Harvard Medical Labcast

October 2016

Blunt Scrutiny
Tackling research gaps in medical and recreational marijuana use

Guest: Staci Gruber
Hosts: Stephanie Dutchen, Rick Groleau

STEPHANIE DUTCHEN: Hello.

RICK GROLEAU: Hello.

[laughter]

GROLEAU: Hello, and welcome to the October 2016 Harvard Medical Labcast. This podcast is brought to you by Harvard Medical School's Office of Communications in Boston. I'm Rick Groleau.

DUTCHEN: And I'm Stephanie Dutchen.

GROLEAU: So in this episode, we speak with HMS professor Staci Gruber about marijuana research. Stephanie, does this make this a 'pot-cast'?

DUTCHEN: Ha, ha. Actually, Staci shared a whole bunch of terrible puns she's used in her paper titles, so stay tuned to hear some of those.

GROLEAU: Oh yeah, I'm looking forward to it. So tell us what else we'll hear about.

DUTCHEN: Staci is an associate professor of psychiatry at McLean Hospital, and she studies both recreational and medical marijuana use. She describes some of what we're learning about the effects of marijuana on brain structure, brain function and quality of life in teens and adults. She says we know 'frighteningly little' about the good or bad side effects of medical marijuana beyond symptom relief. And she's trying to fill that knowledge gap.

GROLEAU: That seems especially critical at a time when more and more states are voting to approve marijuana for certain uses.

DUTCHEN: Exactly.

GROLEAU: I'm intrigued. Let's go to the interview.

[MUSIC PLAYING]

DUTCHEN: So Dr. Gruber, thank you so much for joining us today.

STACI GRUBER: Thanks for having me.

DUTCHEN: I have to start with the big question: Why study marijuana?

GRUBER: Why study marijuana? Why not study marijuana? It's certainly a topic on everybody's mind right now. It's been around for thousands of years, and currently we have five states that have pending ballot initiatives to legalize recreational marijuana.

DUTCHEN: Including Massachusetts.

GRUBER: Including Massachusetts, that's right. We're being bombarded already with advertisements, I don't know if you've caught them.

Twenty-five states plus DC have fully recognized medical marijuana. Another 18 have partial medical marijuana laws, so it's something that's very common at this point. And I think it's on everybody's mind, with regard to whether or not there are really negative effects from using marijuana.

What we know about marijuana predominantly comes from studies of recreational users. We have very little with regard to the effect of medical marijuana use. So people do want to know, 'Is this really something that's bad for me?'

DUTCHEN: So what are some of the things that you have been learning in the years that you've been studying, now, medical marijuana use?

GRUBER: So we started a medical marijuana program a little under two years ago called MIND.

DUTCHEN: MIND—

GRUBER: Yeah, Marijuana Investigations for Neuroscientific Discovery, the MIND program. And it was really launched to be able to begin to understand some of the effects of medical marijuana treatment on cognitive performance. How well can people pay attention? How well can they inhibit inappropriate actions, which is another really big area of interest for us? How well do they perform tasks that require memory, serial list learning versus prose or semantic-related information? How well can they do that? What about measures of brain structure, brain function, brain integrity? How do they look over time?

What we're seeing—and again, it's early on—we've just published this first paper, and it's a very small number of subjects who have come back for their first check-in visit. What we see so far is no decrement in performance of what we call frontal

executive tasks: tasks mediated by the final part of your brain. The frontal part of your brain is the last to come online during development, and the first to go from regular aging. It's also incredibly sensitive to things like drugs and alcohol, especially when you're young.

In our recreational studies, we see lots of differences in the ability to perform tasks mediated by that part of the brain. So the big question is, do we see the same thing in the medical marijuana patients?

DUTCHEN: Sure.

GRUBER: So far, we're not seeing a decrement. And again, this is just after three months, so baseline versus three months. Not only do patients not look worse, they actually look slightly improved.

DUTCHEN: Well, that's promising.

GRUBER: It's very promising, very interesting. So they're performing these tasks a little faster, without an accuracy trade off, which is interesting, and definitely something that's intriguing, and we want to look at this over time. Does that mean that that will hold true when we look at other cognitive domains, like memory? I don't know.

