[Reefer Madness Trailer from 1936]

CB: And today we're discussing, you guessed it, the timely and still-controversial topic of cannabis. This is Cathy, a clinical pharmacist at the MTS Clinic,

MC: and Mike, the drug information guy from Memorial's School of Pharmacy, and welcome to episode three of *The Med Thread*, a medication information podcast from the School of Pharmacy at Memorial! Each month, we explore the history and current impacts of drugs and disease conditions that are common in society and pharmacy practice.

CB: In this episode, we'll brush over the history of cannabis and why it still fascinates and permeates our culture, what's actually in it, its use in recreation and medicine, and its benefits and risks.

And a little later we'll be joined by our colleague, Dr. John Weber, he's an expert in neuropharmacology, neurodevelopment, and neurodegenerative diseases, and he'll be chatting with us about how marijuana affects the brain, and what scientific evidence actually says about cannabis use.

MC: So let's get rolling…

CB: Ah I see what you did there!

A story of cannabis

(History from: Bloomquist, 1971, Grinspoon, 1997)

CB: We wanted to kick off our talk with a short history and geography of cannabis.

MC: Five thousand years ago, a seed is planted in Central Asia. An interesting plant grows that the farmer already knows can be used to make clothing. An herbalist in China also observes that its flower resin seems to have use in many conditions, including malaria, rheumatism, constipation, and ironically, absent-mindedness. They also know about psychoactive effects, like euphoria, stimulation and sedation; the same ones we talk about today.

In some cultures, these mind-altering effects were embraced, while in others, they were not.

CB: Fast forward to Carl Linnaeus and western nomenclature in the 1700s, the genus and species, *Cannabis sativa* was coined. In Western Europe and America, people could use it as an escape from reality, but it also had a place in medicine, with fairly regular use up until the early 1900s for conditions like neuralgia, dysmenorrhea, epilepsy, and appetite stimulation.

Time went on, people used it, doctors prescribed it and word spread westward. If you visited a pharmacy in the late 1800s in Europe or the US you'd see cannabis extract sold to treat common conditions like stomach problems and other ailments.

MC: Putting it that way, it almost seems like cannabis is a wonder drug that can treat all sorts of illnesses.

CB: Yes, the precision of medicine was unlike what we usually expect now from our developed drugs. We expect that there is one target, one drug, one desired response and the rest are side effects.

MC: Yet something changed in society in the early 1900s that we won't speculate on and we'll leave for the political scientists to debate. But, in 1923, cannabis was added to the Opium and Narcotic Drugs Act in Canada and essentially made illegal. I'll post a few references about this online for our interested listeners.
(Carstairs, 2006, Giffen, 1991, Dion, 1999)

CB: This led to the 1930s, when there was a lot of media in the USA, expressing the dangers of cannabis.

Here's a fun fact. We have a ton of slang for cannabis, and one of them used back then was 'muggles'. Now I can't shake that image anymore. Sorry for planting that in your mind, Harry Potter fans!

MC: Once it became illegal to possess and consume, it also became difficult for the scientific community to continue research on it.

CB: Goodman and Gilman's is a renowned pharmacology textbook, but in the 1950s, in one of their early editions, they describe a cannabis user as "usually twenty to thirty years of age, idle and lacking in initiative, with a history of repeated frustrations and deprivations…etc etc." Even today, cannabis is most discussed in the drug addiction and dependence section of the text.
(Goodman and Gilman's, 2nd ed., 1955, as described by Bloomquist, 1971)

MC: But cannabis was far from forgotten by scientists. In 1969, the Pierre Trudeau government established The Commission of Inquiry into the Non-Medical Use of Drugs. 3 Years later, a report was published on cannabis. In the introduction, The Commission writes,

> "Clearly we are required to focus our inquiry not on cannabis alone, but on a very broad range of psychotropic substances. This we have done, and the results of our inquiry with respect to other drugs will be published in a subsequent final report of other subject areas… We believe, however, that the issues surrounding the use of cannabis in Canada today warrant detailed examination in a separate report."
> *(Cannabis, 1972)*

CB: I think it serves as a reminder of how cannabis was and still is a social and medical issue, for essentially every generation of Canadians. I will say that over the years, we have established a more scientific approach to looking at cannabis. And that brings us to today.

Now, we've all walked passed, or visited, a cannabis dispensary, or at least heard of them. And I always wonder, how is it that this therapy is being advertised as a treatment option from everything from pain to Tourette's, anxiety to epilepsy, irritable bowel syndrome to anorexia and everything in between.

MC: Let's get into what cannabis contains and how the compounds act in the body, and of course, look at the evidence.

[Tom Petty – You Don't Know How It Feels]

What are cannabinoids?

MC: Here to join us is Dr. John Weber. He is an Associate Professor here at the School of Pharmacy and our brain and cannabis expert! Welcome John!

CB: Okay, we know there's hundreds of compounds in cannabis. What are they?

