>> Welcome to Session Four. This is the Cancer Symptom and Treatment Side Effect Clinical Management session, and I welcome you back from the break. My name is Alexis Bakos, and I am a Program Director in the Division of Cancer Prevention, and I help to oversee the supportive care and symptom management portfolio. I would like to introduce first my co-chair for this session, Dr. Mark Wallace. Mark received his degree from Creighton University, School of Medicine. He completed an anesthesiology residency at the University of Maryland, Go Terps, followed by an NIH training grant fellowship and a clinical pain fellowship in the Department of Anesthesiology, University of California, San Diego. He is currently a professor of anesthesiology and the chair, Division of Pain Medicine in the Department of Anesthesiology at the University of California, San Diego, School of Medicine. And he's also Director in the Division of Clinical Research in the UCSD Clinical and Translational Institute. Our next speaker will be Dr. Jose M. Garcia. He is a clinician and scientist at the Puget Sound Veterans Affairs and an associate professor of medicine at the University of Washington in Seattle. His basic lab is focused on understanding molecular pathways involved in the development of muscle wasting, fat atrophy, and anorexia, and in the development of novel targets for these conditions. His group is also involved in several human trials in patients with cancer, anorexia and cachexia, aimed at characterizing the pathways involved and identifying the mechanisms of action of different potential therapies and testing them in both key center trials. Our third speaker is Dr. Aminha Jatoi. She is a professor of oncology at the Betty J. Foust and Parents' Professor of Oncology at Mayo Clinic in Minnesota where she primarily cares for patients with gastrointestinal and gynecological malignancies. Her research focus is on supportive care issues in cancer patients, and she seeks to mitigate side effects from the cancer treatment and distressing signs and symptoms related to the cancer itself. He research has been funded by the National Cancer Institute and various foundations. Our fourth presenter is Dr. Michelle Sexton. She is an adjunct assistant professor in the Department of Anesthesiology at the University of California, San Diego, and assistant clinical investigator at Bastyr University. She earned her doctorate in neuropathic medicine from Bastyr University, and completed a postdoctoral fellowship at the University of Washington in the Departments of Pharmacology, Psychology, Psychiatry, and Behavioral Sciences. Dr. Sexton's clinical practice, research, and teaching focuses on the endocannabinoid system and potential roles for cannabis across a range of conditions and lifespan. She maintains a clinical practice in San Diego, California, and is involved in starting the first cannabis clinic within a major institution, which is at the University of California, San Diego. And then our final presenter is Dr. Carey S. Clark. She is the Nursing Program Director and Chair of the Medical Cannabis Certificate Program at Pacific College of Health & Science. Dr. Clark is the immediate past president of the American Cannabis Nurses Association, and she is dedicated to educating nurses and patients around the endocannabinoid system, homeostasis and the safe and effective use of cannabis to support healing. She is the editor of the soon to be released book, "Cannabis: A Handbook for Nurses." So I'd like to welcome all of our speakers for Session Four, and let's get started with you, Mark. Thank you.

>> Thank you, Alexis. And before I get started, I just want to thank Michelle Sexton, that she -- we're responsible for educating our medical students, residents and fellows at UC San Diego, and she keeps an up to date, pretty substantial up to date slide deck, which I frequently pull from to supplement my talks. So I want to just give a brief summary, kind of overview/outline of what I’m going to cover. So first I'm going to just briefly cover the mechanisms behind cannabinoid-induced analgesia. I'm going to briefly cover some of the evidence behind medical cannabis. There's this interest around opioid sparing effect, so I'm going to cover some of the evidence we have with opioid sparing effects and also share some of our own clinical experience. In the last presentations, there was a lot of interest over this biphasic effect. I'm going to cover some of the evidence on the biphasic effect and our experience. And then I'm going to finish off with some of the clinical applications and what we've learned as far as dosing. Michelle and I have dosed in the thousands of patients in our clinic, so next slide. So first, just to -- there are two cannabinoid receptors, cannabinoids CB1 and CB2. They're G protein coupled, and they're positively to potassium channels, negatively to these N-type calcium channels. So the net result is increased post-synaptic potassium conductance and then decreased pre-synaptic calcium conductance. So this is the stabilization of the membrane. Next slide. The CB1 receptors are widely distributed across the nervous system, most widely expressed G-protein coupled receptor in our central nervous system. There are certain areas of the brain that are very highly concentrated. One thing to note is that there's very little cannabinoid receptors located in the brain stem. So that probably is why we don't see these negative respiratory depressant effects from the cannabinoid system. Next slide. Now in the periphery, there are the peripheral cells monocytes, which mainly carry the CB2 receptors. And when they are stimulated, they reduce inflammatory cell mediator release, plasma extravasation, and they reduce the sensitization that we see as a result of these mediator releases on the afferent terminals. The peripheral terminals have the CB1 receptors and, again, the potassium and calcium conductance coupled with reduce terminal excitability and then release these pro-inflammatory terminal peptides. Otherwise, they stabilize the peripheral nerve membranes. Next slide. Now in the spinal dorsal horn cells, they're --mainly the CB1 receptors are involved with the pain transmission, and they're located both pre-synoptically and post-synoptically. And the pre-synaptic terminal, they reduce calcium conductance. So they're going to reduce a neurotransmitter release. Now, there's also some of this co-localization with a TRPV-1 receptor, which is going to affect calcium conductance. And then the post-synaptic membrane, they are positively coupled with increased potassium conductance so they hyper-polarize. So this basically reduces excitability. There are also these CB1 receptors and CB2 receptors located on non-neuronal cells, and it's kind of less clear what their role is, but they do seem to play a role in stabilizing some of the excitability. Next slide. Now in the supraspinal sites, as I said in the previous slide of the distribution, there's a pretty high localization of the CB1 receptors in the basolateral amygdala, the periaqueductal gray, the rostroventral medulla. And the net effect of activating these areas result in this descending inhibitory effect on the dorsal horn cell. So this is a pretty robust mechanism. This is a triple mechanism site of action and actually quadrupled if you look at the pro-inflammatory cells. We don't see many pharmacological agents that have these widespread effects on the central nervous system. Next slide. Now, there's been a lot of discussion on cannabidiol and THC and just to kind put things in perspective, the cannabidiol, understand there's this big hype with cannabidiol, and I know my patients say they want to use it. They go on the web. They get it off the web, and who knows what's in there. I mean, there are patients that report effects with low doses of cannabidiol. You know, it may be contaminated with THC. We're assuming that it's pure CBD, but it probably has low doses of THC in there also. Now, there are no studies supporting analgesic effect of CBD in humans. We need more studies. There is -- CBD has been shown to have anxiolytic effects. This is probably related to the serotonin receptor systems. It's been shown to have anti-inflammatory effects. It's been shown to cannabidiol levels. It may modulate some of the dopamine mechanisms, which is related to addiction, and there's been reports of using CBD to reduce withdrawal and craving. Now, understand the dose is relatively very high compared to THC. I'm going to go into this a little bit more in detail. It's been show to modulate some of the psycho activity of THC, and it's hard to say. Is this competing with THC at the receptor? Probably not. It's probably more along the lines of affecting the metabolism. So you get the lower levels of this Hydroxy THC, 11-Hydroxy, which has a lot of psycho activity. Now, THC, much more evidence supporting THC. That's where most of the studies have been