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Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about medical marijuana for pediatric patients with Dr. Prasanna Ananth. Dr. Ananth is an Assistant Professor of Pediatric Hematology and Oncology at Yale School of Medicine and Dr. Gore is a Professor of Internal Medicine and Hematology at Yale and Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore I thought the goal was to not have kids using marijuana, what is up with this?

Ananth Well, over the last 5-6 years, we have seen this huge surge in legalization of both medical marijuana and now recreational marijuana, and many states that have legalized medical marijuana, meaning marijuana used for treatment of symptoms or illness, have also increased access to children with serious or life-threatening illness. I am a pediatrician who takes care of children with serious life-threatening illness, and so I personally in my clinical practice and through my research have encountered a great deal of interest among children with cancer and their families in using medical marijuana both to treat some of the symptoms of cancer and its therapy and potentially also to treat cancer. There is a lot of theorization around what it could potentially do for cancer treatment.

Gore I see. But it is my understanding, and of course I am not totally up-to-date, but it is my understanding that there is not really any compelling evidence that marijuana per se is an effective cancer therapy, am I wrong there?

Ananth There is really not a lot of evidence and definitely not within pediatrics that medical marijuana can help with any of the symptoms that patients are asking for it for or for cancer treatment. I think we are struggling because the laws are far outpacing the science and there is really no evidence for any of this. There is a little bit of evidence in the adult literature for basically purified THC, a component of marijuana, to assist with nausea, vomiting and poor appetite. But few of those studies really included pediatric age patients and patients are also asking for marijuana for anxiety, for pain and there is really not a lot of evidence for its use under any of those circumstances, at least within the pediatric age group.

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Gore That is really interesting, I had not really thought about that that for any sort of mainstream cancer drugs or mainstream drugs to combat the side effects of cancer, be it nausea or kind of some of the things we think about pain, the FDA has such a rigorous approval process to get drugs certified as effective and reasonably safe and yet this medical marijuana movement, if you will, was just basically really in response I think to kind of population pressure to lobbying from a group that really believed in it despite absence of any data, is that right?

Ananth That is absolutely right. And I think as providers, what we are saddled with is the fact that there are not a lot of data, that this is not an FDA approved medication,

so we do not have any guidance around formulation, around dosages, around different strains, I mean there are hundreds of strains of marijuana, there are different forms you can take it in, either oil or other plant or edibles now, vaporized smoke, I mean I could go on and on. Gore You seem to know a lot about this Prasanna!Ananth And I think as providers and potential legal recommenders depending on your state, we are struggling with what to say to families and patients who are asking for it, what may be perceived to be legitimate reasons. In 2012, the State of Massachusetts where I used to practice, legalized medical marijuana, and right around that time, we started to see a huge spike in patients and families asking about medical marijuana. Patients, at least in my experience, were just asking to see what my opinion was, but many times, patients who had unrelieved symptoms were asking because the therapies we were offering them were not helping. Some of my adolescent young adult patients were asking because they had experienced with recreational marijuana and were wondering whether marijuana in the medical setting might have some utility, and I have to say from my personal experience, it was hard for me to say that it could not help, I obviously worried a little bit about patients smoking or vaporizing, especially patients with suppressed immune systems, I did not necessarily want them to be exposed to infections or to be exposed to the potential of lung cancer from smoking marijuana recreationally or medically, but could I say that in edible form or an oil of marijuana taken in small doses might not help with symptoms, I could not say that definitively. So, around that time, I was discussing this issue with my mentor, Dr. Joanne Wolfe, who is the Director of Palliative Care at Boston Children's Hospital as well as a pediatric oncologist, and she is also my research mentor, and we have been very interested in exploring the potential of medical marijuana as a supportive care agent. And so, what we embarked on was a national study at 3 major pediatric oncology centers to explore what providers' perceptions were of medical marijuana, specifically what were their attitudes about it, how often were they being asked about it, were they recommending medical marijuana and then what did they know about their state regulations?6:36 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3Gore And this is pediatric oncology?Ananth This study included pediatric oncology physicians, nurses, nurse practitioners and psychosocial clinicians, oncologists, social workers, etc. So, a whole range of disciplines. We surveyed over 300 providers; in the study itself, we had 288 professionals that we surveyed, and basically what we found was that, generally speaking, providers were very welcoming or open to recommending medical marijuana for children with cancer for supportive care purposes, so to relieve symptoms. And there was actually a significant proportion of providers who were also open to using it as a cancer-directed therapy. We broke down our data or analyses by whether providers are legally eligible to recommend versus not. And we conducted the study in 3 states – at Seattle Children's Hospital, Lurie Children's Hospital, and then Boston Children's and Dana-Farber Cancer Institute in Boston. All of these states have legalized medical marijuana and then Washington State of course has legalized