JW: There are several hundred compounds in cannabis and it's believed that greater than 100 of them are considered to be cannabinoids. And cannabinoids are found in all types of cannabis plants but the main cannabinoids that most people would be familiar with would be delta-9 tetrahydrocannabinol, so that's THC, cannabinol, cannabidiol, also known as CBD and also terpenes which are terpenoids.

So THC is the major psycho-active cannabinoid that you find in cannabis plants, and that's typically, the euphoric effects that you prescribe to the plant are primarily due to THC. But not entirely – CBD also produces those effects as well. And the terpenes are primarily, so those are non-cannabinoid compounds that are found in the plants, and they determine the sense and flavors of the variety of the cannabis plants, but there's believed to be an "entourage effect" – the belief that the combination of the cannabinoids with these terpenes can produce various effects of different magnitudes and they kind of work in concert with one another.

That being said, all the substances are known to interact, with exception of terpenes, the cannabinoids interact with the endogenous cannabinoid system in our bodies that exists and was recently discovered in the past 3-4 decades. In all our bodies, we have what's called the endocannabinoid system and that contains natural compounds. The main ones are anandamide and 2-AG, which is 2-acylglycerol and those compounds bind to cannabinoid receptors in our body. So those are cannabinoid type 1 and cannabinoid type 2 receptors. And those are the receptors that the cannabinoids themselves, from the cannabis plants are interacting with in our bodies as well.

CB: So, definitely sounds like a complex system with a whole bunch of different compounds!

We continue to hear that cannabis now is different than cannabis in the past. It reminds me of when my parents would say "I know because when I was your age…" I wonder if there's evidence of this.

JW: I think we do have much more evidence for this because there are several types of cannabis plants, which I didn't get into before. So the main species of cannabis are *Cannabis sativa*, *Cannabis indica*, and there's also *Cannabis ruderalis*. *Cannabis ruderalis* doesn't really contain very high levels of THC, so it's not one of the typical cannabis plants that is utilized.

So *Cannabis sativa* and *indica*, some of the basic differences are that *Cannabis sativa* is typically grown in areas like Colombia and Mexico and Southeast Asia. It is typically a taller plant. *Cannabis indica* is found in areas such as Pakistan and Afghanistan and India. They're typically shorter and bushier plants, so that's some of the botany behind them. In both plants though, it's the female plants that are desired. Cannabis is one of the few plants that are dioecious, that

means that they're both male and female plants and the female flowering buds are basically producing a lot of resin that contain high amounts of chemicals like THC and CBD.

Because these plants been basically genetically bred over the course of several decades, you can get the desired effects from both of these. For example, in general, *Cannabis sativa* is typically considered to be more euphoric producing as well as it energizes you, stimulates you, whereas *indica* is more sedative and relaxes you a bit more. Some of the prescribed, couchlock syndrome that you'll hear about where cannabis users can't actually get off the couch because they can't move very quickly, it's probably more related to *indica* versus *sativa*.

But over the past several decades, a lot of individuals have been breeding these together, *sativa* and *indica*, to get desired properties of both, and these are called hybrids. Typically if one of the plants is 70% or higher, for example if it's 70% *Cannabis sativa* or higher, it would be considered a *sativa* plant, but if it's somewhere in the middle there, it is considered a hybrid. And through this breeding, the levels of THC as well as cannabidiol can hopefully be optimized, but you'll see levels of THC in some of these hybrids pushing 30% whereas several decades ago, we probably didn't have any plants that were that high or at least they weren't bred to be that high. Because of, primarily the breeding, as well as the ability to learn good growing techniques etc., is probably why we have plants with higher THC levels, or a combination of *indica* versus *sativa*. So that's probably the major reason why we're seeing differences in cannabis today versus several decades ago or a generation ago for example.

CB: So I think it is important for people to realize that it's not the same substance that people did use, many years ago.

MC: And then we could really design plants that produce a consistent amount of the cannabinoids we want and limit the ones we don't.

CB: What about those synthetic cannabinoids? In Canada, we have nabilone and we used to have dronabinol but that was discontinued. How do these products compare to the phytocannabinoids?

JW: One of the drugs that you mention, dronabinol, which has been discontinued. So that is a synthetic form of delta-9 THC, the major psychoactive and euphoric producing compound in cannabis. It's basically a man-made version versus directly extracted from the plant. Nabilone is a compound that is currently available in Canada as you mentioned, and it's very similar in structure to THC but it is slightly different and because of that, it is actually a little bit more potent than naturally occurring THC at cannabinoid receptors. Also, there's a compound you didn't mention, but Sativex, is a compound that's been utilized for multiple sclerosis. This is a spray, it contains THC and cannabidiol so it's actually compounds that are directly extracted from the plant.