in humans. It's been demonstrated to have analgesic effects in humans. It's been shown to have anxiolytic effects. However, very dose related, and you can go from anxiolytic effects to actually opposite effects with higher doses. It's an agonist of both CB1 and CB2. It also modulates dopamine mechanisms, and it seems to be -- definitely low doses are effective, and we are seeing this synergism with CBD also at low doses. Next slide. So there's the -- as I said, there's this mischaracterization of CBD. Now, CBD may antagonize the effect of THC, and it may mitigate some of these adverse effects, and there has been published -- this has been published on. Next slide. It also has -- it should be preferably as non-intoxicating, but however it does have anxiolytic effects at higher doses. It has this calming effect that patients report at higher doses. Next slide. The CBD at high doses is reported to be sedating and the opposite effects of low dose, because low doses you go from opposite effects, alerting at low doses, sedating at high doses. Next slide. And then we have CBD turns into THC in the body. This has been reported, I mean, been claimed. No evidence of this. Next slide. And there's also been the claim that it treats pain in humans. We actually have zero evidence of CBD to treat pain in humans. That's not to say it doesn't. It's just we don't have the studies to show that. Next slide. And then dosing is not equivalent to THC as I'll go into a little bit more in detail. The dosing range is widely different. Next slide. Now -- next slide. Okay. Now, you've got to understand that patients that use the full plant, and they will report that the full plant is better than any of these components. And understand that there's also these other, these terpenes in the plant that also have some pharmacological and medicinal activities such as analgesic effects and anti-inflammatory effects, anxiolytic effects, and so there may be some of the additional effects that we see with the terpenes. Next slide. Also, THC has been shown to be effective in a lot of different animal models. It's been robustly tested in animal models. Next slide. There has been nerve constriction models, which have shown it to be effective. Next slide. There's the diabetes, the strepozotocin model. Next slide. The chemotherapy models have shown to be effective. Next slide. And then it's also been in HIV neuropathy. Next slide. And then a bunch of other pain models. So this is one of the most studied what we would say analgesics in animal models, and it has very robust positive effects in all of these models. Next slide. Now as far as human studies, they're not as much, and there are good reasons, because it's very difficult to study cannabis because of the regulations we face. But, however, if you look at this one, this was a systematic review of randomized trials. Fifteen of 18 trials that met the inclusion criteria demonstrated significant analgesic effects over placebo. Now, we've just recently gone through a pretty substantial review with a committee in the International Association for the Study of Pain, and the outcome of that is not as good as this because the bar was set much, much higher as far as what studies would be included. And when we raised the bar so high, almost all of the clinical studies were eliminated, because -- and, again, it's so hard to study that you can't do multi-center trials. You can't do large numbers of patients. Next slide. Now, this is the -- the Center for Medicinal Cannabis Research was established in 2000, and it was from funding from the State of California. And the goal was to do rigorous placebo controlled studies in medical cannabis. And this was limited to the State of California though. Next slide. These were the studies that came out of it, and there's been others, but these were studies that looked at pain. And all of them were double-blinded, randomized, cross over studies, and every one of them were positive. Now with a caveat though, because there -- if you look at my study in healthy volunteers, I looked at zero, 2%, 4% and 8%, and this was using an experimental pain model with capsaicin. And what we showed was that the zero and 2% had no effect. The 4% actually reduced the pain whereas the 8% worsened the pain. It increased the pain. And then you come down to my diabetic neuropathy study, and I'm going to get in more detail on this in just a moment, those were pretty much the same doses, and I saw a dose dependent reduction in the pain. However, that 7% started to turn the corner. It started to go in the opposite direction, but it still was reduced. But understand, these were inhaled studies. The blood levels were all over the place, and I'll go over in a little bit more detail what we saw when we looked at the blood levels in a moment. Next slide. Now, there's also this interest on opioid-sparing effects, and at UC San Diego, Michelle and I have been using medical cannabis to wean patients from opioids in hundreds and hundreds of patients. And if you look at some of the animal, the preclinical studies, next slide, there are 19 preclinical studies, 14 studied THC and 10 other synthetic agonists, and there was the pain out with tail-flick and hotplate, and they looked at a variety of different opioids. And 90% of them demonstrated significant synergistic effect. Two studies show duration of effect was extended with co-administration of low-dose opioids and cannabinoid. Next slide. And so, you know, overall, the median effect of dose of morphine and codeine was 3.6 and 9.5 times respectively lower when given in combination with THC. So there is this opioid-sparing effect we've seen in animal models. Next slide. Now, look at the issue of the biphasic effect of THC. So we do know that there's been animal studies looking at conditioned placed preference, and you put a rat in the central chamber, but you have one chamber associated with aversion and one chamber associated with preference. If you put high doses of THC in one chamber and low doses of THC in the other chamber, the rats will migrate to the chamber that has the low doses, and they will avoid the high doses. And humans have reported this opposite effects also. Next slide. So when coming back to the diabetic neuropathy study, when we looked at all the blood levels, some of the patients that were in the high dose had blood levels than like the medium dose. And so that's the problem with inhalation. So what we did is we pulled the blood levels and THC and did a correlation analysis between pain reduction and we saw this inverted U shape relation. So as the dose of THC goes up, their pain reduces to a point where it's starts going in the opposite direction, and they'll start reporting worsening of the pain. Next slide. So there's this biphasic effect of THC and CBD. Next slide. And that the THC -- now, these are naïve patients. You can go from a positive effects, beneficial effects to negative effects. So two to five milligrams, you get anxiolytic, you get analgesia. Ten to 15 milligrams you're going to get up into paranoia. You get 20 to 25 milligram, you get psychosis. And next slide. Now, the CBD also has biphasic effects, 15 milligrams, alert. High doses going through anxiolytic and antipsychotic effects. Next slide. And so there's this interesting concept of low dose endocannabinoid -- or low dose stimulation that's associated with endocannabinoid deficiency. Maybe things like migraine, fibro, chronic anxiety. We are actually starting a first randomized controlled cross over trial, placebo controlled trial using cannabis as a migraine abort. We're going to be enrolling our first patients in the next couple of weeks. Next slide. As opposed to this issue of high dose inhibition, maybe endocannabinoid excess, schizophrenia, substance abuse, obesity, all these things. So this endocannabinoid excess and deficiency probably is associated with certain disease. Next slide. So next slide. So there's also this issue of cannabis dosing in pharmacology. Now, there's a big difference between inhalation, ingestion and topical. Inhalation is the best way to deliver it, because you're going to get very consistent early peak effects, but it's not going to last very long, as opposed to ingestion. Very delayed onset. Very erratic absorption, but much longer onset. And in topicals, you know, patients report some benefits. Other report no benefit. There's very little evidence for topical though. Next slide. Now, we do not recommend smoking it. If we're going to inhale it, we recommend using vaporization of the organically grown leaf. Here in California, we have the Bureau of Cannabis Control that is mandating product testing, so we're getting better and better and better quality, high-quality cannabis that we can give to our patients. Next slide. We do not recommend vape pens, the extraction process. We don't know what is in there. We don't know what contaminants are in there, and we tell our patients to