We also see changes in things like quality of sleep, some measures of quality of life and very interestingly, change in their regular or sort of standard medication treatments. Their pharmacologic regimen has changed a lot in three months.

DUTCHEN: How so?

GRUBER: So for example, we saw a 42 percent reduction in opiate use in the medical marijuana patients. That's a big change.

DUTCHEN: That's a big deal in an era of opioid crisis.

GRUBER: That's a very big deal. And people are basically saying, 'I don't need 18 or 20 Oxy[contin] a week anymore. I don't think I took one last week.' That's a tremendous statement. We see changes in antidepressant use, benzodiazepine use, anxiolytics. Pretty much every category we looked at—we can't really do statistics; this is a very small sample size, and I'd be reticent to sort of run and say absolutely positively this is going to hold, but it's certainly something that's interesting that we need to follow up. And that's why this study continues for two years.

In terms of brain imaging, we haven't published this yet, but it looks very promising. Again, what we're seeing is what I would call a quote "normalization" of brain activation patterns, which is pretty interesting.

We didn't restrict the study to people with a single clinical indication. For example, there are patients whose primary indication is pain, PTSD, or anxiety, or sleep disorders—all different indications, and most of them have more than one, which I think is also interesting. So we're sort of taking all comers at first. That's the first phase of this particular study.

We have some others. We're about to launch a study of veterans, actually. It's very exciting. And we have we've been approved for a clinical trial. So it's—

DUTCHEN: Congratulations.

GRUBER: Thank you. It's an exciting time. There's a lot of ground to cover. Policy has outpaced science, and now we have to catch up.

DUTCHEN: Speaking of policy… In a few weeks, Massachusetts residents are going to be voting on a ballot question about whether to legalize recreational marijuana for people over 21.

GRUBER: Right.

DUTCHEN: Does your research have any relation to that?

GRUBER: So our research really in the recreational domain suggests that regular, consistent marijuana use prior to the age of 16 results in a different pattern of performance on lots of different tasks, and measures of brain structure and measures of brain function, relative to those who start later.

So I've had some people say well, that's 16. This is—the law allows only 21-year-olds and over to have access. And that's true. Would it perhaps be slightly better to have a slightly older age limit? Sure; most neuroscientists will tell you, 'Oh, if we could only push that number out a little bit.' But I certainly think it's better than 16 or 18, which I think a lot of people were pushing for.

I think it'll be an interesting time to see what happens with the election. I've heard very, very mixed things from lots of different people.

DUTCHEN: Is it hard to keep politics separate from the research that you're trying to do?

GRUBER: For me as a scientist, I'm really interested in the truth, not necessarily whether it's good for you, bad for you, but it does have policy implications, right?

And so the one thing I would say is what we've seen over the last several decades is an exponential increase in potency. Potency is measured by the amount of THC, tetrahydrocannabinol, in the products. That's what's going to get you high. Higher

numbers, greater potency. That number's gone up almost 200 percent since '95. Between '95 and 2004, average potency has increased.

We don't have data from human subjects on the effects of increased potency products. I wish we did.

We also don't have data yet on what we call concentrates. Concentrates are products that are specifically designed to have super-high levels of THC, in some cases 50, 60, 80 and higher, in terms of the percentage of THC. Shatter, wax, butter, dabs, these things are all very high in THC. And I think it would be great to know what the impact of those things might be, or at least give people some guidance and say if you're between the ages of this and this, you can only have access to products that go up to this point in THC. I think there are some states that are considering that type of legislation.

DUTCHEN: Do you ever have trouble being taken seriously because of the area of your research?

GRUBER: What I get a lot is, 'Well, I mean, how—you know how it is. I mean—clearly, you must use a lot of this to study this,' which I think is pretty interesting.

And I think, I wonder if everybody in some area of research gets hit with that a lot. I think a lot of people assume that this is something that isn't necessarily the most hard-science topic one could choose. And I really fell into this. It wasn't as if I started off and this was my calling. But once you're in it, you really can't walk away, because it's one of the most amazingly complicated and fascinating areas I know I've ever been involved with. And the medical marijuana aspects of all of this research is probably some of the most compelling and exciting I have ever done.