There are other synthetic cannabinoids that we haven't found as much in Canada, but in the United States, there've been a lot of synthetic cannabinoids that again, are alterations from the actual THC chemical but similar enough. For example, they'll be sprayed on plant material that can be smoked. They're also producing concentrated liquid forms, some of the big ones out there are known as K2 and Spice. And these are not actual naturally occurring compounds but they are synthetically produced and they are much more potent at the cannabinoid receptors

that any of the other synthetic cannabinoids that I know of, as well as the naturally occurring cannabinoids. And because of this, they're often quite dangerous. For example, some of the effects of THC and other cannabinoids are not just the effects that you get on the central nervous system but there's effects on the heart and cardiovascular tissue. So you can get heart palpitations, nausea as well and then you get an exacerbation of these types of effects with these synthetic cannabinoids. So I think these synthetic cannabinoids have to be used with caution.

CB: So there's definitely a lot of distinctions that we're going to have to be aware of as pharmacists, that will help us explain to patients, certainly the side effects you mentioned. And we know that people are going to start to talk about them more openly, perhaps after legalization, so we do want to be aware of all of the different products and I'm sure there's a lot more to come.

[Bone Thugs n Harmony – Weed Song]

Routes of administration

MC: One defining aspect of cannabis is the number of forms it can be made into and equally numerous ways to get the drug into the body.

CB: It can be burned and smoked. Dried and packed into pills. Extracted into oils and tinctures for sprays, edibles, and vaping. It can be consumed raw and even mixed into creams and lotions. While the internet will tout pros and cons of each method and provide interesting anecdotal stories, what's the difference from a scientific perspective?

Let's break it down using pharmacokinetics, the study of how drugs get in, around and out the body.

MC: First, what's the fastest?

JW: Well, the fastest way of getting cannabinoids into the body is by smoking. So obviously smoking a cannabis cigarette or in a vaporizer, for example, a lot of the [same] ways that individuals are using vaporizers in place of tobacco cigarettes. So that's the fastest way we get cannabinoids into our body. So the onset, if you were to smoke either a cigarette or with a vaporizer, you would get an onset of the effects within 5 minutes in most individuals, so those are the effects like the euphoric feelings, the pleasant body feelings, things like reduced nausea, pain relief, etc. which we'll get into more detail a bit later.

But the peak effects once you smoke should last anywhere between 10 and 30 minutes. Again, that's going to be highly individual, based on the person. The duration of effects though, when smoking, typically, in almost every individual, is going to last for about 2 hours but in most individuals will probably last even longer up to 4 hours and probably some individuals even last to about 6 hours. Even with this quick onset and a quick peak of action, you still have lingering effects for several hours.

MC: What about the sprays?

JW: So the sprayed cannabinoids, something like Sativex?

The absorption there would primarily be through the cheek or buccal route, but also sublingually as well. There, it would be a little slower, you would get effects within 15, all the way up to 60 minutes, [and] every individual should start seeing effects. Now the peak effects probably wouldn't take place to within an hour or two, but you could get effects up to between 4, 6, even up to 8 hours with that route of administration. So it's a little bit slower than the smoking route and the effects do last significantly longer in most individuals.

MC: Right, so the other form would be the edibles.

JW: Yes, so edibles, which of course aren't going to be legalized this year, but should be legalized in 2019. They're a bit slower and there are several forms of edibles. So some of them, for example, are medications such dronabinol or nabilone, as well as things like oils, so oils that are produced from extractions from the plants. And there's often, what are called soft gels, so these are going to be the edible, basically pill forms, from extractions from plants. And they're all quite similar but variable, for example depending on if someone has food in their stomach. If you have food in your stomach, it's going to slow down absorption.

But in general, something like a pill or soft gel, the first effect you start seeing is probably going to be at least 30 minutes, and you may not even see effects within the first couple of hours. And it's probably going to peak within the 2 to 4 hour range. Oils for example, you probably see effects that last up to 6 to 8 hours and some of the soft gels, which are a little bit slower release, you may see effects between 8 to 12 hours. So it's kind of hard to predict and anyone that's going to be using these products is not going to know how they affect them or the duration of action until they try it for themselves and see: How long the effects last. What effects they're getting. Are they getting adverse effects? Are they getting desired effects, etc.?

CB: Right, so that's why we would recommend not to drive for at least 6 hours after using it.

JW: Actually, I would be a little more specific that you should wait at least 6 hours after smoking cannabis products, but if you were to eat the products, I would wait even longer. And as I mentioned a bit earlier, everyone's affected by it a little bit differently and the duration of action can be different in every individual, so I would wait even longer if you were to eat the products until you knew exactly how it was affecting you.

CB: This is all very good information for us to know!

MC: But while we talk about driving, the National Cannabis Survey found that 14% of users reported driving within 2 hours of using cannabis. It will be interesting to see how this compares to alcohol-related accidents in the future.

But what about those topicals, the stuff you put on the skin?

JW: The topicals are now gaining momentum in use. So obviously these would be applied to the skin. And there is some evidence for them being efficacious and actually being useful to treat things like inflammation in the periphery because there are cannabinoid receptors found on peripheral neurons. So those are the neurons found outside the central nervous system.