just avoid vaping. Next slide. Now, the primary benefit is from THC. Next slide. And, again, there's no human data to support CBD as an analgesic. Next slide. And patients do -- I don't see patients reporting much benefit from CBD. Now, the patients do -- some do, and I just wonder how much THC is in there, because even the CBD, I think it's probably contaminated with low doses of THC, that they don't have the psychoactive effects, but they get the benefit. Next slide. So -- and, again, CBD may help reduce some of the drug craving and decrease the psycho activity of THC. Almost of all our patients get a combination of CBD/THC as their dosing protocol. Next slide. So dosing guidelines, it's all about self-titration. Dr. Sexton and I have been doing this for many years. The process that we use is I evaluate the patients and make sure they're candidates, good candidates, making sure they haven't tried more other conservative therapies. If they're a candidate, I give them the medical authorization. Dr. Sexton does the dosing consultations, gets them set up, and they follow-up with me and we kind of monitor and self-titrate that. So the key is start very low, go slow. And in the daytime, we use a pretty high CBD to THC ratio of 20 to 30:1, and then at nighttime maybe bump is up to 1:1 to get more of that THC for sleep. Next slide. And, again, the dosing we're starting at is around 0.5 to 2 milligrams per dose up to two to four times a day. Next slide. Patients usually develop a tolerance to the psycho active effects of cannabis over a period of days without this tolerance to the analgesic benefits. Next slide. THC-mediated side effects such as fatigue, tachycardia, dizziness, they're avoidable if you start at low doses. I mean, oftentimes patients come to me and I ask them, "Have you tried cannabis," and they said, "Oh, yeah, Dr. Wallace. It was horrible. I don't want to ever do it again," and they just got started at much too high doses of THC. If we get them to start over, start very low and titrate, they seem to have more benefit. Next slide. Less can be more. Lower dose is often more effective than higher doses, again, coming back to the biphasic effects. Next slide. So take home message. Next slide. The low doses of THC is producing synergistic and antinocicpetive effects in our patient population as opposed to co-administrating with opioids. We're able -- I've been successful in actually weaning patients completely off of opioids with THC. But, again, most of them are in combination with CBD. Next slide. Pain relief is occurring at relatively low dose of THC while minimizing the side effects. Next slide. Cannabis provides a therapeutic strategy to enhance the analgesic effects of opioids, allowing for an opioid-taper. Now, the process that I take is that I tell the patients -- a little bit of my history is when I first starting using cannabis, I would tell patients they have to be off of their opioids before I will allow them to take the cannabis, and I'll put on these weaning protocols, very slow weaning. What I saw is that most of these patients were really hanging in there. They were compliant. They were trying to wean. They were having withdrawals. They were having increased pain. And I said, "Okay, let me introduce the cannabis." And then I noticed that they would chill out. They would be able to wean down. So what I do now is I tell them -- I give them the weaning protocol. They see Dr. Sexton, do the dosing consultation, get their cannabis onboard at home. Then I tell them to wean down as far as you can go before you introduce the cannabis. Some of them will go a 20% reduction before. Some of them will go 80%-90% reduction before they start the cannabis. Next slide. And then a mild euphoria or a sense of well-being can play an important therapeutic role in patients' faced with this chronic pain. And one other comment on the CBD. I know there's been a lot of talk on the dosing of CBD. Again, we don't know. I think that the doses patients are using kind of in the community or on the web or in the dispensary are way below therapeutic effects. I think that in my experience, we probably are going to need doses in the 200 to 400 milligram daily range if you want to just use CBD alone, maybe even 800 milligrams a day. But the doses we're seeing patients using are 10 to 20 milligrams per dose, and it's probably either placebo effect or just not effective. Next slide. And that's the end of it. I'll hand it back over to Alexis.

>> We'll start the presentation for the next speaker. Thank you. Dr. Garcia?

>> Thank you very much. Can everybody hear me okay?

>> Yes, we can hear you.

>> Excellent. Thank you. Well, first, I would like to start by thanking the organizers for taking the lead, putting this excellent meeting together, and for this invitation. Next slide, please. I have nothing to disclose. I am a federal employee and as such the views and opinions that you hear today represent my own and not necessarily those of my employer. Next slide, please. I know that this slide will be kind of basic for a lot of people. But for those that do not work in this space, or that do not interact with patients on a regular basis, I would like to start by just giving a framework for this. And we know that nausea and vomiting in cancer patients are actually very common, and they're (unint.) usually multifactorial. Paradoxically, a lot of the process of nausea and vomiting in patients with cancer are related to some of the treatments that we use in those patients, in those (unint.) chemotherapy, which is usually a big contributor. And within the chemotherapy-related nausea and vomiting, there's actually different types of chemotherapy-induced nausea and vomiting. So there's one call anticipatory emesis, which is essentially a conditioned response in patients who have had nausea and vomiting before with administration of chemotherapy. There's also acute nausea and vomiting, which typically starts one to two hours after chemotherapy and it peaks somewhere around four to six hours. And delayed nausea and vomiting, which usually takes place 24 hours and thereafter the administration of chemotherapy. Radiation is also a big contributor to nausea and vomiting. It tends to be field-dependent. So, for instance, abdominal and pelvic radiation is oftentimes a contributor to nausea and vomiting. There are other medications in addition to chemotherapy and radiation that also contribute, such as opioids, but also other medications such as antibiotics, like Erythromycin, for instance, can contribute to nausea and vomiting. And then there are other causes of cancer-related nausea and vomiting that are not related to the treatment, such as obstruction of the GI tract, hypercalcemia, prime metastases, for instance, that can contribute to the nausea and vomiting per se. I think this is important to keep in mind when we develop models, pre-clinical models to make sure that they're relevant to the conditions that we see in the clinic and also, of course, to take them into account when we do clinical trials in this space. Although there are several agents that are currently used for the prevention and treatment of nausea and vomiting, these remain -- you know, there's still a significant unmet need and a significant number of patients still have uncontrolled symptoms, nausea and vomiting, that takes a tool in the quality of life. Next slide, please. I'm not going to go into a lot of details, and we actually just -- you know, in the previous session, we heard an excellent talk covering a lot of the pathophysiology and the pre-clinical data by Dr. Parker. And so I will actually just focus more on the clinical evidence available. But I'll say that there's actually two types of cannabinoid receptors, as others have discussed, including the cannabinoid receptor 1 and 2 that are present throughout the central nervous system, more so the cannabinoid 1 than cannabinoid 2 receptor, but there are also other cannabinoid receptor 1 and 2 independent effects that have also been described. And from pre-clinical models and as we heard, there's evidence that both acute and delayed emesis related to chemotherapy are improved by cannabinoids. Next slide, please. In regards to the mechanism (unint.) anti-nausea and antiemetic effects of cannabinoids, the body of knowledge available suggests that there's activation of cannabinoid receptor 1 and possibly cannabinoid receptor 2 deceases nausea and vomiting by reducing the release of excitatory transmitter like serotonin. And some have postulated that there's an antiemetic endocannabinoid tone and constitutive receptor activity as potential mechanisms for this. Also another possibility that actually has therapeutic implications is that we potentially could raise endocannabinoid levels, and that also may hold promise as a potential target for nausea and vomiting treatment. So one example in that would be the fatty acid hydrolase inhibitors. And then we also need