Article:
Amol Deshpande and Angela Mailis.
Medical Cannabis and Pain Management: How Might the Role of Cannabis Be Defined in Pain Medicine?
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Guest: Dr. Amol Deshpande is a clinical associate at the University of Toronto-affiliated Toronto Rehabilitation Institute.

Randye Kaye: Hello, and welcome to this edition of "JALM Talk" from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

Marijuana, or cannabis, is a charged topic, and its use as a therapeutic agent for pain management evokes strong arguments both for and against. For clinical laboratorians, THC and cannabidiol are established markers in drugs of abused screening panels. Recently, other metabolites of cannabis have been added to therapeutic drug monitoring panels for pain management.

Cannabis plants express hundreds of different phytocannabinoids, terpenes, and flavonoids. The biological activity of these compounds is largely unstudied. Only a few clinical trials had been reported using cannabis or compounds derived from it in a context of pain management. This is particularly remarkable considering the complexity of pain management and the recent rise in medicinal cannabis. An Editorial titled "Medical Marijuana and Pain Management" in the January 2018 issue of JALM points out that the rise of medicinal cannabis is not a result of new or compelling data. The first author of this article is Dr. Amol Deshpande, a clinical associate at the University of Toronto-affiliated Toronto Rehabilitation Institute, and he is our guest for today's podcast.

Welcome Dr. Deshpande. In your article, you mentioned the lack of clinical trial data on cannabis in pain management. Could you elaborate on why so few trials have been reported?

Amol Deshpande: Yeah, I think probably the first and foremost issue is the regulation around cannabis. So I think as most of your listeners may know, cannabis' offside is a Schedule I drug and that really means that, it's implied that there is really no medicinal use for cannabis, and it's quite highly addictive.

So, when you are looking at research it means you actually have to get a number of agencies to sign off on that, and that includes an approval from the FDA, an approval from the DEA, and an approval from National Institute on Drug Abuse. So, obviously with that many hurdles, there's a lot of time involved in that, there's a lot of effort. So I think a lot of researchers just prefer to avoid that because that's even before you get your research started.

I think the other issue is that, there has been a number of dollars, and I don't have the exact number, but it's around from $1.1 to 1.4 billion over the last, let's just say five to seven years, directed towards cannabis. But most of that, and the numbers I've heard are around 80% of that funding, has really been directed towards cannabis addiction and abuse rather than actually directed towards trying to further understand the medicinal uses of cannabis. So I think that's the challenge. So where the funding goes, obviously that's where the researchers go, And finally I'd probably say, and this less of an issue, but I think part of this is around the narrative of cannabis itself.

So I mean, even now I still find a number of clinicians both in the academic and non-academic world who are still quite skeptical of the benefits of cannabis, even as an analgesic in chronic pain, and are still focused around sort of why people are using it, i.e for the euphoric effect, the potential for addiction, rather than looking at what it might be able to do, they're looking at really the narrative of what cannabis use is in society. So I think that's rapidly changing but I think when you are a researcher, when you've got to put a grant in, and you've got a number of your peers who are reviewing it, I think that narrative really has a role to play in terms of whether that research is going to get funded or not.

So, a number of issues, I think, have resulted in a lot of researchers potentially staying away from this area, and a number of--very few--small sized clinical trials.

Randye Kaye: I say, yeah it's kind of hard to shake loose some of those old paradigms of thinking for sure. So what do we know so far from the clinical trials in pain management about the effect of cannabis?

Amol Deshpande: Yeah, so I mean -- I think that's where I think it gets interesting. So, let's talk about cannabis as opposed to cannabinoid-based medicines. So, if we just talk about cannabis, there have been eight randomized control trials involving just over about 280 patients. And all those trials, all eight trials, have really been on neuropathic pain, and we define that clinically as pain caused by any lesion or dysfunction of the somatosensory system.