They work very locally and where you would apply them to the skin, you would limit the amount that would be taken up into the blood system, into systemic circulation. Now you can't rule it out but it should work most likely at the site of action. And because one of the effects I didn't talk about yet, about cannabinoids, is that they're anti-inflammatory in general. They could be useful for treating something like arthritis, because arthritis is known or at least believed to be by most scientists and clinicians to be an inflammatory disease. So if you applied a topical cream to joints, arthritic joints, you should see a decrease in inflammation and therefore a decrease in pain. And also just some other inflammation you might get, just for example, like spraining your ankle. You could apply a topical cannabinoid product and it may be helpful. That being said, there's not a whole lot of research on it yet and we need a lot more research to verify efficacy of these products. But, the science is there to support why it could be useful in these types of conditions.

MC: Right, so as legalization happens and it becomes more accessible, I'm sure more research will come out of it.

CB: Most recently in the national survey, the top product is the dried flower or leaf with 78% of users reporting this form. Presumably, they're smoking that. It is followed by 28% using edibles and 11% using hashish, which is the flower resin only. 11% used oil cartridges or vape pens and other forms have lower uptake. If you add all that up, you'll notice that it's more than 100%, which tells us that people will often use more than one form. Thinking about pharmacokinetics, this can be complicated for doctors and pharmacists.
(The Daily, 2018)

[Brandy Clark – Get High]

The Pharmacist's Role

MC: The perspectives of professional pharmacy bodies directly impacts the public message you'll hear.

From pharmacy, the National Association of Pharmacy Regulatory Authorities issued a position statement in 2017. "Pharmacy practitioners must not be involved in the distribution of cannabis for non-medical purposes". However, they recommended a larger role for pharmacists in medical cannabis.
(NAPRA, 2017)

CB: Pharmacists certainly have a place in cannabinoid-based therapies, because as mentioned earlier, a synthetic cannabinoid, nabilone exists. Sativex, that John mentioned earlier is an oral spray used for multiple sclerosis and advanced cancer pain. At easily $500/month, it's definitely not cheap. I suspect that cannabis in the future will be significantly cheaper.

MC: As we talked about earlier, the list of conditions people have tried cannabis for is enormous. But what does the scientific evidence say about it. There is quite of bit of information out there. I think we have time to dive into 2 or 3 conditions, so here we go.

CB: First, multiple sclerosis:

JW: Okay, so as you just pointed out a minute ago, Sativex has been used to treat multiple sclerosis and that's based on some clinical studies that showed that it was efficacious in treating the spasticity and pain associated with this disease. So let's talk about what cannabinoids can do to treat spasticity. What is spasticity first? Muscle spasticity is essentially when muscles are contracted excessively and basically that's almost in a state of paralysis so this is very debilitating for patients that suffer from it but it's also quite painful.

So in general, studies that have used THC alone, so not smoked cannabis, but THC alone, have really not shown any promise in treating multiple sclerosis at least in the long-term in the few clinical studies that have been conducted. However, there's a story by Corey-Bloom and colleagues published in 2012 that showed that smoked cannabis – this was in a randomized placebo-controlled trial, showed there were decreased symptoms of spasticity and the pain versus placebo. So this suggests that smoked cannabis could be efficacious in treating patients with multiple sclerosis. This combined with the studies that showed kind of a negative effect or no effect, no positive effect, I should say, of THC alone, show that maybe you need more than just THC. Maybe you need more than one cannabinoid in a substance or in the body to get beneficial effects for treating the spasticity associated with multiple sclerosis.
(Corey-Bloom, 2012)

CB: And it's interesting, because you mention the entourage effect a little earlier, so maybe that's what's at play here.

What about pain and its relationship to opioids?

JW: There are several types of pain. Of course there's acute pain, so pain that we've all experienced at some point. Something like a headache or if you cut your skin, that's acute pain. There's chronic pain, so pain that lasts for several days, weeks, months, even years. And one of those types of pains is neuropathic pain. Neuropathic pain is when there's physical injury to the nerves and it's very difficult to treat. So multiple sclerosis is a good example because there's actual physical damage to the nerves, that's a type of neuropathic pain. Also things like, there can be peripheral nerve damage if you cut a nerve and it just doesn't heal properly. If you have a spinal cord injury and you have physical damage, this can lead to neuropathic pain.