to remember that there are other effects outside of the central nervous system that may play a role in how effective and save cannabinoids are, and these include the role of cannabinoid in reducing cramping, but also in altering or modulating GI motility. Next slide, please. So as I mentioned before, I'm going to focus on the clinical trial data using cannabinoids. And we know that there are actually a couple of these synthetic cannabinoids, Nabilone and Dronabinol, which are orally active analogues of delta 9-THC. They are approved for the treatment of chemotherapy-induced nausea and vomiting. "Approved" I refer to as approved by the Food and Drug Administration for clinical use here in the U.S. These are both partial agonists of cannabinoid receptor 1 and 2. These are not the only compounds that have been tested in this space. So we've seen trials using delta 9-THC that have been tested, although these are not approved for use in the U.S. And then (unint.) a combination of delta 9-THC and CBD showed activity in a small phase II clinical trial for delayed chemotherapy-induced nausea and vomiting. Although to my knowledge, it's not currently in development, at least here in the U.S., for this particular indication, although it is approved outside of the U.S. for cancer pain and neuropathic pain associated with multiple sclerosis. Last month there was another study that was reported, such an important study. Unfortunately, I was not aware of the results by the time I made these slides, but I will discuss the results of this phase II trial in a couple of slides. Next slide, please. Okay. So I'm going to review first some of the clinical trial evidence used in cannabinoids versus placebo, and then I'll move onto some of the studies that tested the effect and safety of cannabinoids versus other anti-emetic agents. A lot of this data, I'll start by saying, was generated quite a bit of time before the current standards for chemotherapy-induced nausea and vomiting treatment were in place. And so this data, the main limitation is that it's kind of outdated in terms of the comparator that they use. You can see here on the slide that there are a good number of studies that tested the effect of cannabinoids against placebo. But if you look at the number of individuals, you can see that most trials were fairly small. And as a result of that, the quality of the data is not very high. So, you know, it's listed there as a (unint.) probably some time ago was either low or very low. The majority of the studies had actually quite a bit of risk of bias. It was actually high in the majority of them. And then some of the differences were not statistically significant in these studies. As you can see on the top of the table with regards to the efficacy, those looked at the effect of cannabinoids versus placebo nausea or in the combination of nausea and vomiting. The results suggest that there is a favorable effect of cannabinoids versus placebo. The four trials combined looking at vomiting specifically, the differences were not statistically significant. If you move down in the table and you look at the self-reported treatment preference, we can see that there's actually -- that most subjects in the two trials that looked at the treatment preference favored cannabinoids over placebo even though there was a higher rate of adverse events, mostly psychotropic adverse events like feeling high or sedation with cannabinoids. So these are not uncommon, and I will say they're certainly not unexpected adverse events. And, you know, for people working in another space, like anxiety, for instance, they will say, "Well, why is this an issue?" And I think that the cancer patient population can be quite different in a number of factors, age being one of them, and why these were perceived as adverse events. Nevertheless, as I just pointed out, the patients preferred cannabinoids over placebo. Next slide, please. If you look at now the effect of cannabinoids with other drugs, again, there are a fair number of trials. But if you look at the total number of individuals exposed in these trials to cannabinoids, it's fairly small. So as it was the case where the trials of cannabinoids versus placebo, the quality of the data is low to very low. The other thing that is evident in this table is that the comparators that were used in these trials, which are, as I mentioned before, outdated, are not the ones that we typically use today for the treatment of chemotherapy-induced nausea and vomiting. And so that is also, I think, one of the main limitations of the clinical data available today. If you look at the effects of cannabinoids versus other drugs on nausea, vomiting, or the combination of both, the data is kind of mixed and some of them found no difference between some of the agents that were used, like Prochlorperazine, although some did favor cannabinoids over this agent. In a similar fashion to what I just showed you compared to placebo, cannabinoids did induce a number of adverse events, primarily feeling high, and there were also more withdrawals due to cannabinoids, the comparators. Nevertheless, patients still prefer the cannabinoids to these agents. Some of the other adverse events that are reported in these trials include disorientation, drowsiness, confusion, hallucination, loss of balance, euphoria, fatigue, dry mouth, (unint.). So, again, for some of the subjects, these drugs do induce a significant number of adverse events. Next slide, please. And so now moving forward to the current treatment of chemotherapy-induced nausea and vomiting, I think this is an important slide to see, you know, if we're going to use cannabinoids in this setting, what is the current standard of care for these important symptoms. And first, let me start by saying that, you know, there's kind of a range of nausea and vomiting likelihood with different chemotherapy agents. And so you can see there a table, and I apologize if it's not very readable. This was taken from the European Society of Medical Oncology and MASCC Guidelines from 2016. And so agents are divided by the likelihood of inducing nausea and vomiting. Those agents that you see there listed as "high" are those that have a 90%-plus chance of inducing vomiting. Those that you see list there as "moderate," which, as you can see, is an extensive list as well, are those that induce vomiting in 30% to 90% of patients. This (unint.) with different tumor types, and the majority of the treatments involves a combination of three or four of these agents, and these are 5-hydroxytryptamine 3 receptor antagonist. It was mentioned before. Ondansetron is one of them. There are several actually that are clinically available and approved for use. Dexamethasone, neurokinin 1 receptor antagonist such as Aprepitant. There are other examples as well. And more recently, Olanzapine. So this is -- a combination of these agents is really the standard of care today for the prevention and treatment of chemotherapy-induced nausea and vomiting. Next slide, please. And so when we review the data on the effects of cannabinoids versus other agents, you probably saw that the agents that were used as comparator were not the ones that are currently used today. And so that's really a big gap in the knowledge in terms of how can these cannabinoids be added to the current standard of care. So there's one study, which you're seeing there, that actually looked at this, and it was a design that was interesting. That's why I'm including it there, using Dronabinol versus Ondansetron for delayed chemotherapy-induced nausea and vomiting. So if you look at the first day, so the day of chemotherapy, pretty much everybody received a similar combination of drugs, including Dexamethasone, Ondansetron, and Dronabinol for the three arms that you see listed there on top, Dronabinol, Ondansetron and the combination arm. The placebo subjects, however, only received Dexamethasone and Ondansetron. Post-chemotherapy then the first three arms received Dronabinol versus placebo that was given to the placebo-receiving subjects. So the main difference really was on day two and day three to five where the Dronabinol arm received only Dronabinol. The Ondansetron arm received only Ondansetron, and the combination received both versus the placebo of course that received only placebo. Next slide, please. So these are the sort of summary results of this trial. And as you can see, there's a couple of limitations. One of them is that the trial is fairly small, including only somewhere between 10 to 15 subjects per arm. And then you can see that there was essentially similar effectiveness for the treatment of chemotherapy-induced nausea and vomiting in between the arms. So you can see that the complete response in the small number of subjects was somewhere around 60% for the Dronabinol, the Ondansetron and the combination arm compared to only 20% for the placebo arm. And so the combination therapy was no more