So, what do I mean by that? We mean things like diabetic neuropathy, that's painful. We talk about peripheral nerve injuries that might be painful. We are talking about spinal cord injuries that might be painful. We are not talking about ankle sprains. We are not talking about chronic low back pain, so very specific areas. But having said that, even though there is very sort of specific diagnosis for which it's been assessed in, a few trials, so eight as I have said, and a few number of patients, trials have been short durations. I think there is some real important key takeaways that clinicians sort needed to walk away with, and what are those?

Well first, all eight trials have shown that there's statistical benefit to alleviating pain with use of cannabis. But it goes for the one further. In pain medicine, as clinicians, it's nice to be statistically positive but we use an outcome that's called clinically meaningful pain relief and we define that as any pain reduction of 30% or more. So, if we look at those eight trials, out of the five that actually measured that outcome, four were found to be positive for clinically meaningful reduction of pain. So, it's not just a statistical anomaly but patients actually reported a significantly less pain in a meaningful way. So, that's one.

Two, the doses I think they're important. When you look at these trials, even though they were short duration, all trials used between 2 to 34 milligrams per day of THC which is a really low dose. So, if we look at the stand back, it means that we can actually get analgesic effect without cranking up the dose of THC and causing necessarily all these euphoric effects. So, low dose is important.

And finally, all these trials looked at side effects, and there were no serious adverse effects across any of these trials, though all trials did report through some mild short-lived well-tolerated side effects. We're talking about things like headaches, dizziness, sedation. Yes, some people had euphoric mood, but all of these stopped after the cannabis wore off, but nothing more serious or long lasting relative to those issues.

So, you know, there are some important points I think to take away even though the number of trials is relatively small.

Randye Kaye: So, why has cannabis been treated differently than opioids in pain management and therapeutic drug monitoring?

Amol Deshpande: So, I think that is a really interesting and great question. I'm going to go back on something we opened with, which is a lot of these in terms of the differentiation between

cannabis and opioids, I really think hinges on the narrative around cannabis and its association with addiction and abuse. And I think there is the sense that cannabis addiction, both in terms of its instance rate is much higher and some people, I still think, believe it's much worse than other substances including opioids out there.

But a lot of that I think is perception rather than evidence. So, if we kind of back up a little bit and we look at what evidence is out there, I mean, the rate of addiction for use of cannabis is not zero, it's really around 9% for long-term users. So, it's an important thing to keep in mind. But let's compare to other substances. When we look at nicotine, that's 32%, heroin 23%, cocaine 19%, alcohol 15%, so those numbers are significantly higher than the 9% rate of cannabis.

So, it's not zero but at the same time I think we have to put it in perspective. If we look at opioids themselves, opioids are also in the high single digit. So again, in terms of instance rates, we're really comparing apples with apples. So I think that's got to be put in perspective.

I think the other interesting thing which I think people may forget or may not be aware of, is really sort of the safety margin. So, we know particularly, you know, I mean Canada, in U.S., both countries are having an opioid crisis. A lot of that is related to the low margin of safety of opioids. So we know when you crank the dose up, we start to get into the issues of respiratory depression, fatality, and that's a big issue with opioids.

With cannabis, the levels of consumption are, extrapolating from animal models, are really 15 to 17 grams of THC, not just smoking a plant but 15 to 17 grams of THC to achieve a fatal dose. So, the safety margin of cannabis is really much higher.

So, again, I think ,why the difference? I think it's the narrative that really sort of influences clinicians' views of how to treat this substance relative to other stuff that we are using.

Randye Kaye: Okay, thank you. So the traditional sources of clinical evidence might not be as useful to understanding the role of cannabis before we can get widespread support of its use. So, why might that be true?

Amol Deshpande: I mean I would probably maybe rephrase that a little bit. It's not so much that traditional clinical evidence is not useful. I think the more important question asked is, when might it be more helpful to us? when looking at cannabis. You know, when people talk about cannabis, most people

are using it as a synonym for THC and probably a little bit more recently, maybe CBD.

But what we know about cannabis is there are a number of cannabinoids and terpenes in that plant, depending on who you read, it may be up to 500. And a lot of those molecules, if you again go through the literature, are actually biologically active when we take them in so they're not inert.

