

[MUSIC PLAYING]

KEVIN L. KRAEMER: Thank you, Dr. Rubin. Good morning. The reason I was asked to give this talk is because of it's kind of shown on this map. So Pennsylvania is about to join the number of states that will have medical marijuana available to patients.

Here you see the dark green states here are those that actually have both medical marijuana available and have legalized marijuana for recreational use. The light green states are those that have medical marijuana only. So currently, there's actually 29 states that have marijuana available plus District of Columbia.

And so I'll start off with a little mea culpa. And so even though I've trained in three of those dark green states and I spend most of my professional life in Pennsylvania, I've actually never prescribed medical marijuana. I've used some of the FDA-approved medications like Marinol, for example, for certain indications.

I imagine that some of you in the audience perhaps have lived in states where medical marijuana was available. And perhaps even some of you would have prescribed it in the past. And if we have time at the end for questions, I'd be interested to hear folks' experience.

So today I'm just going to talk a little bit about quick review, some trends in opioid prescribing and opioid harms. Then we'll move on to the evidence base for medical marijuana for pain. And then I'll talk a little bit about the Pennsylvania's medical marijuana policy and procedures, the program that's getting ramped up now.

So in the United States, 11% of US adults have some chronic pain. In the late 20th and early this century, we saw a great increase in opiate prescribing. This often started as there are a lot of advocates for using pain as the fifth vital sign.

In 2001, pain management mandate from JCAHO required that pain be recognized, assessed, documented, and treated. At the same time, the drug companies were coming out with certain opioid preparations that were sort of very easy to abuse and to use very high doses. And we saw a four-fold increase in opioid prescriptions.

In 2014, about 10 million persons reported using prescription opioids non-medically as well things that they were buying on the street. It's also important to notice that even though some of the advocates for using pain as a fifth vital sign said that the rate of opioid use disorder was as low as 1% of people. And prescription opioids are actually seeing rates as high as about a quarter of those on prescription opioids.

And so I think you've all have seen trends like this. We've seen a great increase from the early '90s to recently in terms of the number of opioid prescriptions. Things actually started to take a little downturn a few years ago, then upturn again. And so people do seem to be getting the message to dial back their use of prescription opioids.

And in fact, some unpublished data from the last year shows that the rates are down by about 11%, 12% this year. However, when CDC takes a closer look at individual counties, there are actually many counties where rates are still rising in terms of opioid prescriptions. And that's been particularly true in rural counties across the country.

Well, we've seen, though, even as opioid prescribing has gone down a bit, we're still seeing opioid overdose deaths rising. And this indicates the number of deaths from 1999 to 2016. You can see that things are skyrocketing particularly for heroin and then synthetic opioids other than methadone. And a lot of this is from fentanyl.

And so sometimes, if patients have come off our prescription opioids, they'll turn to street drugs, which are pretty cheap. And we've seen a huge rise in heroin and fentanyl deaths.

I was at a meeting in recent months at the Allegheny County Health Department. And the chief of police was there. And the chief medical examiner was there. And they actually said that they're actually seeing some bags of pure fentanyl being collected from the street.

This shows age-adjusted overdose rates in the United States in 2015. And so the green states are those that are actually statistically lower than the national rate of 16.3 deaths per 100,000. The dark blue states, which unfortunately includes Pennsylvania and a lot of Appalachia, is statistically higher than that baseline death rate.

In Pennsylvania, we have about 13 opioid overdose deaths each day. And it surpasses motor vehicle deaths. The same is true for the country. And so when I was here last year, I actually spent quite a bit of time talking about the new CDC guidelines for prescribing opioids for chronic pain.

I just have one slide on that this year. But basically, there were 12 recommendations in key areas-- determining when to initiate or continue opioids for chronic pain; recommendations regarding opioid selection, dosage, duration, follow-up, and discontinuation; and then assessing risk for addressing harms of opioid use.

And of course, there's been lots of interest. This has been disseminated widely. Some health care systems have adopted these and spread them out to all of their prescribers.