effective than either agent alone, even though the active treatment was well tolerated. As I was mentioning before, last month, a multicenter placebo control randomized cross over phase II trial was published looking at the efficacy of adding a combination of THC and CBD on a one-to-one ratio, 2.5 milligrams three times a day to a more standard of care regimen that included Dexamethasone, serotonin receptor 3 antagonist and NK1 receptor antagonist. The study included 81 subjects that were not responding well to sort of the standard of care, that Dexamethasone, serotonin receptor antagonist and NK1 receptor antagonist. And the design was interesting in which they -- there was cross over, so everybody received placebo and/or THC plus CBD in random order. But then on the third cycle, they allow the subjects to choose which treatment they wanted to get, treatment A or B, to not break the blind. And that was an interesting and clever way in my view of actually testing the preference of these individuals. The complete response rate was low in both groups, although there was a significant difference with the active drug. So there was 25% of complete responders versus those receiving placebo, that it was only 14%. Nevertheless, two-thirds of the patients in the cannabinoid arm required rescue for symptoms with conventional antiemetics. And one out of three subjects in the study still had vomiting. Some of the side effects were moderate to severe, again, in one out of three subjects. But nevertheless, 80% of the individuals, when they picked the third dose, they selected the cannabinoids versus the placebo arm. So these results, I think, are interesting, are very encouraging, and this is actually a phase II/III study, and so the study is still ongoing, and we'll test another 170 patients to complete 250 subjects. And hopefully these results will be available in the future. Next slide, please. In terms of what's going on here in the U.S., last week I did a search on clinicaltrials.gov, and as you can see there, I did not see a lot of clinical studies in this space, which is something that Dr. Parker was mentioning before, that there's really a big gap in terms of the clinical research. And I think this is something that is urgently needed. So hopefully, you know, some of these results that were recently published will stimulate the field and will allow other investigators and industry partners to spend more time and resources into this space. Next slide. So to summarize the data that I just showed you, the first thing that you can see there is that the quality of the evidence is actually quite low. So there's a big opportunity here for improvement. When you look at the trials that tested the effect of cannabinoids versus placebo, there's actually a trade-off between the benefits and harms in adults. I did not mention children, but actually there's insufficient evidence to recommend cannabinoids in children for this indication. If we look at cannabinoids versus other antiemetic agents, you know, with the caveat that the majority of trials did not compare cannabinoids to current standard of care, there's also a trade-off between benefits and harms in adults and a big lack of data with regards to comparing it to more current anti-nausea and anti-medications such as the 5-hydroxytryptamine 3 receptor antagonist or, you know, neurokinin inhibitors and Dexamethasone. There's also not enough evidence to make a recommendation in children. And the objective regimen is -- you know, we can draw the same conclusions, Next slide, please. So what do the current guidelines say? I mean, these cannabinoids have been approved for this particular indication of chemotherapy-induced nausea and vomiting for a while. So the American Society of Clinical Oncology and the NCCN guidelines most recently in 2015 and 2017 recommend these FDA approved agents, Dronabinol and Nabilone, to treat nausea and vomiting that is resistant to standard antiemetic therapy, that is also indicated for use as a rescue antiemetic, so somebody who is having nausea in spite of having these agents. However, they say in the guidelines that there is insufficient evidence regarding the use of medical marijuana for chemotherapy or radiation-related nausea and vomiting prevention, or in place of FDA approved cannabinoids. Other organizations like MASCC and European Society of Medical Oncology do not recommend cannabinoids for this indication in their most recently guidelines in 2016. Next slide, please. Something that was, I believe, a comment that I saw in the chat that I think is true, and that's why I included this slide is that we also don't know enough about a condition that I think is important, because as cannabinoids are being used more is something that we're going to have to keep in mind and we're going to see more often, which is this cannabinoid hyperemesis syndrome. And this is actually cyclic nausea and vomiting and abdominal pain that's sometimes is seen associated with chronic cannabis use. There's still a lot that we don't know about this condition, and the mechanisms that have been proposed include the presence of toxic metabolites, high exposure leading to down-regulation of the cannabinoid receptor and some genetic factors that can predispose an individual to this condition. It has not been reported in patients taking only pure THC products on a scheduled regimen, so that's reassuring. And it's really hard to treat. So there's usually not -- it's usually resistant to standard antiemetics and patients report reduced symptoms after taking hot baths, so that's typically what's recommended to patients. And so they only effective treatment for this condition is really a drug holiday. Next slide, please. So some of the conclusions that we can draw based on the current evidence is that there's not enough evidence really to support the use of cannabinoids as first-line therapy for cancer-related nausea, unfortunately. And these FDA approved agents, Dronabinol and Nabilone, may be helpful to treat nausea and vomiting resistant to standard antiemetic therapies. Unfortunately, given the widespread distribution of the endocannabinoid system, the off-target side effects have limited the clinical development of this pathway. Next slide. So what are the gaps in the knowledge? Well, a better understanding of the endocannabinoid system, I think, is needed to develop clinical trials that will establish the safety and efficacy of modulating this pathway. So the relative contribution of the two receptors to nausea and vomiting is being studied as we speak. And given that the activation of the cannabinoid receptor 2 is less psychotropic, this may represent an opportunity to treat nausea and vomiting with less side effects. Also selective modulation of this pathway either with a specific antagonist or a mix of them or by modulating the endocannabinoid, they represent opportunities to advance the field. Next slide. So the quality of the evidence from clinical trials comparing them to placebo and to standard of care antiemetic therapies is really low. In particular, there's a paucity of trial comparing cannabinoids with newer antiemetics that are the standard of care today. So something that I think is -- there's also a lot -- is a big opportunity is to improve our understanding of the specific patient population that could benefit from some of this pleiotropic effect of cannabinoids. So we know that cancer patient typically present not with an individual symptom, but with a cluster of symptoms. That may include pain, anorexia, so lack of appetite and nausea. So is there a specific group of patients that may actually benefit from what is, you know, to some extent considered side effects in these clinical trials that I just shared with you? Other features, for instance, taking younger patients, which are less likely to suffer some of the side effects of these agents. So all these things can help optimize the risk/benefit ratio of this intervention. As it was mentioned before, there's some regulatory and legal issues that are also kind of a burden now to the research. Next slide. And this is my last slide. It's, you know, an example of, you know, how we can move the field forward. What I think is really needed is, you know, a randomized -- so high quality clinical trials. And this is an example of it, a randomized, double-blinded, clinical trial of what's currently used as a standard of care versus the standard of care plus cannabinoids. And some of the factors that I think are going to be important to take into account include the type of chemotherapy, the age, the gender, the type of nausea and vomiting, as I was mentioning before, anticipatory, acute or delayed, and then also paying careful attention to drug interaction issues, which is going to be something important given that the prior data did not use this agent, these cannabinoids, with the current treatments. And then, of course, safety and tolerability. Thank you.