There's also types of pain associated with HIV or with cancer. So this is probably a combination of direct nerve damage, so it's partially neuropathic but it's also more likely a neuro-inflammatory type of pain. When you get inflammatory pain with cancer, HIV, and with the possible anti-inflammatory effects of cannabinoids, they could be useful. In one study for example, Wilsey et al. in 2007, showed that smoking cannabis could produce analgesia in neuropathic pain patients. And this was in a variety of different types of neuropathic pain. So in the study, there were MS patients, there were patients that had suffered peripheral nerve damage as well as spinal cord nerve damage, so this was very positive and showed that these cannabinoids and all the cannabinoids in cannabis may be useful for treating pain.
(Wilsey, 2008)

You asked about the relationship to pain with the use of opiates. There was a really good study by Abrams and colleagues in 2011 that showed that if you vaporize cannabis, so not actually smoking it. Smoking in a vaporizer, as I mentioned earlier, like the way you would replace

tobacco; that you could increase the analgesia in patients that were already on morphine or oxycodone. So what it did, it kind of produced a synergistic effect, so not just an additive effect, but the pain killing effects of the morphine or oxycodone were accentuated or even increased by cannabis. But what they also did is that they measured the levels of these opiates in the plasma of these individuals and they didn't see any alterations in the levels of the opiates. *(Abrams, 2011)*

So what this suggests is that there was not a major interaction with the metabolism of the opiates and cannabinoids. And it does suggest that you could potentially lessen the dose of opioids if you were to supplement with a cannabis product. That being said, I thought it was a very good study but at the same time, we need a lot more studies and it does show promise that we could try to decrease opiate use by using cannabis in certain types of conditions.

CB: It's interesting and I'm sure they'll be lots of research done in the future. And I have a lot of clients in the community that have all kinds of different chronic pain syndromes that are certainly reaching out and trying medical cannabis as the next option.

I guess lastly, let's touch on epilepsy, considering that the FDA just approved a CBD product for this indication.

JW: There has been evidence growing that cannabinoids would be useful, especially CBD, for treating epilepsy. And this makes a lot of sense scientifically because basically what cannabinoids are doing in the body, just the natural cannabinoids, they're causing an inhibition of neurotransmission in the central nervous system. And in essence, epilepsy is an over-excitation of the nervous system. So what you need to do is to kind of calm it down. So it makes complete sense that if you were to supplement someone that has epilepsy with something like CBD, it would cause an inhibition and hopefully stop seizures from occurring. And of course there have been studies on this and this has now led to a new drug finally being approved to treat individuals with very difficult epileptic syndromes and I'm hoping we'll see more studies in epilepsy as well.

CB: Absolutely, and like you said, it is good that there is some evidence that shows this is effective and now there's another treatment option for people that have been suffering with the condition.

MC: We should keep in mind that, as we discussed, the plant variety, amount, and the individual person, is variable, making it even more difficult to really know what and how much works.

CB: Yes, and even thinking about getting it from one source and then changing to another may be problematic. As humans, we are akin to self-diagnosis and self-treatment for many things, so it will be important not to do so carelessly with cannabis.

MC: And, one of the big things we're concerned about as pharmacists, is drug interactions. We know a few already like with certain blood thinners, but also we know that CBD can inhibit a major drug metabolizing enzyme in our bodies. This means there's a potential for a number of significant drug interactions for combinations with cannabis that haven't been studied yet. It'll be important for health professionals to ask about cannabis use and know what, when and how much patients use.

[Cab Calloway – Reefer Man]

Risks and recreation

CB: When we talk about drugs and pharmaceuticals, we understand that there are risks and adverse events that, as pharmacists, we try to minimize, mitigate or sometimes, simply accept. For example, some antispasmodics can cause significant dry mouth or some anti-epileptics can cause significant nausea or headaches. And we are fully aware of the problems associated with opioids.

MC: Today legalization opens the door to recreational use, which is quite different than medicinal use. Often compared to alcohol and tobacco, the understanding is that recreation is for enjoyment of the psychoactive effects of cannabis. Just as we talk about responsible drinking and those anti-smoking campaigns, we need to talk about safety of cannabis.

CB: Right, when we read the news or listen to groups talk about cannabis, there is a tendency to talk about harm and very negative effects, detrimental to the individual, to family, friends and society. We've got John to help us clarify some of these issues.

MC: Here's a big question people are concerned about. Knowing that majority of users are younger, how does cannabis affect the developing brain?

JW: Well, this is an excellent question, and we now know, most neuroscientists will accept that the adolescent brain really goes up to about the age of 25. So the brain doesn't fully develop until about that age, so you wouldn't be considered an adult brain age until the age of 25. And most individuals are considering adolescence to go up to 25 for other reasons as well, like socioeconomic factors. But when it comes to the neuroscience, it is true that the brain doesn't fully develop to about the age of 25. Because of this, there has been a lot of debate around the legalization, of what should the proper age be for legalization. And there's a strong argument scientifically that it should be 25.

That being said, it's being used by a lot of young individuals already and I think we'd really have to revisit other drugs, other legal drugs for example, ethanol, or nicotine and tobacco. Because without question there's users that obviously have been using, much younger than 25 for many years. So I think we really have to revisit that. That being said, we don't really know a lot. Scientifically, there just aren't enough studies to determine what are the effects on the adolescent brain versus an adult brain, because there just hasn't been enough research funding for example, to do that.