UPMC has a pain strategy, and it's got a number of important points. One is to, of course, improve opioid and nonopioid care. We had a lot of providers here complete a best practices requirement. How many, Fran? 1,500, 2,000 completed the SCOPE training?

FRAN: [INAUDIBLE] 1,500.

KEVIN L. KRAEMER: 1,500 completed the SCOPE training, which is a two-hour online Safe and Competent Opioid Prescribing Education program developed at Boston Medical Center. The system is [INAUDIBLE] 90-90 plan. It's targeted at the providers who were in the top decile of having patients on at least 90 morphine milligram equivalents for greater than 90 days and did some academic detailing and also some support for those practices.

The system is working on expanding multidisciplinary pain services for doing comprehensive pain management with physical therapy, behavioral therapy, nonopioid prescriptions, et cetera, and a few other things that are listed here. For those of you that use Epic within our system, there is a pain management synopsis, or dashboard, that you can use to track your patients with chronic pain.

So the question is where does marijuana fit into all this? And why would we consider it? And one clue actually came from a JAMA article or JAMA Internal Medicine article a couple of years ago by a Robert Wood Johnson fellow at Penn and looked at national data for opioid mortality and compared them between states with medical cannabis laws and those without medical cannabis laws.

And here, the light blue line is actually the states with a medical cannabis law. And those in the dark blues, or the dark line, is without laws. And you see that actually the states with medical cannabis laws had higher opioid mortality over the years. But then it started to kind of come down in recent years, whereas in the states with outlaws, it kind of--

When they took a closer look to see what happened in opioid mortality, after the law was instituted, this is what they saw. And the x-axis here shows the number of years after the law was started and the difference in age-adjusted opioid mortality rating. And you can see that it dropped after the medical marijuana laws were implemented.

And so the authors for this speculated-- and the author actually also wrote a New York Times editorial about this-- speculated that in those states with medical marijuana laws, people were using less opioids. And they were using marijuana as an adjunct for pain control.

It doesn't prove causality. And it's speculation. But that's what one of the ideas was. Scientific American took up that thought in an article last year. And they asked the question, could medical cannabis break the painkiller epidemic?

A body of research suggested yes. But scientists are having to fight red tape to study whether medical marijuana could substitute for opioid drugs. And that last point is that in the United States, marijuana is still a Schedule I drug.

And so it's actually extremely difficult to do research on medical marijuana either in the lab or to do clinical studies. And I'm not anticipating the law is going to change within the next few years.

So we're moving on to just what is the evidence base for medical marijuana for pain. Marijuana has been around a long time. It was first used as a medicinal agent in China as early as 2700 BC. Even Dr. Osler had this quote-- "Cannabis indica is probably the most satisfactory remedy for migraines." I'm not sure if he had migraines and took it himself. But perhaps he saw it in his patients.

In the US, marijuana is the most commonly used illicit drug. And as recently as 2015 or so, they have about a 12% prevalence abuse in the adult population-- higher in the adolescent population.

And then as, I mentioned, as of April this year, there were 29 states and the District of Columbia that now have laws legalizing the medical use of marijuana.

So cannabis is actually the plant genus, OK? Cannabinoids are the actual chemicals that cause the effect. And they bind to the CB1 and CB2 receptors in the body.

Phytocannabinoids and the ones that are found in the cannabis plants and the ones that-- the one that most people know about is the tetrahydrocannabinol, which is THC. The second most frequent one in the plant is cannabidiol.

And it's interesting that the THC is very psychoactive. As you all know, the cannabidiol, actually in some ways, counteracts some of the psychoactive effects of the THC and actually has also a anxiety-lowering effect. But when you actually look in the plants, there can be as many as 113 different kinds of cannabinoids, cannabinoids in the leaves.

Synthetic cannabinoids such as nabilone and dronabinol are also present. And these are the two that are actually FDA approved in the United States for chemotherapy-induced nausea and vomiting, wasting diseases such as from AIDS, et cetera. And then the endocannabinoids are produced naturally in the body.

And the way they work is the CB1 receptor is actually a presynaptic receptor. And so when it's activated, it actually has a depressing effect in that it actually decreases the release of certain neurotransmitters. OK, and so the CB1 receptor is found in the central nervous system and the spinal cord.