And so for that reason alone, I wouldn't be able to walk away. But, you know, I get a lot of that. 'But do you really study it, or is it just a bunch of people sitting around smoking?' I think a lot of people think we just give people marijuana. We sit around, we chat, that's the end of the study. They eat Cheetos. They have a Coke.

DUTCHEN: That's not how it is?

GRUBER: That's not how it is. They do get snacks. Our subjects, our recreational subjects and our medical patients, everybody gets snacks. In fact, I don't feel happy unless they've had several snacks during their visit. Makes me feel good if they're eating. I feel like that's a good thing.

So they get paid, they get snacks, and they get someone to listen to them for as long as they want to talk about what they're doing, how they're doing it, et cetera. I've never seen a more invested group of individuals, either. The recreational users are desperate to get people to understand why they're smoking, or vaping, or however they're using it. And they take this very seriously, and we should too.

It's like rock and roll. It's here to stay. We need to figure out the very best and safest ways that people can be using it recreationally. And from a medical perspective, we need to figure out how to exploit every possible benefit. And for some people, how to ensure that that doesn't come with unnecessary and unwanted side effects, like lots of psychoactivity or an altered state of being. And I think that's possible, given what we know about this miraculously complex plant.

DUTCHEN: You said this is one of the most exciting things you could think of to work on. So what's exciting about it for you?

GRUBER: Well, I see tremendous clinical promise. I mean, when you look at stories or you listen to—I listen to patients who come back in three months, six months, and they say, 'This changed my life. This changed my life. I can leave my house. I can go shopping. I don't worry anymore, and I'm not walking around stone. This is like a new existence.'

When you hear stories like this, it's really one of the things that got me interested in doing marijuana research. I was doing a lot of work on bipolar disorder. And patients with bipolar disorder use marijuana—it's the second most commonly used substance, if you have bipolar disorder. Alcohol is the first. And—

DUTCHEN: Great.

GRUBER: Yeah, good to know. And it's legal. I always say if alcohol were discovered tomorrow, it would probably be in Schedule I, just like marijuana.

And there were lots of different stories that I heard from patients. And many times, their psychiatrist didn't know they were using marijuana at all. And they would say, 'You know what, I feel really down or I feel like I'm spiraling, I take a hit or two and I feel better.' And on the other side, you have people who say, 'When I feel like I'm getting manic, I can't settle myself, I take a hit and everything is OK.' And I thought, wow, that's amazing.

And as it turns out for at least a subset of patients, there appear to be some mood-stabilizing effects from cannabis. I'm not saying for everybody, I'm not saying all products. But that deserves far greater exploration, because there's a reason that people do what they do, and we should understand it.

DUTCHEN: You had a study come out this spring or this summer about marijuana and bipolar disorder.

GRUBER: That was our second study of that group of patients with bipolar disorder who used marijuana and those who didn't, pure marijuana smokers and healthy controls. We gave people handheld devices. I took a lot of heat for that. People said, 'Oh, the marijuana-using people will never bring them back. They're going to sell

them, that's it.' We didn't lose any devices. These people were, again, as invested as anyone could be, and they kept track of their mood during the day for four weeks.

And we looked at changes in mood before using versus after using marijuana. And we saw some really striking differences in the marijuana using patients with bipolar disorder versus the non-marijuana-using bipolar patients. And it's pretty interesting.

Again, I think there are ways to exploit and explore cannabinoid-based therapies without having people smoke a ton of cannabis-based products that are going to cause lots of psychoactivity and potentially negative effects.

We hear just as many stories of people who smoke or try cannabis and they say, 'Oh my god, I got so paranoid, I couldn't do this, I couldn't do that,' and certainly that happens. That's why it's important to know what you're using and how you're using it.