But some studies are out there and for example, there are some acute effects of cannabis. Things like some of the impairing effects would be; slower reaction time, altered motor coordination, and inability to concentrate as well. These are a lot of the reasons why you shouldn't drive while you're under the influence. But these effects, if you stop smoking, most of those effects are going to recover. So for example, the effects on short-term memory as well, can be impaired. But if you wait 3 or 4 weeks after smoking, typically all of those effects wear off and you'll have no deficits in memory. There are some deficits, things like decision-making and planning that have been documented. That being said, I would suggest that we need more

studies to say that unequivocally.

I think one aspect of the adolescent brain or young brain in general that's been pointed out and the worry, are things like depression, anxiety and also precipitating things like psychiatric diseases. Although there's not a lot of evidence out there for precipitating psychiatric diseases, there have been some studies that suggest a strong trend. This being said, it's possible that an individual in the adolescent brain age that is using cannabis may precipitate an underlying psychiatric disorder, for example, something like schizophrenia. It is possible.

On the flip side, it's possible that individuals that may have developed psychiatric disorders eventually, they may be more drawn to drug use because of their altered brain chemistry. That being said, I think with caution, I think we should provide caution to individuals to suggest that yes, the brain doesn't fully develop to the age of 25. And then individuals will have to decide for themselves, if they want to use cannabis or not.

MC: Does this have anything to do with the controversial 'amotivation syndrome' we hear about, like how Goodman and Gilman's described the cannabis user in the past?

JW: Well, there's likely some overlap with it. But amotivation syndrome, it's still very controversial and there's no strong scientific evidence for it. But, this amotivation syndrome, it can occur not just in adolescence but also in adults. But it is more typically described in adolescence and there could be a lot of reasons for that, for example, *Cannabis sativa* versus *Cannabis indica*. It's possible, as we now have more and more hybrids that include higher levels of *Cannabis indica*, it's possible that you get a couchlock syndrome with *Cannabis indica* because as mentioned, you get more sedative effects with *Cannabis indica* than you would with *Cannabis sativa*. So that would be a botanical reason that's possible, but also we don't have enough data on it. One thing I should point out is that anytime we're using cannabinoids, we're disrupting the natural endocannabinoid system in our body, at least on a temporary basis.

Another example I'll give is, there used to be a drug, rimonabant, which was used for obesity. And this drug is an antagonist of cannabinoid receptors and as I mentioned, it was used to get individuals to decrease your appetite, so that they would lose weight. It's an antagonist of CB1 receptors but it was pulled off the market because it was producing depression and also suicidal tendencies in a lot of individuals on the drug. And a big reason for that, as I mentioned, is you're inhibiting or disrupting the natural endocannabinoid system. So on the other side of that, if you were taking cannabinoids in the adolescent brain age then you are actually, obviously, increasing the amount of cannabinoids in the brain and therefore you could get effects that are unpredictable.

CB: That's pretty interesting and I'm just thinking of clients that are trying to find a more natural approach of treating conditions. Even though it's something naturally occurring in the body, it is disrupting our natural chemistry. So it's something certainly to think about.

[Afroman – Because I Got High]

CB: What about other parts of our bodies? We know that tobacco smoke is harmful, leading to COPD, cancer and heart disease. It took us decades to draw a link between smoking and lung cancer, what can we say about cannabis and its effects on other parts of the body?

JW: Okay so for other areas outside the brain, or outside the central nervous system, first we'll talk about the lungs because it would be pretty obvious, especially if you are ingesting cannabis by the traditional route of smoking. There has been no strong link to COPD and cannabis smoking that has been shown, but that being said, it's pretty obvious that smoking cannabis could lead to similar disorders. There has been some evidence of long-term chronic bronchitis that's been produced. If you're smoking cannabis, this would potentially exacerbate asthma or asthma effects, but of course a lot of this is probably related to the amount of cigarettes that you smoke. Typically someone smoking cannabis cigarettes is not smoking as many cigarettes as they would a tobacco cigarette. Now if you were to ingest cannabis by other routes for example, THC or CBD, they could actually have a beneficial effect on asthma because those chemicals actually cause bronchodilation so they could be useful for asthma. But the smoke of course is inhibitory for asthma and wouldn't be used.

As far as cancer producing effects, not just lung cancer, but other types of effects, cannabis does have a lot of carcinogens. And a lot of them are produced actually when you combust the materials, when you're burning the plant material. But even then, there is not a strong link to cancer in cannabis users. There is some, but it's really not strong enough and it's really counterintuitive in a way because, especially if you're a smoker. That being said, again, it could just come down to the amount of cannabis cigarettes that an individual is smoking versus tobacco cigarettes. But also, the cannabinoids, THC, CBD and others, have anti-tumour effects. So if you give them in the absence of smoking, they have anti-tumour effects. So in a way, you're kind of counteracting the effects you think you might get from the carcinogens versus the natural cannabinoids that produce anti-tumour effects.