recreational marijuana. In all states, physicians are theoretically eligible to recommend. Washington State additionally allows nurse practitioners and physician assistants to recommend also. So, we theorized as we were going into the study that your attitudes might differ depending on whether you would be able to recommend medical marijuana versus not. What we found was, those providers who were legally eligible to recommend medical marijuana were a little more circumspect about recommending it or a little more cautious about recommending it as a cancer-directed therapy, recommending it in smoked formulations, but in general, providers were actually largely welcoming of recommending it for therapeutic purposes, and I think that was really surprising, particularly given decades of data largely coming out of the National Institute of Drug Abuse looking at recreational marijuana use in youth and demonstrating a lot of potential harm. Gore That is why I started off the interview that way. I was thinking that this is not just what we were taught that kids should be doing optimally. Ananth Right. And as a pediatrician I am attendant to all of those concerns, for habitual use, the potential for habit formation for mental health effects or effects on a developing brain, I am fully aware of all those concerns. The challenge is that when we are taking care of children with serious illness that is potentially life threatening, the calculus shifts or decision making changes and these are families who are already using habit-forming medications, things like opioids, pain medications, benzodiazepines, things like Ativan, which is also potentially habit forming, and so families will sometimes say, how much worse could medical marijuana be compared to the chemo which can be toxic or some of these other supportive care medications that we are taking. And I have to say, I cannot argue with that decision making, especially if family is facing a child's illness that might be life limiting.9:52 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3Gore Except that you do not have the data for surviving patients, for example, what the long-term impact may be, right?Ananth Right. In our study, we asked whether providers would be in favor of clinical trials because one of the concerns that providers cited not surprisingly was the lack of data, and by and large, providers were very much in favor of rigorous clinical trials to help demonstrate the efficacy of medical marijuana. What we have been struggling with nationally is that marijuana is classified as a schedule 1 controlled substance by the Drug Enforcement Agency, and so what that means is it is classified right alongside LSD, heroin, drugs that are not thought to have any medical benefit, and that goes back several decades, and unfortunately, the DEA has declined reclassifying marijuana even though there is some emerging medical evidence in the adult population that maybe it has some medical benefit. They declined reclassifying it, and as a result, it becomes really difficult to do any sort of research studies on it. Historically, there was only a handful of institutions that could even access marijuana for research purposes. Supposedly, the DEA was as of last year trying to make marijuana more accessible to be able to conduct clinical research, but I am not sure how that has borne out because I have not done the research myself. You know, federally, marijuana is illegal. So, that is