So, we shouldn't be just looking at THC and CBD but, you know, we could bring off a whole alphabet of CBC, CBG, ThCB, I mean, it goes on, that potentially are effective. So that's one aspect.

And then the other interesting aspect is we look at these molecules individually but a lot of these molecules have synergistic action, what we call sort of an entourage effect, that's kind of a nomenclature that's used when two of these cannabinoids or cannabinoids and terpenes get together and potentiate their effect.

So, when we look at a traditional randomized control trial, arguably sort of the gold standard, one of the presumptions is that we should know what that intervention is. But arguably when you give cannabis, you're not giving one molecule but you're giving multiple molecules that each individually have their own effect and in combination, may have a different effect. So I think when you look at doing an RCT, it complicates things, what am I actually measuring.

So, one of the things I propose in the article is let's maybe take a step back and actually understand which chronic pain patients are really using cannabis, what kind of cannabis or chemo type are they using? So, what are the actual chemicals in that particular plant that that particular individual is using, and what's getting better. So patients will report in the pain rule if their anxiety gets better, their depression gets better. Maybe some report it's an analgesic effect towards sleep. So, it's not sort of one size fits all but I think what looking at that large data set then allows us to do is say, "Hey, this particular plant with these particular chemicals results in this particular effect. I think that's when you need to go back to the RCT when you compose sort of more relevant questions to ask, then the RCT in my mind becomes much more relevant in terms of looking at a cause-and-effect relationship.

So it's probably more of the timing rather than saying that traditional evidence is not useful but I think up front, I think that will be a very long hard slow slog that might not actually be all that worthwhile.

Randye Kaye: So, the last thing I'm going to ask you about, is we've all heard the arguments about exposing patients to the harmful effects of cannabis including the risk of addiction, which you've already addressed a little bit, and impaired driving, so how do you respond to those arguments?

Amol Deshpande: So, again it's a good question, I think both of those issues of addiction and impaired driving are very important, so I don't want to minimize them, particularly in my field of chronic pain management. But the first thing I think it's important to do is, let's talk about them in the right context, so when we talk about cannabis, there is sort of recreational user or as the vernacular is changing to "adult use" now, versus "medical use." And I think those two different uses are very important when we talk about addiction and impaired driving.

So, let's just talk about medical use because that's really what I'm talking about and what the article is really focused on. But in the context of medical use of cannabis, I don't think we should treat this any differently than opioids or benzodiazepines or number of other medications that could alter the cognitive status of patients. So, whether it be cannabis or opioids or anything else, as a clinician, my job should be really to weigh the risks and benefits of any pharmaco-therapy, properly inform that patient of the potential risks and benefits, and then determine appropriately with the patient whether this is an appropriate medication to use going forward. And then as part of that discussion, I think we need to inform patients properly, again, as clinicians should do with benzodiazepines, as they do with opioids, about what the risks are of driving, what the risks are of potential addiction.

So at the end of the day I really don't see cannabis as any different than any of the other pharmacological interventions we use, and I think that's really the light in which we should look at this.

Randye Kaye: All right, thank you. Any last words before we say farewell?

Amol Deshpande: No, but I want to thank you for inviting me on the show. The purpose of the article is really to take a more objective view and I think that's what we need to do with cannabis. There is a lot of stuff that we still don't know and I think the narrative so far, while it's changing, is really trumping the research, and as clinicians, as scientists, I think we really need to dig deeper into that. And the basic scientists I must say, have really taken off with this and I would sort of encourage all the clinicians that are interested in researching, to sort of take up that baton, and now actually see whether that basic science proves to be valid, or

whether these are just a bunch of interesting anecdotes. And I think that's where the chasm lies and I think that's our challenge going forth.

Randye Kaye: That was Dr. Amol Deshpande from the University of Toronto Rehabilitation Institute, talking about the JALM Editorial, "Medical Marijuana and Pain Management" for this podcast. Thanks for tuning in for JALM Talk. See you next time and don't forget to submit something for us to talk about.