>> I very much appreciate the invitation to be at this conference and to be talking about Cancer-Associated Anorexia and Cachexia: Defining a Palliative Role for Cannabis. Next slide, please. I'd like to first say I have no conflicts of interest. Next slide. So in giving this talk, I'd like to follow this outline: First, provide some definitions and some demographics associated with cancer-associated anorexia and weight loss, then go on to talk about the standard of care, then to provide some data on cannabis, or I should say THC interventions and then provide some comments related to lessons learned. Next slide, please. So with regard to definitions, there as a notable paper that was published by the late Ken Fearon and others. I was part of that publication. In that paper, there was a definition put forth for this cancer-associated weight loss, anorexia syndrome, and it was what follows: This syndrome is a multifactorial syndrome defined by ongoing loss of skeletal muscle mass, not fully reversed by conventional nutrition support, leading to progressive functional decline or impairment. Importantly, and I think the most important aspect of this definition is that this is not able to be reversed by means of caloric repletion. So patients with advanced cancer, who have a cancer that cannot be cured, who are possibly on chemotherapy, possibly not on chemotherapy, suffer from weight loss and with that and not mentioned in this definition is also this absence of appetite where patients struggle to eat. Next slide, please. And these investigators went on to describe this syndrome further, characterizing it based on degree of weight loss. There's a pre-cachexia part of this syndrome where the weight loss is less than 5% or equal to 5%. There's also, as mentioned on this slide, anorexia and some metabolic changes. Many of these patients become hypermetabolic. There's a next segment called the cachexia segment where you can see based on degree of weight loss, patients would fall into this category. And then lastly, there's a refractory cachexia definition, which precedes death of the patient. This is the portion of the cachexia spectrum where the weight loss is much more severe, where patients decline in their performance score, where such issues as loss of appetite become much more concerning and difficult for patients. But, again, as you can see here, this is a whole spectrum of change that happens over time and that ultimately in patients with advanced cancers is associated with early demise. Next slide, please. So what about this issue of weight loss? And put simply, one can view this syndrome in sort of a two-prong manner. One is the weight loss aspect, and the second is the aspect that's associated with loss of appetite. So with respect to weight loss, what specific comments could we put forth to justify this 5% or 2% change as was shown in the previous paper? Next slide. Well, there have been many studies that have looked at this, and this is really a classical study by DeWeese and others, which was published decades ago. And as these investigators show, this was a cooperative group-type study. Well over 3,000 patients were a part of this study, whether the cancer type was small cell lung cancer, non-small cell lung cancer, breast cancer, colon cancer, prostate cancer. Those patients who maintained their weight, as you can see in the second column here, lived longer than those patients who manifested weight loss as you can see in the third column. And these differences in survival provided here in terms of weeks were statistically significant across the board, as you can see in the final column. So weight loss at the time of diagnosis is highly predictive of early demise in patients with advanced cancer. Next slide, please. And how much weight loss does it take? It really doesn't take very much to see this prognostic effect. In fact, greater than or equal to 2% is all that it takes. Next slide. And some data from our group, which were published relatively recently, looked at this 2% threshold, and then went beyond the DeWeese study. These are patients with lung cancer. What Jennifer Le-Rademacher and others showed here was that it isn't just at the time of original cancer diagnosis that patients manifest this prognostic effect. But over time, if a patient is diagnosed with cancer and loses weight down the road, even that later degree of weight loss is associated with early death. And you can see that in these survival curves with the green line indicative of patients who have lost less than 2% and the red line, which is lower, indicative of patients who have lost greater than or equal to 2%. Next slide, please. So it isn't weight loss alone, but rather some changes in body composition that account for this prognostic effect. There was a case control study from many years ago, which looked at healthy individuals and looked at cancer patients who had lost weight. A variety of body composition assessment tools were used to assess how these patients were doing from a body composition standpoint. And these investigators made the following conclusions. First, the loss of body weight in patients with solid tumors consists of loss of muscle mass and fat. However and very importantly, this loss of muscle mass, which is predominately lost. And finally, cancer patients appear to retain notable amounts of body fat. So this particular aspect of body composition, muscle mass gets hit the hardest. And it's really the muscle mass that results in patients being less functional, being at greater risk for morbidity such as pneumonia, such as less activity, which predisposes patients to blood clots and ultimately results in this early demise. Next slide, please. So what about the other aspect of this syndrome? What about this aspect of loss of appetite? Well, with regard to loss of appetite, there's also similar information that says that this is also very concerning to patients. Next slide, please. If one looks at any list of symptoms in cancer patients who are approaching the end of life or who are at the end of life, one sees that within this list of symptoms that bother patients, poor appetite is on the list. And it's typically within the top five of symptoms. Patients could describe lack of energy. They can describe dry mouth. They can describe pain. They can describe nausea. But they also describe poor appetite. And sometimes it's even higher on the list depending on the group of patients who are being studied. Another notable point on this study, this is not uncommon. The majority of patients in this particular series, over 60% of patients describe loss of appetite as a troubling symptom. Next slide, please. And we also see a prognostic effect with loss of appetite. So these are data from Quintan and others, a group of patients, well over 1,300 patients with advanced cancer who rated their appetite. Those patients who had great appetite scores lived longer than those patients who had somewhat poor appetite scores than those patients who had worse appetite scores than those patients who actually lost their appetite appreciably. And as you can see here that these curves are totally lined up dependent on degree of appetite loss that has occurred. So appetite too has this very strange, but very strong prognostic effect with poor appetite at the time of cancer diagnosis, indicative of poorer survival. Next slide, please. So just to make the point, standard of care, what is a standard of care approach for a patient with advanced cancer who is suffering from loss of appetite and suffering from loss of weight? Next slide. Well, there have been countless studies that have tried to improve body composition, that have tried to make patients stronger. In absent effective chemotherapy, it is extremely hard to impact body composition and the prognostic effect associated with loss of appetite. As a result, what we have focused on more over time as clinicians is this loss of appetite, and that has been primarily the fault. Patients describe anorexia, loss of appetite as a troubling symptom. We have found ways to help deal with that symptoms. So we apply those sorts of interventions to patients. So as a first step in terms of standard of care, we educate patients about this whole syndrome. We try to make sure the patients know and their family members know that this lack of eating, this poor appetite, this poor oral intake really isn't the patient's fault. It really isn't the fault of any family members. It's a part of the cancer. It's a part of this syndrome that very often goes with the cancer. In patients who choose to try some sort of a pharmacological intervention, we think about two types of drugs. The first is progestational agents or Megestrol Acetate and the second is Dexamethasone. And the reason for making these recommendations for these two classes of agents is based solely on the fact that randomized placebo controlled trials show that these two classes of agents work. They work to improve appetite. In patients who are anticipated to live for several months, Megestrol Acetate is thought to be a better choice in large part because the side effect profile with Dexamethasone is worse. But importantly, as I think many at this symposium might now, Megestrol Acetate is associated with higher risk of thrombosis. And so in a patient who has had a blood clot in the past we generally don't give Megestrol Acetate. Next slide, please. So how effective is Megestrol Acetate? There was a study that was done many years ago by Charles Loprinzi and others. This was a study that was funded by the National Cancer Institute, and it was conducted within the cooperative group mechanism with heavy reliance on the CCOPs back then. This is a study that basically looked at 133 patients with advanced cancer. Patients were randomly assigned to receive either Megestrol Acetate or to receive a placebo. As you can see from the very bottom row in the study, it's notable that 70% of patients assigned to the Megestrol Acetate arm reported that their appetite was better as a result of the Megestrol Acetate. But I'd point out to you another very important finding under the placebo column. Forty-four percent of patients who were given placebo, an inert substance, also reported that their appetite was notably better. So I think it's important to make a couple of points from this slide. First of all, yes, Megestrol Acetate does work. But on the other hand, this sort of research, looking at symptoms and assessing outcomes with improvement of symptoms with an intervention, can be quite precarious. Placebo effects are quite strong. And as you can see here, a 44% placebo effect is quite notable. But nonetheless, if you look at the winner here, it was Megestrol Acetate that resulted in the majority of patients in this study reporting improvement in terms of their appetite. Next slide, please. So what about this whole issue of cannabis and interventions? What else is out there specific to this issue of loss of appetite and this issue of trying to improve appetite in patients with advanced cancer? Next slide, please. Well, there was a study from many, many years ago, decades ago by Abel and others, which was published in the journal *Nature*. And the goal of this study was to look at