also kind of conundrum. Gore Right, we are crazy. Ananth Yeah. And then this new administration, we are also hearing some rumblings about potential prosecution of states of businesses that provide marijuana even if it is for medical purposes of providers that recommend marijuana, and so I think we are in this legal turmoil that makes it really hard to obtain that rigorous clinical evidence that patients and families are desiring, and providers are desiring to be able to recommend this legitimately. Gore So, in states in which medical marijuana is legal, unless it is Connecticut as our local example, where medical marijuana is legal, do the laws regulate the prescription of such products based on age, is there any lower limit beyond which they are not allowed to dispense? Ananth Every state is different, and in general no. So, there is no lower age limit generally speaking. It is interesting because if you actually go and dig into the legislation, it is often quite vague and it is left up to state departments of public health to delineate who they would allow access to, and in Connecticut, I am relatively new to Connecticut, just in the last less than 6 months, and so I am not 100% familiar with the laws here, but I do know that we sometimes recommend it for children who have intractable symptoms, so symptoms that have not been relieved by standard medications, 13:17 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3 symptoms such as nausea, vomiting, pain, and the providers that I know that are recommending it, generally have set their own thresholds but are generally recommending it to the patients who have severe terminal illness. So, not necessarily to the patient with a cancer that is anticipated to be curable, whose symptoms could be relieved by our standard medications. Gore Got it. Ananth But every provider kind of comes up with their own thresholds, and so age is not necessarily, if a child has a serious debilitating illness, age is not necessarily a limiting factor. Gore I see. It is a fascinating topic and we have got a lot to talk about in the second half, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about medical marijuana for pediatric patients with cancer with Dr. Prasanna Ananth. Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-us.com. This is a medical minute about smoking cessation. There are many obstacles to face when quitting smoking as smoking involves the potent drug nicotine, but it is a very important lifestyle change, especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments, decrease the likelihood that patients will develop second malignancies and increase rates of survival. Tobacco treatment programs are currently being offered at federally designated comprehensive cancer centers and operate on the principles of the US Public Health Service Clinical Practice guidelines. All treatment components are evidence based, and therefore, all patients are treated with FDA-approved first-line medications for smoking cessation as well as smoking cessation counseling that stresses appropriate coping skills. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio. Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore,

and I have been joined tonight by my guest, Dr. Prasanna Ananth and we have been discussing the use of medical marijuana for children with cancer. So, Prasanna, it is so interesting to me this whole thing of medical marijuana and I can tell you within the last couple of years I remember when I started prescribing, I had a number of my adult patients requesting it and I did not see a downside as long as they were not smoking. So, I figured I would get myself credentials to do so because I was providing an adjunctive thing that to me15:50 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3 seemed of little harm to an informed adult patient, and I found out that all I had to do to credential myself was to sign up on the website, there is no training module, there is nothing. I cannot do anything in licensure in medicine without taking board exams and recertification and continuing medical education, and this was just really filling your DEA number and your medical license and your prescriber and the other peculiar thing to me about it is that I can say the maximum amount per month that they should get, which I do not really know how to even gauge, and then the dispensary really determines the rest; what kind of product they are going to use and how much, it is really very different than every other prescribing model in any modality that I can think of that we do, it is one in which I have almost zero quality control. It is got to be worse for kids because there is even less data I am sure. Ananth Right. There is not a lot of data period across the board, and every state is a little different in terms of what they mandate for people who actually are recommending medical marijuana, it is not a prescribed medication, so I do not really call myself a prescriber, but in Massachusetts you do a 4-hour online training. Gore Well, that seems reasonable. Ananth Yeah, but you could kind of skip through it fairly quickly. I mean there is not really an expectation that you have a certain baseline knowledge. So, in our study, we did ask questions of providers in terms of how much they knew about state and federal regulations, and what we found was providers were largely quite unaware of their specific state regulations, and we asked them detailed questions about what quantity of medical marijuana patients could possess, do they have to have a registration card or not, and even in states that have had access to medical marijuana, like Washington State, where recreational marijuana has existed for a while, even then providers were not necessarily aware of their state regulations, and so it does suggest that there is a substantial knowledge gap. In that, as I started to talk more about this, I was talking a little bit about what medications could marijuana could interact with and that was a huge unknown for a product like this. Gore That could be super-important in cancer, like what if it is interfering with the chemotherapy. Ananth It is also very important and relevant when enrolling patients on early phase clinical trials, because it could have potential interaction and the challenge is that if we do not ask about it, if patients do not disclose that they are using medical marijuana, they may be using it unbeknownst to us and they may be subject to a lot of toxicities, and so what I have learned from this research and what I have been encouraging my colleagues to do is to ask about alternative remedies, to ask about use of medical19:13 into

mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3 marijuana and then documenting in the medical record, which I think is controversial by documenting the medical record what formulation they are taking. I agree with you that there is a lot of unknowns about formulations, strains and that, dispensaries may have variable practices in terms of how cleanly they are, what their practices are. In general, every State Department of Public Health, has some degree of regulation over dispensaries, but really they are for profit businesses. And so, their intent in going to the business is sort of different than what our purposes in healthcare are. Gore Well, the pharmaceutical industry is also for profit, let us not forget. Ananth True, but there is not any universal oversight over the dispensaries. So, you have no idea when you are suggesting to a patient to take, say a marijuana oil, what they are actually getting or what dose that is. I have not personally recommended medical marijuana to anyone only because I have not gone through that additional sort of training and licensure to be able to recommend medical marijuana. Gore Here in Connecticut that does not seem to matter, so go ahead. Ananth Many of my colleagues who have, generally have been steering patients in dispensaries away from recommending vaporized or smoked formulations, but beyond that, we know that some edible forms, so marijuana can come in edibles like candy or brownies, and we really do not know anything about the strengths of those formulations. Gore And I would think that is very challenging among kids where they think candy and brownies, wow! Try to stick to just one. Ananth And there actually have been reports out of Colorado of children inadvertently ingesting grandma's medical marijuana edible and have come in with intoxication from marijuana. We have not seen death from medical marijuana, so I think the perception is that marijuana is pretty safe, but it can have some toxicity, especially in younger children and we do not have, apart from sort of cautioning patients that there can be variable strengths, I am not sure at the dispensary level how they are able to differentiate strengths. Gore Anecdotally, among your colleagues who have prescribed medical marijuana for kids with cancer, have you heard any scuttlebutt about it, or does it seem to be helping or maybe it is helping or they did not notice any difference? Ananth I think it is hard to say because oftentimes the circumstances in which medical marijuana is recommended are in patients who are really sick. 21:49 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3 Gore Desperate, sure. Ananth I think my colleagues have seen and in my own patients, I think they have experienced some reduction in nausea, some improvement in appetite and maybe some reduction in anxiety and pain. And so, that is why I say it is kind of hard to deny that there may be some benefit to it, it is hard to say also whether it may have some additive benefit or synergistic effect, combined effect with some of the prescribed medications that we give. I have not seen a lot of harm, and I think my colleagues would say that too. In the episodic use that patients have, so occasional use of marijuana to help relieve symptoms, it is not sort of at the level of habitual use, and if they are not smoking, I have not

