most people, but a third of the people that use frequently would experience. This is a phenomenon that was long debated, but finally recognized by the DSM-5 in the 20-teens. And it you know, a lot of clinical trials have been done to help with symptoms of withdrawal and what we know what is shown some evidence is that use of synthetic THC such as the dronabinol, nab- nabilone, and nabiximol show to help with the symptoms along with gabapentin.

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So, what how do we diagnose cannabis withdrawal? Well, you have one- needs to meet the criteria by having distress in the setting of abstinence or an absence of use, and any of the three of the following: irritability... which are irritability, anxiety, sleep problems, reduction in appetite and/or weight loss, depressed mood and restlessness and one of the following: which is abdominal pain, sweating, shakiness and tremors, fevers or chills, and headache.

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So THC potency has been on the rise over the past few decades, products can have most of almost on average up to 30% concentration. When it comes to products such as butane extracted hash oils or other edible forms, the concentration can be even higher and close to 90%. And this has this increase in concentration has and potency has resulted in an increase rates of ED visits. And over the past few decades, here's a graph that shows the increase in THC concentration over the past few decades. And it's quite alarming and it continues to rise due to different techniques that are being used in both in the botanical field where they try to increase the concentration of THC in plants that are grown by identifying high-THC-producing plants and mating them for you know, progeny for to create progeny that has even higher or consistently higher THC production or extraction techniques that tend to tend to consolidate higher concentrations.

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So who does all of this affect the most? Well, it's adolescents and pregnant persons. And let's address that individually. So perception of harm associated with marijuana has been has been decreasing over the past few decades. 36% of teens think cannabis is harmless. 43% favor legalization in comparison to the 80s and 90s. These numbers used to be 15 and 30%, respectively. And, and the harm perception is lowest it's been in the past 40 years. And that har- reduced harm perception often leads to a higher prevalence of use.

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When we look at different age groups, within in the teen population, we see that it's the rates of use have increased across the board and in different categories as well. So there's there's higher level of folks that have ever tried, teens that have... reporting current use has also increased and past year use as well and the use has actually surpassed rates of use of alcohol and tobacco.

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Now, why is this important to discuss? Well it's an important important for a number of reasons and mostly because they they're teens are in and their brains are very susceptible there they have developing brains, and they're especially vulnerable to the addictive nature of cannabis and the neurotoxic effects and, and... One study showed, it's a bit controversial and debated, but that, you know, individuals using cannabis before the age of 18 suffered declines in IQ and have less recovery of the deficit they incur with abstinence.

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The National Survey of Drug- of Drug Use and Health showed that there is more risk of dependence with individuals using before the age of 16. You know, in comparison to individuals using after that age. It was 9% versus using before the age of 16. It's close to 17. And, and the most areas of the brand neurocognitive function that are impacted are reward and motivation and cognition. And, you know, there there's also an one systematic, systematic review that came out in the previous year that showed that estimated a 40% increase in risk of psychosis among the youth who had ever tried marijuana and a large effect- 50 to 200% with heavy and frequent use.

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In the pregnant- in pregnant persons, the endocannabinoid system plays a significant role in the brain maturation of the fetus and particularly the emotional responses with their developing brains later on. It's important to know that because of its lipophilic characteristics, THC crosses the placenta and also introduces risk from the combustible... the effects of smoking are also added on.

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So babies who are exposed to THC can be can have neurological and developmental effects. There is- there is notable reduction in fetal growth. Also other negative effects on infants have been reported. The children exposed to THC experienced problem-solving... issues with problem-solving skills, memory and attention deficits. It's hard to specifically associate that with THC. However, because there are so many other environmental factors to be sorted out and they're this these deficits that we just talked about are have been the subject of some debate and research ongoing- ongoing research.

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Now let's focus in on the effects of use. With acute.... with the use of marijuana immediately what is noted is the adrenergic- that there is an adrenergic look-alike effect at a physiological level where

individuals experience some tachycardia, hypertension, increased rates of breathing, dryness of the mouth or also referred to colloquially as cottonmouth, conjunctival injection or referred to collloquially as bloodshot eyes, and increase in appetite, which people often call the munchies.

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Um, we see that use results in decrease in ability to learn and impacts domains of attention and concentration. And abstract reasoning and decision-making is also impacted and so is memory. And we'll get into the specifics but short-term memory is is more specifically impacted. Judgment can be impaired and our motor coordination being impacted also increases the risk of motor vehicle accidents. And this can be often this often can come up as a vignette in your, in your board exams to know the acute effects of THC and how they specifically impair motor coordination and as it relates to impaired driving. So what we see is that acute THC use impacts peripheral vision, reduces our motor coordination by increasing our reaction time, and impacting our perception of time and distance, the judgment that it takes to in perception of time and distance, the and it is the number one reported illicit drug in involved in accidents and fatalities that doubles the risk of an accident risk and triples up to seven times, seven times the risk of causing accidents as well.

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At a physical health, the physical health level, we see impacts on with respiratory, causing respiratory problems where it can reduce respiratory function increase the risk of infections. Because of its temporary blood- brain blood constriction it can also increase the risk of strokes.

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At a, from a psychiatric standpoint, it at first can help in quelling anxiety, reducing anxiety. However, over time tends to be the cau- become the cause of worsening anxiety. Same, same goes for depression, where people might be self- self medicating at first to numb their depression. However, over time, it actually worsens depression. And as we mentioned earlier, it can actually contribute to the first break psychosis in younger, younger individuals, and can be a cause of exacerbation of psychotic symptoms in those that are predisposed to having a primary psychotic illness.