various aspects of marijuana. And one of the aspects of marijuana that they looked at was appetite stimulation. It was somewhat of an interesting study. It's actually kind of hard to find it, because it's so old. But what these investigators did was they took some college students or some overall young people, and they gave them marshmallows, which were spiked with marijuana. And they actually assessed them for how much eating they did, how many marshmallows they consumed. And they made the conclusion based on a very small sample size among very young people that as a result of what they observed with either the marshmallows that were spiked with marijuana and these young people were in a room, or another room where the marshmallows were not spiked, they found that the people who were in the room with the spiked marshmallows ate a lot more marshmallows and ate a lot more other food. So they concluded that there is orexigenic effects related to marijuana as they concluded in this particular study. So those sorts of data, again, from decades ago got people to thinking that maybe there's a role for looking at cannabis, or maybe there's a role for looking at THC in patients with cancer with the goal of helping cancer patients deal with this loss of appetite. Next slide. So based on those data as well as based on some single arm studies from other groups, including a group from the Cleveland Clinic, we embarked on the study whose title page is shown here. The study was entitled: "Dronabinol Versus Megestrol Acetate Versus Combination Therapy for Cancer-Associated Anorexia." And, again, I want to say that this was a study that was funded by the NCI. It was funded by means of the cooperative group mechanism, and we're very grateful for that. This was a three-arm study. It was a double dummy design. In other words, patients who received Dronabinol also had a Megestrol Acetate appearing agent that they took at well, although that dummy form of Megestrol Acetate was just that. It was a placebo for Megestrol Acetate. Patients who were assigned Megestrol Acetate also had a formulation that looked like Dronabinol, but was in fact inert. And then the patients who received combination therapy did in fact receive both agents. So a double dummy design performed within the cooperative group setting, multi-institutional and, again, grateful for the NCI for having funded it. One other comment I should say regards dosing. The Dronabinol dose used in this study was 2.5 milligrams twice a day. This study has been criticized because some people say that that's a fairly low dose and that we should have given 2.5 milligrams three times a day. Although I do have to say that the pharmaceutical company that provided the Dronabinol advised us to use 2.5 milligrams twice a day, the dose that was chosen here. The Megestrol Acetate dose was an oral suspension, 800 milligrams a day, which is the dose that we typically use or perhaps a little bit higher than what we typically use for cancer-associated loss of appetite. So a little low on the Dronabinol, a little high perhaps on the Megestrol Acetate. But nonetheless, we used our best judgment at the time that the study was designed. Next slide, please. So these are the baseline characteristics, and to make a couple of points here. This was a fairly large study. A hundred and fifty-nine patients received Megestrol Acetate, 152 received Dronabinol, and 158 received both agents. And as you can see here just glancing down the columns, groups were fairly well balanced by means of randomization and some degree of stratification with regard to all of these baseline characteristics. Next slide, please. So what were our results? So we administered a questionnaire to assess appetite, and our primary goal was to boost appetite in these patients with advanced cancer, all of whom said that they were suffering from loss of appetite. And as you can see here, the percentages of patients who described improvements in appetite pretty much across the board found that Megestrol Acetate compared to Dronabinol, Megestrol Acetate was the winner. A greater percentage of patients assigned to the Megestrol Acetate arm described that their appetite was improved as a result of the agent assigned to them in contrast to what we saw on the Dronabinol arm where the percentages were somewhat less. Looking at the other columns to the right, if you look at the Megestrol Acetate, or I'm sorry. You look at the combination arm and compare that to the Megestrol Acetate arm, you could see that basically there was no statistically significant difference. So adding Dronabinol to Megestrol Acetate resulted in outcomes that were no better than Megestrol Acetate alone. So we saw, for lack of a better term here, some equivalence between the two drugs and the one drug with Megestrol Acetate alone. So basically we did not find that Dronabinol was much of an appetite stimulator compared to Megestrol Acetate. Next slide, please. These are similar data as shown before, but in addition, we looked at other factors such as weight. We also looked at other quality of life assessment tools. Again, these first bars show that the winner arm was in fact the Megestrol Acetate arm. Secondly, compared to the Dronabinol arm, which is the checkered column to the -- the last checkered column. Weight gain was seen more commonly with Megestrol Acetate. Other quality of life indicators seemed to suggest, again, that the Dronabinol arm just didn't fare quite as well. So next slide, please. So our findings were not -- are not aberrant compared to another placebo controlled trial study that was published by Florence Stronser (ph.) and others. This was a study that was primarily conducted in Europe. And these investigators showed very similar results to what we had reported. Next slide, please. As you can see here looking at placebo, looking at cannabis, looking at THC, these investigators basically found that the curves were on top of each other, and there was no statistically significant difference between the three different interventions that were paired with, again, a placebo arm, a pure placebo arm also incorporated into this study design. Next slide, please. Now, in contrast, other studies have suggested that cannabis is more promising. And I don't know if the difference was that we looked at THC and other investigators have looked at cannabis, or if there's something else (unint.) study where a 96% improvement in appetite was reported, but no placebo arm was used. It's just somewhat hard to know how to interpret these data. But nonetheless there seems to be, based on studies such as the one presented or shown here, that maybe there is something going on despite our study results in favor of some anorexigenic factor, some palliation of loss of appetite. Next slide, please. And another study looking specifically at cancer patients showed similar findings, improvement in appetite and improvement in weight. But, again, this was a pilot study, smaller sample size, and there was no placebo arm as well. Next slide, please. Just to make the point as others have done, Jose did it also, looked at clinicaltrials.gov. There are studies going on. There are studies that have matured with results to be reported hopefully in the near future. So this is not an area where there's an absence of research. There's active investigation looking at cannabis and cannabis-type substances to try to help patients who are suffering from loss of appetite or suffering from loss of weight. Next slide, please. So lessons learned. You know, having undertaken a fairly large study with 460-plus patients, I'd like to just describe some of what I personally learned in doing this type of research and also in having done other sorts of studies in this area in the past. So next slide. The first is that healthy people differ from sick people. And of course we know that, but importantly, if an intervention works in a health person, so if appetite if improved in a younger person who is healthy, that might not necessarily mean that a sicker person with cancer can derive similar benefits. And that may account for the negative findings that we saw in our trial. But nonetheless, there might have been other reasons to account for the negative findings on the Dronabinol arm that we reported and the fact that others have reported that cannabis just doesn't seem to be quite as effective as well. Next slide, please. Another lesson learned is the importance of placebo. And in the studies that I pointed out that showed clear benefit from cannabis or from THC, those studies did not have a placebo arm. And the more I do research in this area, or in the palliation of other symptoms, I struck by the fact that we really do need to integrate a placebo into our study designs, or at least some sort of a comparative arm so we have a better sense as to what exactly is going on. Clearly, if -- and there are times that I've thought that I've understood the placebo effect only to learn that perhaps I didn't understand it as well as I thought I did. For example, if you are conducting a study and you're giving an intramuscular injection and you have a placebo arm, will that placebo effect be higher with an IM injection than with an oral type of intervention? And the answer is yes. Similarly, if you have an agent and you're giving it multiple times a day and there's a placebo arm, will we see a larger placebo effect with an intervention that's been given multiple times a day as opposed to once a day? And the answer is yes. Similarly, if you have a five-arm study and one of the arm is a placebo arm and you have a two-arm study and one of the arms is a placebo arm, where will you see the more notable placebo effect? You tend to see it in the five-arm study. So there's something that goes on with placebo. It's not always the same. It varies a lot depending on the circumstances of the study. And as a result, I believe it's important to always integrate placebo into most trials if you can to better understand what's going on. And just one final sort of scenario. If you have an investigator who is supper enthusiastic about his or her study and talks about it and plays it up, will you see a higher placebo effect in that study? I don't think that's ever been studied, but I would submit to you that the answer is probably yes. So a placebo, I think, is extremely important to really understand what's going on with an agent hypothesized to be active and helpful to patients. Next slide, please. I also think that there are some challenges in studying unique substances. So a criticism that had been waged in addition to the dosing issue that I've already mentioned is that, you know, Dronabinol is a synthetic form of THC, and others have said we have to test the real thing. It's very hard, however, to test a unique substance, whether it be a type of cannabis, whether it be alcohol or wine as we've tested in the past, whether it be such a substance such as honey, because patients know what's being tested. And basically, it's very hard to then capture a placebo effect. But nonetheless, there are challenges here with setting a unique substance, but I think that nonetheless one can press on as I believe we did with the study of Dronabinol. And next slide, please.