And the central nervous system mostly in the basal ganglia, hippocampus, adjacent cortical regions as well as the medullary trigeminal nucleus. And so it tends to decrease the release of acetylcholine, glutamate, dopamine, and then has indirect effects on serotonin and MDA and GABA.

And so it has a lot of effects. The CB2 receptor is actually found mostly in the periphery and in the immune cells. And actually some people think that it has an anti-inflammatory effect. But this is the one, which people think that it has an effect on the pain pathways.

I'm just going to read you a few studies. The first one is retrospective. Here, the title here was Medical Cannabis is Associated with Decreased Opioid Medication Use in a Retrospective Cross-sectional Survey. And what they did is they examined if medical marijuana for chronic pain changed patterns of opioid use.

It was a cross-sectional survey of 244 patients with chronic pain patronized a medical cannabis dispensary. And the results were that the marijuana was associated with a 64% decrease in reported any opioid use and then decreased number and side effects of medications and improved quality of life in 45%.

And so they concluded that medical marijuana may benefit some chronic pain patients. This was all retrospective. It was self-report of people already at a dispensary. This is a prospective study in which they looked at the effect of cannabis on pain and quality of life.

And their aim was to determine the long-term effect of medical cannabis on pain and quality of life in patients with intractable chronic pain. Again, about 274 patients with chronic pain-- primary outcome was the change in the pain symptom score at the six-month follow-up.

At the follow-up, the pain symptoms were decreased from a median of 83.3 down to 75. And that was statistically significant. And opioid consumption and follow-up decreased by 44%, also statistically significant. And so they concluded that it seemed to result in improved pain symptoms and reduction of opioid use.

Now there's been a few pretty high quality meta analyses done in the last couple of years that take a much more comprehensive look at the literature regarding medical cannabis. And this first one is from the UK.

And it was this-- Cannabinoids for Medicinal Use-- A Systematic Review and Meta Analysis that was reported in JAMA. They actually looked at medical cannabis for all sorts of indications, right? And they identified about 79 studies.

But of the eight trials that they found that we're focused on pain, this is what they found. You can see that only one was smoked marijuana with the main agent being THC. All the other studies that they looked at were this nabiximols. And nabiximols, it's a cannabinoid that's extracted from the cannabis plant. And then they basically spray it sublingually, OK.

And so it's not available in the United States. But it is available in Europe. And what they found overall was that there was an odds ratio of 1.41 favoring the cannabinoids. OK, so about a 41% increase in significant pain relief, OK, which they defined, I think, as a 30% decrease in pain symptom scoring.

The confidence interval barely crossed one. But they concluded that there seemed to be a signal here that it was beneficial. And a meta analysis of inhaled cannabis now focused strictly on chronic neuropathic pain. A meta analysis that was in *Journal of Pain* a couple of years ago also showed a benefit and perhaps a higher benefit.

Now, a little odd that they identified nine studies. And four of them were by Wilsey. And three of them were by Ware. So I'm not sure how much of an overlap there were in terms of patients. And you can also see just in terms of the denominators there, these are very small studies.

But they found a larger effect. And they found actually an odds ratio favoring cannabinoids of 3.22. Now probably the best meta analysis was just recently came out in *Annals of Internal Medicine* this summer, entitled *The Effects of Cannabis among Adults with Chronic Pain and An Overview of General Harms*.

And they did a very comprehensive-- they looked at results of former meta analyses as well as getting a lot of data directly from investigators. And for chronic neuropathic pain, they found 11 pretty good quality studies that found a higher proportion of intervention patients had clinically significant pain relief up to several months later.

And then they did a meta analysis of nine studies that they could actually analyze in that manner and found that patients receiving cannabis were more likely to report 30% or better reduction in neuropathic pain symptoms within risk ratio of 1.43. So basically a 43% greater chance of improvement using the cannabis compared to placebo.

When they looked at the studies for chronic pain due to other reasons such as multiple sclerosis, cancer, and other causes, most of the studies showed some benefit but often not statistically significant. And they really felt that they couldn't make any conclusions and said, there is insufficient evidence to show benefit.