Marijuana is as complex as anything could be. We use that term to describe anything that comes from the plant *Cannabis sativa L*. But there are hundreds of constituents. And the ratio and the amount of the individual constituents make a whole lot of difference in the effect and the mode that you use to use the product, whether you're smoking it or vaping, or using it edible or topical, the sublingual tincture, all these things make a difference. How much and how frequently do you use? So you have to keep it all in mind.

DUTCHEN: Is that true of medical marijuana, as well as recreational?

GRUBER: I was speaking specifically, actually, about medical marijuana, because those folks are really interested in sticking to some kind of regimen. And so they'll often say, 'I figured I'd use it three or four times a day,' and they realized very quickly, maybe not. That might be too much, especially if they've chosen something that's high in THC. Again, that's the psychoactive constituent.

DUTCHEN: What's the most interesting thing to you that you have learned in your 27-ish years now of doing this research?

GRUBER: Yikes, that's a long time. I think the most interesting things have come really more recently from the medical marijuana exploration. I think that there really is tremendous potential. I think that there's way more that we don't know. There are way more questions that we have to answer, and some of them are hard. How do you standardize a plant? How do you know that Purple Kush is the same if I get it here versus getting it in California? Soil is different. All sorts of things are different.

DUTCHEN: Right.

GRUBER: And the answer is, you can't really. So you have to rely on other methods to do that.

How do you ensure that people who are, quote, "smoking" are getting the same amount if they're inhaling versus, you know—there's lots of things to address. But I have never seen anything that has been quite as compelling or life-changing as this particular cohort and what they report. And this really keeps it going for me.

I mean, it's extraordinary. And when you think of the potential and all of these cannabinoids and what they perhaps could do, I think the future is quite bright.

The recreational folks, I think one of the best things that we've been able to determine is that when you separate people into those with early versus later onset, you really do begin to see differences that make sense. We never say to people when we give these lectures, when we talk to teachers or policymakers, we never say, 'Just say no,' because those messages did not work. We say, 'Just not yet.' Give your brain a chance. You have plenty of time. Nobody likes to hear somebody say to them, 'You can never do X.' What do you think they're going to do the minute they have the opportunity? If you just give people the information, usually they can make a better decision than if you don't.

DUTCHEN: Do you have a main goal or a couple of goals that you want to achieve as you continue to do this work?

GRUBER: I think one major goal would be to determine how best we might be able to help people with what I would call pretty chronic conditions that don't always get a ton of attention because they're walking and they're talking. We're not talking to people who are hospitalized because they have a psychotic disorder. People who walk around with a fair amount of something like, anxiety, who say, boy, on any given day I'm about a 7 of 10, but I just keep it sort of to myself, I don't talk about it.

I think that there's tremendous potential to harness some of these constituents and really see them at work. I think that, again, for as many indications as we have, there are possible solutions and treatments. I think that's a huge goal, to see how some of this product and drug development may very well change the lives and the courses of people's lives over time.

I also think that for individuals who have this idea of what it means to use marijuana, it would be really great to be able to explain to people that there are different reasons that people use these products and it isn't always just to get high. In fact, for most of our medical marijuana patients, they don't want to get high at all. They just want to feel better. That's their goal. So, you know, I think another major goal would really be to help educate the public. I was surprised at what people didn't know.

DUTCHEN: So as you work with patients and as you go out and give talks across the city, and across the country, do you get frequent questions from people that it might be useful to share the answers for our listeners?

GRUBER: I would say yes. There's lots of things that I think people ask in some of these venues that I wish more people understood better. I did have somebody say, 'If I were going to start making this on my own…' and I thought, OK, I'm not sure I can walk you through the steps of how to do it, or even if I could, I'm not sure I'd want to do that.

I do get questions about how long things linger in the system, typically from the recreational cohort. 'How can I get this out quickly? How can I make sure I'm going to be negative?' There's no single tea that I know of that really pulls it straight out of your system. I think whoever discovers and creates a product like that is going to be a very, very wealthy person. That's a really big one.

Because despite the fact that we have the majority of states who have legalized some form of medical marijuana and a growing number legalizing recreational use, there is still the fact that it's a Schedule I substance. So at the federal level, this is illegal. And so people who work for companies across the country, if they find out you're using it, you can be fired.