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And then there is amotivational syndrome, which is often the subject of debate and, but, you know, just just so that you're aware, it is the syndrome is characterized by mental slowing, reduced ability to make a plan, impairment in domains of judgment, concentration and memory. And apathy is quite pronounced and reduce- reduced pursuit of goals.

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So in this slide, we compare the rates of psychiatric conditions in individuals that use marijuana in comparison to the general population and as noted it's... the rates are significantly higher.

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And you know, if you want to compare with just casual use and more frequent use, the rates continue to be higher in individuals that have used less than once a month, and comparison to those that have been using once a month or, or more often, which is somewhat concerning.

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Next, let's talk about diagnosis. The diagnosis of cannabis use disorder is made like any other substance use disorder. It's under 12 Point criteria, you need to meet meet two or more of these criteria to make a diagnosis of cannabis use disorder.

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Oftentimes, not to harp on this topic of cognitive effects, but oftentimes the question comes up that you know, with residual cognitive effects that are often noted shortly after even discontinuation, which include you know, issues with memory, attention and concentration and executive functioning and more specifically in when it comes to memory learning and retention. Retention of new information becomes difficult. And with regards to attention, concentration, response speed and variability. It's noted to be a bit of a deficit and then working memory and verbal fluency is also going to be impacted.

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And so, the question is, how, how long are these? Do these ever get better? How long is one expected to experience these? And what we what we see is that in in adults with abstinence for four weeks or longer, a lot of these cognitive areas tend to nor- these cognitive deficits or areas, issues and cognitive errors tend to resolve and this you know, we see, cannabinoid receptor density normalizing, cortical blood volume is also normalizing after four weeks. It the data around adolescence, the deficits they experience is not yet conclusive. It's still being researched.

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So, when it comes to treatments there are few evidence based supported approaches. There's no FDA approved medication out there that can help with cannabis use disorder. You know, oftentimes ind- individuals try to go cold turkey. 50% are able to achieve abstinence or over 70% would return to would have a relapse or return to use.

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Our psychosocial treatments are, are very valuable and in helping individuals with their recovery: motivational enhancement therapy, CBT, contingency management and family based programs have been shown to have the best effect.

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When it comes to pharmacological treatments, medication... with all the medications listed here have been trialed to see if they can be useful in helping individuals achieve abstinence or work through withdrawals. And of the listed medications gabapentin, n-acetylcystene and dronabinol seem to be the most effective in different ways.

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The others here worth mentioning are naltrexone which surprisingly, showed enhanced subjective effects of cannabis and showed no change in frequency of cannabis use. When it with regards to the medication such as atomoxetine and bupropion that are going to be working on the noradrenergic model of addiction they seem to actually enha- exacerbate withdrawal symptoms and increase agitation in users that were trying to reduce their use.

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So so let's talk about these medications individually. N-acetylcysteine which is available over the counter, does not require prescription, is an amino acid derivative and it helps with restoring normal glutamate action. It's important to note that glutamate is is involved in the regulation of the reward system. And so it helps in normalizing the glutamate activity at that level. The pros are that the research has shown us that that it's helped reduced use amongst non-treatment-seeking adolescents, but it does not seem to be as effective in in adults. So and nucleosomes in cannabis dependent adolescents led to significant decrease in cannabinoid negative urine samples in the same size, that's what it was shown. And the cons are that it does not impact with does not impact cravings at all.

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The risks associated with use are worsening of nausea, vomiting, increases in drowsiness, insomnia, vivid dreams and as a

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So gabapentin was another medication that was seemed to be very effective. And you know, its mechanism of action includes blocking alpha-2d subunit of the voltage-gated calcium channel which modulates GABA and the amygdala. And 1200 milligrams per day is the target dose. Oftentimes can start small and titrate up to 300 in the morning, 300 in the afternoon 600 at night, over the course of three to four days to achieve that effect. And the clinical benefit noted was that it increased- there was increased rate of negative urine drug screens, decreased self-reported cannabis use and reduction in withdrawal symptoms such as mood disturbance, craving and sleep disturbances.

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This slide just goes over how it's well tolerated however, it can cause headache, nausea, insomnia, some depression in individuals and it is worth mentioning here as well that it it can be abused by

some folks. So, it should be used with some monitoring.

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So, then we have our CB1 receptor agonists. This is a, these are all used and FDA-approved for different purposes. Cannabidiol in the form of Epidiolex is, you know, prescribed for Lennox-Gastaut syndrome or Dravet syndrome of patients one year, one years of age or older, and seizures associated with tuberous sclerosis in in patients one year older.

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And dronabinol is often used in anorexia associated weight loss in patients with it that have AIDS. Cesamet is used in severe nausea and vomiting caused by cancer. Stavivex is not approved yet here in the United States, but is used I believe in Canada and other European countries for treatment of spasticity due to multiple sclerosis.

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So this basically just covers what we just discussed. And here are some of the therapeutic potentials that are associated with the THC molecule, that it helps with pain, nausea, loss of appetite, wasting and wasting and HIV, increased ocular pressure that accompanies glacomas, and helps with inflammation, inflammatory conditions such as rheumatoid arthritis, Crohn's, ulcerative colitis, and specific conditions that have epilepsy such as Lennox-Gastaut.

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So in summary, cannabis includes plants and synthetic cannabinoids. Cannabis use is common. Risk of use disorder increases with earlier onset of us. Cannabis contains more THC now than it did in the past. Cannabis can affect cognition, but it is reversible in adults and impacts on adolescents are less clear. Most treatment is psychosocial, but several drug targets have been investigated, such as the gabapentin, n-acetylcysteine, and the

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other THC agonists we discussed earlier. On that note, thank you so much for your time. Have a great rest of the review course.