As far as another part of the body, so the cardiovascular system and the heart. Cannabis is well known to produce an increased heart rate, tachycardia, palpitations in individuals and can cause chest pain, sometimes long-term. But it's very rare because most individuals that experience these types of side effects are probably not going to continue to use cannabis in that way because they don't actually want an increased heart rate, tachycardia, etc. But in some individuals that do use long-term, you may get some chest pain related to those effects.

The last part of the body I'll mention is the liver. As you mentioned earlier, most of the cannabinoids are metabolized through the liver, through a variety of enzymes there and there's never really been a strong link with abnormalities. For example, something like ethanol, the way ethanol causes cirrhosis of the liver with chronic use, there hasn't been a strong link with cannabinoids causing any similar types of dysfunction in the liver. That being said, it may just be because we have not had any controlled studies on long-term cannabis users for one reason, is that it's been illegal for a long time and it was very difficult to get these types of studies approved as well as getting patients enrolled in them.

CB: Obviously there's certainly effects on other areas of the body and like you said, a lot of room to be done, in terms of research on what those effects are.

Another question on people's minds is the risk for addiction and dependence. There is a condition called cannabis use disorder. Can we talk about that a little?

JW: The first thing I'll talk about is just addiction in general. I think, because as cannabis becomes legalized and all the products associated with cannabis become legalized, that's going to probably increase the amount of users, at least initially. Anytime you increase the amount of users of a particular drug or substance you're likely going to increase the amount of people addicted to that.

So how addictive is cannabis? The percentage of people that are addicted to cannabis is typically estimated to be very low, probably 2% or even less of individuals that actually try cannabis. Compared to something like ethanol for example, anyone that tries drinking at any point in their life probably about a 10, 12% chance that they're going to be addicted to the substance. And anyone that uses alcohol on a somewhat regular basis, again those individuals, probably about a 10, 12% of them are addicted to the substance. And with opiates, it's a bit higher. In something like nicotine, it's even double, probably close to 25 or 30%. That being said, the cannabis and the cannabinoids are much less addictive than most other substances we call substances of abuse.

But there is, as you pointed out, a condition called cannabis use disorder. This is recognized by the DSM-V, that's the Diagnostic and Statistical Manual of Mental Disorders, as a type of addiction. So for the longest time, and I say long time, for decades, you often hear anecdotally people saying, 'oh, cannabis isn't addictive'. Well, it is and some of the criteria you need to meet to get addiction are tolerance. That means you need a greater amount of a drug to get the same effects, the same desired effects. And any drug causing addiction, you get a withdrawal syndrome. Typically it's a physical withdrawal syndrome that's more powerful than the psychoactive effects, things like, desiring the euphoric effects. And so you try to take or get more of the drug in order to fight off those physical withdrawal syndromes. And for a long time, it was suspected that cannabis didn't produce this. But cannabis use disorder has shown, or I mean, that is one of the criteria, that they actually do have this type of physical withdrawal and it's now been well-documented. The fact that it is recognized by the DSM does show that, yes, cannabis is addictive, it is potentially addictive, so everyone should be cautioned about this. But at the same time, the addictive potential is much less than, I would argue, any other, what we would call, drug of abuse that is in society today.

MC: That really clarifies things. And I think we have to make sure that we have programs in place, to capture the people that might suffer from addiction and dependence.

[Ben Harper – Burn One Down]

MC: It is difficult to do research and figure out these issues when the drug was illegal. And the experience of other nations who have legalized it years ago will likely help inform western research trends.

CB: What's a little comforting is that comparing nations, a study in 2010 found that rates of cannabis use in 10th graders were not different across The Netherlands, US or Canada and we know legalization in these countries looked quite different.
(Simons-Morton, 2010)

MC: I think there'll be more to talk about when the research catches up in the future, but that's our time today. Do we have a final message about cannabis for our listeners?

JW: Well I think every individual that plans or is currently using cannabis products, at least those that plan to use the new cannabinoid products, should make an informed decision, learn as much about cannabinoids as they can before they try various products. And again, use caution when selecting different products and become as informed as possible about those products.

[Peter Tosh – Legalize It]

CB: We think caution and staying informed is important. There's certainly a lot of monitoring to do when using cannabis, so it's a good idea to let your doctor and pharmacist know.

MC: I agree! We'd like to thank our guest again, Dr. John Weber, for his insight and helpful explanations. Check our website at mtsclinic.ca for resources and please – send us a comment on Facebook via The School of Pharmacy or email medthread@mun.ca

CB: Thank you for joining us for another episode of The Med Thread and check-in next month for a talk on biological drugs. We've got another surprise guest for you then!

I'm Cathy

MC: And I'm Mike

CB: Did you notice we didn't even say marijuana once?