I've had a few people in our study—our medical marijuana study—say, 'Will anybody find out about this? Because I don't want to run the risk of being fired.' And that's a really important thing, and it's something to keep in mind as we move forward.

You know, the nation has warmed toward the idea of marijuana. Right? As medicine and perhaps recreationally. It's really important to make sure that we also are doing things to make sure that people are protected. So state and federal regulations are at odds with each other currently. I'm hoping that that changes.

DUTCHEN: You said 'a growing number of states' and that made me think about the number of possible marijuana puns that must be in your work all the time.

GRUBER: Absolutely. Especially, you know, again, we did—we do a lot of work in recreational marijuana users, specifically those who are young, 'half-baked,' 'up in smoke.' We have lots of things like that that people sort of hit us with.

I always like to say, it's 'high times' in marijuana research. I never even think of it that way. I always say, 'it is high times in marijuana research.' People start laughing, you know. There's a 'growing' number of strains. Yeah, it's true. 'Budding efforts,' I mean, you know, we take them anywhere we can get them. 'The grass is always greener.' I think this last paper is called 'Splendor in the Grass.'

So you know, any place I can get these things. 'Going green.' We try very hard. Going green doesn't just mean making sure that you're recycling.

DUTCHEN: It must be a requirement to have a good sense of humor.

GRUBER: I wish that everybody had a good sense of humor about this. There are some people who are very clearly on one side of this issue. And that's fine. But they have no sense of humor about it and to them it's absolutely not funny. And I've had just a couple of people say, 'How can you make your life's work out of the devil's weed?' And I always say, 'Don't say it.' I can't say anything really in response to that. You know, I'm not sure I'd label it the devil's weed. Do we know the devil had something to do with it? Is there evidence?

You know, I show a slide that actually shows Adam and Eve in the Garden of Eden and instead of a fig leaf, it's a cannabis leaf, to make the point that this is not new. It's been around for thousands of years. For reasons that we are still trying to understand. It was part of our U.S. pharmacopoeia until 1942, which meant people prescribed it for lots of different things. So it's important to keep those things in mind. And when people get too serious about it I always remind them of that.

DUTCHEN: I feel like we should close on a "high" note.

Yeah, OK. Go ahead.

DUTCHEN: What is the most fun part of being a marijuana researcher?

GRUBER: Well, first of all really, truly, the people that I get—I feel like I have the best job on the planet. I do. I get to see really some of the happiest people on the planet, that's for sure. The recreational people are pretty happy, by and large. And the medical people are pretty invested and pretty devoted to doing these studies.

The most fun thing is probably charting their use. I know that sounds like it's really boring. You have no idea how varied and how interesting some of these strain names are.

DUTCHEN: Like what?

GRUBER: Well, I mean, you know, like Super Cheese. Or, I mean, they sort of range from the sublime to the ridiculous. And people are not put off by this. We've had very, very conservative-looking people who come in and they pull out a binder and they've kept very, very good records of what they've purchased and how much they use. They say, you know, 'When I used Strawberry Cough, what I noticed…' You know, its hard to take someone seriously when they're talking about that. But it's serious.

You know, I think all of that is a lot of fun. And it's great to see people's lives change in such a positive way.

For the recreational people, it's great to be able to have the ability to talk to people about their use and not have them feel judged and not have them feel stigmatized and not have them feel like they have to somehow tell you something that is not really the truth. I think they know that that's what we're after. And as a result, again, the recreational people are like, 'I'll bring you this—' and we tell them 'No, no, don't—please don't. Please don't, please leave that there.'

But they're desperate to share this because it's important. It's a part of their life. And it's on us to understand it. It's on us to try to figure out the ways in which they can use it the most beneficial and safest way possible.

DUTCHEN: That's great.

GRUBER: Is that helpful?

DUTCHEN: Well, thank you very much for coming here to talk with us today.

GRUBER: Thanks for having me. It's been great.

[MUSIC PLAYING]

GROLEAU: This podcast is a production of the Harvard Medical School's Office of Communications. Thanks for listening.

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