seen a lot of harm come to my patients, but I also have not seen hundreds of patients using medical marijuana. There is a lot of stigma that the patients and families will talk about, they are afraid to disclose that they are using it or they are afraid to talk about it in the clinic, in part because of the perception that it is an illicit substance and that they might be labeled as I do not know, "druggies," there might be some sort of connotation attached to it. Gore Yeah, I have not found that among adults. Maybe I do not know the ones who are not disclosing. It is interesting because you mentioned the medical, better-studied purified THC which is marketed as dronabinol, Marinol is the brand name I think, and my experience with that particular formulation, which is usually prescribed for nausea, has been almost uniformly negative that patients who are accustomed to recreational marijuana do not feel that it gives them the high benefit or the mood benefit that they expect and patients who are not used to recreational marijuana just tend to not like the way they feel and it is too sleep inducing, that has been my anecdotal experience, I do not like to prescribe it. I have found that patients who ask for medical marijuana most often it is because of anxiety and I think mostly people are very happy with it, and I have seen some major mood improvement in at least 1 patient who was having problems, not to say that I would recommend to anybody because I do not know that I should and I think this was kind of a particular one-off in somebody who really felt that marijuana helped him in life, but it is quite different than my experience with the prescribed dronabinol form. Again, it is totally anecdotal. Ananth We prescribe dronabinol a lot and what patients will say is that it does not help fully with the symptoms of nausea or poor appetite, it might help a little bit, but it also has, for many pediatric patients, they will complain of that high or dizziness or sort of an altered sense, and they do not like that. There actually has been some pediatric research in children with bad seizures. There has been some research looking at a purified CBD oil. Gore That is the other part of the hemp? 25:34 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3 Ananth Right. Marijuana is made up of more than 200 cannabinoids, these chemical compounds. The 2 major classes are THC, which gives you that high and then CBD. There is a purified form of CBD that is commercially available, you can buy it on Amazon. It is not totally devoid of THC, but it has less than 0.03% THC, so most states actually allow access to it even if they do not have legal access to medical marijuana, some consider it the same as cannabis. And so, there were a couple of national studies, multi-center studies, that were very rigorously conducted, randomized controlled trials looking at purified CBD oil on children who had terrible seizure disorders and had been on multiple seizure medications, and from reading those studies, what I could glean was that there may be some benefit in terms of reduction in the seizure frequency, but there are also some potential risks. Anecdotally, there are many families whose children suffer from seizure disorder who speak very highly of purified CBD oil in helping to reduce seizure frequency. There is a particular strain of CBD called Charlotte's web made in Colorado and there is a family that went on CNN and talked about how their

child regained developmental milestones after having lost them with terrible seizure disorder. This was a story that Sanjay Gupta covered. Gore Does not take a lot of stories like that to really have a lot of impact. Ananth Exactly. Sanjay Gupta, as a neurosurgeon, writes very eloquently about how he had a very negative perception of marijuana and then having met this family and saw the benefits overtime of medical marijuana for people with serious illness that his attitude changed. And so, there may be some role for trialing CBD oil in pediatric patients with cancer. Anecdotaly again, what patients will say is that they have this perception and maybe it is rooted in some science I am not aware of that it is the THC component that may be active against cancer. And so, I think patients and families are not looking for that purified CBD oil always, that many families are asking for that recommendation for medical marijuana specifically because they want some combination of CBD and THC. Gore What has been your experience in your surveys, formal or informal, or your discussions with patients and families about how acceptable they would find randomized trials of medical marijuana? Are people willing to be randomized to a placebo, could you randomize them between medical marijuana and CBD so they would always be getting something, it seems like a pretty hard sell, and you pretty much know if you are on the placebo I think? Ananth You know what, I have not asked patients and families that. I think in general, everyone that I have talked to has been in favor of research, but I have never asked specifically about how they would feel about being randomized and potentially being subjected to a placebo. 28:36 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2018-YCA-0527-Podcast-Ananth_334353_5_v1.mp3 Gore How else would you study this? I mean this is something where you really would need some control I would think. Ananth Yes. And the other challenge to conducting research in this arena is that there are lots of different formulations. So, back in the 1970s, some folks at Dana Farber actually conducted very rigorous research using a purified THC, naturally occurring THC product that was actually supplied by the National Institute on Drug Abuse, and the specific question they were seeking to answer was whether this purified THC could be helpful as an anti-nausea medication for cancer patients, mostly adults, and they did find that it was better than nothing and better than some of the sort of antiquated anti-nausea medications. That study has not been replicated in recent eras and we have other anti-nausea agents which may be better. But I think in general, people are in favor of research and I think research could be very complicated with the federal regulations being what they are, that also complicates things. I actually feel like there are countries around the world, Canada for example or Israel, where laws around marijuana are much more permissive, where rigorous randomized control trials could actually potentially feasibly be conducted to help provide the scientific basis for our practice. Dr. Prasanna Ananth is an Assistant Professor of Pediatric Hematology and Oncology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week

to learn more about the fight against cancer here on Connecticut Public Radio.