FYI: Although often used interchangeably with cannabis, marijuana refers to preparations of the plant for use, such as the dried leaves, rather than the plant itself. The scientific community and research generally prefers to use the term cannabis as it can be further defined and differentiated.

Cited references

Abrams, D. I., et al. "Cannabinoid–opioid interaction in chronic pain." *Clinical Pharmacology & Therapeutics* 90.6 (2011): 844-851.

Bloomquist, Edward R. *Marijuana: The Second Trip [by] Edward R. Bloomquist. with a Foreword by William Cahn*. Beverly Hills, Calif: Glencoe Press, 1971. Print.

Cannabis: A Report of the Commission of Inquiry into the Non-Medical Use of Drugs. Ottawa: Information Canada, 1972. Print.

Carstairs, Catherine. *Jailed for Possession : Illegal Drug use, Regulation, and Power in Canada, 1920-1961*. Toronto: Toronto : University of Toronto Press, 2006. Web.

Corey-Bloom, Jody, et al. "Smoked Cannabis for Spasticity in Multiple Sclerosis: A Randomized, Placebo-Controlled Trial." *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 184.10 (2012): 1143. Web.

Dion, Guy Ati. "The Structure Of Drug Prohibition In International Law And In Canadian Law." *https://sencanada.ca/content/sen/committee/371/ille/presentation/dion-e.htm.*, 1999. Web.

Giffen, P. J. *Panic and Indifference : The Politics of Canada's Drug Laws*. Eds. Shirley Jane Endicott, Sylvia Boorman, and Canadian Centre on Substance Abuse. Ottawa: Ottawa: Canadian Centre on Substance Abuse, 1991. Web.

Grinspoon, Lester, and James B. Bakalar. *Marihuana, the Forbidden Medicine*. New Haven: Yale University Press, 1997. Print.

NAPRA. "Cannabis Position Statement | NAPRA." *http://napra.ca/policies-and-positions/cannabis-position-statement,* 2017. Web.

Sampasa-Kanyinga, Hugues, et al. "Cannabis use among Middle and High School Students in Ontario: A School-Based Cross-Sectional Study." *CMAJ open* 6.1 (2018): E50. Web.

The Daily. "National Cannabis Survey, First Quarter 2018." *https://www150.statcan.gc.ca/n1/daily-quotidien/180418/dq180418b-eng.htm*. , 2018. Web.

Wilsey, Barth, et al. "A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain." *The Journal of Pain* 9.6 (2008): 506-521.

Other interesting reads

Boehnke, Kevin F., Evangelos Litinas, and Daniel J. Clauw. "Medical Cannabis use is Associated with Decreased Opiate Medication use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain." *Journal of Pain* 17.6 (2016): 739-44. Web.

Carter, Gregory T., et al. "Cannabis in palliative medicine: improving care and reducing opioid-related morbidity." *American Journal of Hospice and Palliative Medicine®* 28.5 (2011): 297-303.

Cerdá, Magdalena, et al. "Medical Marijuana Laws in 50 States: Investigating the Relationship between State Legalization of Medical Marijuana and Marijuana use, Abuse and Dependence." *Drug and alcohol dependence* (2011) Web.

Degenhardt, Louisa, et al. "Experience of Adjunctive Cannabis use for Chronic Non- Cancer Pain: Findings from the Pain and Opioids IN Treatment (POINT) Study." *Drug and alcohol dependence* 147 (2015): 144-50. Web.

Keyes, Katherine M., et al. "How does State Marijuana Policy Affect US Youth? Medical Marijuana Laws, Marijuana use and Perceived Harmfulness: 1991–2014." *Addiction* 111.12 (2016): 2187-95. Web.

Romero, Kristoffer, et al. "Multiple Sclerosis, Cannabis, and Cognition: A Structural MRI Study." *NeuroImage: Clinical* 8 (2015): 140-7. Web.

Vaney, C., et al. "Efficacy, Safety and Tolerability of an Orally Administered Cannabis Extract in the Treatment of Spasticity in Patients with Multiple Sclerosis: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study." *Multiple Sclerosis* 10.4 (2004): 417-24. Web.

Vigil, Jacob, et al. "Associations between Medical Cannabis and Prescription Opioid use in Chronic Pain Patients: A Preliminary Cohort Study." *PLoS One* 12.11 (2017): e0187795. Web.

Ware, Mark A. et al. “Smoked Cannabis for Chronic Neuropathic Pain: A Randomized Controlled Trial.” *CMAJ : Canadian Medical Association Journal* 182.14 (2010): E694–E701. PMC. Web.

Wilsey, Barth et al. “Low Dose Vaporized Cannabis Significantly Improves Neuropathic Pain.” *The journal of pain : official journal of the American Pain Society* 14.2 (2013): 136–148. PMC. Web.

Zajicek, John Peter, et al. "Multiple Sclerosis and Extract of Cannabis: Results of the MUSEC Trial." *Journal of neurology, neurosurgery, and psychiatry* 83.11 (2012): 1125. Web.