Now most of these meta analyses also looked at safety issues. And cannabis was associated with a greater risk of some short-term adverse effects that are listed here, including car crashes. And so if people are intoxicated, you can expect that.

The longer term use, of course, especially with inhaled marijuana can lead to some significant pulmonary adverse effects as well. One thing that, of course, prescribers worry about is risk of illicit use and addiction. And the usual thought with frequent use of marijuana is that about 9% to 10% people will become addicted to it and then meet criteria for a cannabis use disorder.

In a national study that was just reported in *JAMA psychiatry* earlier this year, researchers from NIDA found that overall from early '90s to just a few years ago, that illicit cannabis use increased significantly more in states that had passed medical marijuana laws than those that didn't.

And cannabis use disorders also increased more in those states that passed medical marijuana laws. Now, if you look at the percentage points, you see that the increase in both illicit marijuana use and cannabis use disorders was very small, around 1% or something.

Now these studies that I just cited, there's lots of limitations. Most included few or highly selected patients, most for short duration often just on the order of weeks and several months. So not really many studies of long-term effects.

This point is very important. There's very variable cannabinoid dose and different methods of delivery, right? You can see all the way from inhaled leaf marijuana to pills to oils to ingestions and things like that. And huge ranges in dose-- the [INAUDIBLE] that I mentioned from the UK, the stuff that you spray under your tongue, I mean, that dose is around, I think, 2.5 milligrams of THC.

If you go to dispensaries and other states that have had laws for a while now, you might find doses anywhere from 10 milligrams to 100 milligrams of THC in some of the products. And certainly, there was uncertain effects of cannabinoids when used with other pain medications and treatments.

And actually, none of these studies really kind of assessed the impact when used along with opioids or when compared directly to opioids. And so we don't have much information about that, at least not in the randomized controlled trials.

So just some occlusions regarding this part of the talk-- there's limited evidence. But there are some good studies out there to suggest at least moderate effectiveness for chronic neuropathic pain. The efficacy of cannabis for other types of chronic pain is uncertain, mostly due to the lack of good, high quality controlled clinical trials with adequate number of subjects and adequate follow-up.

Now I will say that this absence of evidence does not mean there's evidence of absence of an effect. It's just that we really don't have the scientific data to support it yet. The best formulation and dose is quite uncertain. And higher quality studies are needed.

But there are a lot of federal barriers to cannabis-based based research in the US that will need to be relaxed if we actually want to make a lot of headway in this. A couple of years ago, along with one of the JAMA meta analyses, there was a Clinical Crossroads paper on medical cannabis.

And I thought they kind of had a nice approach of when to consider prescribing medical marijuana for patients. First, the patient should have a debilitating medical condition that randomized controlled trials suggest may respond to medical marijuana. And really now, I'd say the best evidence is for nausea and vomiting, spasticity in patients with multiple sclerosis, and chronic neuropathic pain.

I mean, even the commonly used one, let's say, patients with advanced HIV and AIDS, I think there's only been one good quality randomized controlled trial with marijuana in those subjects. The patient should have failed multiple trials, the first and second line therapies being above other pharmaceuticals as well as non-pharmaceutical approaches.

In pain, we're talking also about physical therapy, massage, behavioral therapy, et cetera. The author Dr. Hill suggested that they should also have failed a trial of one or two of the FDA-approved medications in the US, which are dronabinol and nabilone. You can prescribe these now without having to get any kind of special waiver to prescribe medical marijuana.

And these are based off of-- these are synthetic cannabinoids, which might have an effect. If they work, great. If they don't work and you still think that you want to prescribe this for your patient, you can then move on to one of the other products.

They should have absence of substance use disorder or an unstable active mental health disorder. These individuals are much more likely to abuse the medication and/or to develop an actual cannabis use disorder. And of course, the patient needs to reside in a state with medical marijuana laws, which brings me to what's going to happen here.

And so Pennsylvania actually has a medical marijuana program site. It's listed there. And so the governor signed the legislation into law back in April of 2016. In January, the state released applications for growers and dispensaries. Excuse me.

In June, they actually awarded permits to 12 growers and processors across the state. Later in June, they gave permits were awarded to 27 dispensaries out of a planned 52. And actually, I don't know if they've awarded additional ones.

Each dispensary has six months to become operational, OK. And each dispensary can actually operate three sites, OK. And you can go to the website and check out where the dispensaries are. There will be some in this area.

Then in July this year, the state launched a practitioner registry for medical marijuana. And the expectation is that sometime in early 2018, it will be available for eligible patients. And so these are the qualifying conditions for patients. I'm just going to go through these quickly.

You can see there's a lot of them, as I mentioned. Some of these are not based on really strong scientific evidence that they work. But the two that are relevant to chronic pain are the neuropathies, OK, and then severe, chronic, or intractable pain.

And so at least by the state criteria, the patient needs to have intractable chronic pain if it's not neuropathic. And you have to have tried multiple different modalities already before they would be eligible. The vehicle that the state is going to allow is either a pill, oil topical form such as gels, creams, or ointments, or some form of that's amenable to basically inhaling through a nebulizer or a vape device.

In this state, you will not be able to prescribe a dry leaf or plant form of marijuana. You can also use tinctures, which can be placed under the tongue and other liquids which can sometimes be mixed with vegetable oils and baked into cookies and brownies and other foods.

I really don't know at this point what's going to be available at the dispensary. Our pharmacists in our clinic actually plans to make a number of field trips when they become available just to take a look and see what they actually are providing.

The vehicle is hugely important. There was a group from Hopkins that actually went and purchased edible marijuana products from a number of dispensaries and then actually tested the amount of THC and cannabidiol in the products and were horrified by what they found in that I think over 50% had very low doses, much lower than the advertised amount. And they actually found some products that had zero THC.

And then on the other hand, they actually found some dispensaries that had more than the advertised amount. When patients get it, they'll be able to pick it up for 30 days at a time. I'm actually-- for Pennsylvania, I'm not exactly sure what the dose limit will be.

I know in one of the New England states, they allow up to something that would average to about 10 joints a day for patients that require huge amounts of relief, I guess. Patient steps-- they'll need to register with the Department of Health. They'll need to obtain a physician certification. It doesn't necessarily have to be from their primary care physician. That's an important point.

They then apply for a medical marijuana ID card and submit the application fee. I'm not sure what the fee will be. And then obtain medical marijuana from an approved dispensary. For a physician steps, of course, you'll have to decide if you wish to do this.

You have to join the physician registry at the state website and then complete a four-hour training and that's either in-person, online, or some combination of the two. And right now, if you go to the state website, there's actually four training sites that are advertised.

Some of them are private organizations. One is at Jefferson in Philadelphia. Only one actually listed their fee for the training on the website. And that was \$399. Also if you go to website, you'll see that for prescribing, they kind of focus on physicians.

But they do say that physicians, nurses, advanced practice providers that went to work at the dispensaries can also take this training. And so that also raises the question of whether if you have health care professionals at the dispensaries, whether patients will be able to go there and get the provider certification in order to do it.

I'm not sure if that's going to happen or not. But it's something the kind of watch out for. One thing that Pennsylvania's law does explicitly do is it protects prescribers from arrest, prosecution, or penalty, or denied any right or privilege including civil penalty or disciplinary action.

As you all know, the federal law is still it's illegal, whether our current attorney general will come down on some of the laws around the country is uncertain. The administration, actually, I think had a work group put together to see if they could change medical marijuana laws around the country. And I think their conclusion was that they really couldn't or that wasn't an easy way to do it. But we'll see what happens.

But in all the states that have had laws up to this point, there actually have not been any prosecutions of prescribers-- probably not unless they were prescribing to themselves. This is a screenshot of the web page for the physician registry.

And just in terms of summary-- and it looks like we'll have some time for questions-- observational data suggests medical marijuana use may decrease opioid use for chronic pain. But the meta analyses suggest that marijuana may be effective for chronic neuropathic pain but its efficacies for other kinds of pain is uncertain.

It'll be available here soon in this state. And you'll need to decide what to do. And I'm happy to take any questions.