>> Aminha, we're going to need to jump to your conclusion, so please wrap up in the next minute or so.

>> I will. Thank you. The other point is the pachyderm principle, or the thick skin. So next slide. A pachyderm is a very mammal with thick skin, and I've also thrown some mud into this picture for emphasis. And next slide. So for our study on Dronabinol, a comment came across as a letter. "It seems rather obvious the study's authors believe marijuana is too unhealthy to use as a medicine for advanced cancer patients." This is hard. It's a hard area to study any type of an agent that people really believe works, especially if some populations believe that it works. But I think it behooves us as investigators to be dispassionate and to present our results the way we find them, to present them honestly, and to also be critical of our own findings. So next slide. So conclusions: Loss of appetite and weight are distressing to patients with cancer. But nonetheless, I think we should continue to study ways from any and all sources to treat and try to palliate the syndrome. So next slide. Thank you very much.

>> Thank you, Aminha. Michelle?

>> Hello, and thank you to the organizers for the invitation to present on this topic of cannabis for the clinical side effect management of anxiety. Cannabis to Enhance Wellbeing: A Worthwhile goal. I attribute this title to Dr. David Nutt (ph.). And this is my disclosure. The employment of cannabis for its medicinal, relaxing, calming, and sedative effects has been documented across ancient civilizations. In 1922, Harvey Wickes Felter published the following cannabis monograph in his *Materia Medica* with specific indications of cannabis use for marked nervous depression, insomnia with brief periods of sleep, sleep disturbed by unpleasant dreams, spasmonic and painful conditions with depression. He continues with the quote, "It produces an agreeable semi-delirium, taking on the character of a sense of well-being an exhilaration, a state highly coveted by its devotees who call it loftily: The increaser of pleasure, the laughter mover, the cementer of friendship." We now know of the endocannabinoid system, a highly conserved pleotropic mammalian biochemical system with which THC specifically interacts and has been described as one with homeostatic roles, allowing us to relax, eat, sleep, protect and forget. In this talk, I'll be focusing on the aspects of relaxing, sleeping, and forgetting. A 2009 systematic review noted that anxiety and panic attacks were the most common side effects of cannabis use. Paradoxically, reduction in anxiety is known to be a motivator for cannabis use. To explain this paradox, clinical studies support the biphasic or bidirectional effects of THC showing that cannabis effect on anxiety is dose dependent. And that there may be a likely role for low-dose of THC in breaking some cyclic symptomology that patients experience related to pain or tension, leading to poor sleep, which can then exacerbate their stress and anxiety leading to loss of quality of life, more pain, less sleep and on and on. So there may be a role for THC in helping to break this cyclic symptomology. This graph complies observational data from human cannabis users, illustrating results of seven cross sectional human studies, reporting anxiety relief as an effect of cannabis used for therapeutic purposes. Across these studies, there was an average of 52% of responders reporting for anxiety benefit from cannabis. The numbers above each of the bars is showing you how many individuals were in each survey. Subsequently, there have been studies asking responders about their substitution of cannabis for prescription drugs, finding that the benzodiazepine class of drugs among those and along with other anti-anxiety medications that are being substituted. Subjects reported reasons for cannabis substitution of other drugs as a safer alternative, fewer adverse side effects, better symptom management and with fewer withdrawal symptoms. A prospective observational study reported on the medical necessity of cannabis in cancer care in 211 patients who were issued medical cannabis licenses for disease related symptoms, or side effects of chemotherapy in Israel. Data was collected at baseline and at a follow-up telephone interview six to eight weeks after initiating cannabis use. Outcome measures were the common terminology criteria for adverse events and the National Comprehensive Cancer Network distress thermometer. At six to eight weeks, 50% had continued cannabis use, reporting that all cancer or anti-cancer treatment-related symptoms, including nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching, and pain had significant improvement with the strongest interaction found for depression or anxiety. Additionally, 33% of those who were using anti-anxiety medications and employed cannabis reported that they had discontinued them. The authors conclude the paper by asking the question, "Is cannabis being prescribed too late?" A prospective analysis of safety and efficacy of medical cannabis in 2,970 cancer patients examined the epidemiology, safety and efficacy of cannabis therapy. Patients were followed at one and six months for physiologic and cognitive side effects and a global assessment of self-rated effects. At the one-month time point, 70% of patients were still using cannabis and 66% of these reported significant improvement in overall symptoms. At the six-month time point, 60% of the original cohort were still using cannabis. And among the most improve symptoms were anxiety, depression, and sleep disturbance. Reporting on cannabis administration, high TCH cannabis was predominately utilized wit 72% using more than one chemotype. About one-quarter of these responders reported discontinuing anxiolytic prescriptions. Cannabidiol has been reviewed for efficacy in treating anxiety disorder. An animal showed that there was a biphasic or dose-response effect of CBD in animals using the elevated plus maze. These anxiolytic effects have been replicated in healthy human subjects who were exposed to an acute anxiety-provoking stimuli at 300 to 800 milligrams of CBD. There have been several pharmacologic mechanisms reported to be responsible for these effects, such as at the 5-HT1A receptor as a modest agonist, through TRIPV1 activation, as well as maybe indirect action on the endocannabinoid system through inhibition of AEA degradation of reuptake, and heterodimerization of cannabinoid receptor with serotonin receptor. The utility of these high doses of CBD that may be required for treating anxiety may limit the use by cancer patients due to the potential for direct drug interactions and effects on liver enzymes or other GI effects, all which are relevant for cancer patients. In a recent survey of CBD use, anxiety was reported as the top condition for which participants reported using CBD, and those who reported using CBD for four or more conditions were significantly more likely to report that they were using cannabis for anxiety rather than those with fewer conditions. And those with more than four conditions were claimed to be managing their symptoms using products advertised at a one-to-one ratio of CBD to THC with higher frequency than those with fewer conditions. So in general, these subjects were using cannabis with some THC component, especially those with more symptoms or those who were perhaps sicker. So this THC effect could not really be easily separated from the CBD effect when taken in combination. These data indicate that overall, THC is likely playing a significant role in modifying conditions and symptoms for which this cohort used cannabis. Meanwhile in the United States, hemp-derived CBD products have appeared ubiquitously online and health food stores, gas stations, tobacco shops despite a dearth of clinical trials to build an evidence base for CBD to treat anxiety. And here is just a small example of an online search illustrating the kind of advertising flooding the media. I was involved in the care of a 54 year old male. He was an MD who had a diagnosis of glioblastoma. He was post-resection, radiation and chemotherapy, and now presenting with leptomeningeal metastases. He told me he had always been a workaholic with chronic insomnia for a lot of his life, and currently he is really suffering with significant anxiety and still the insomnia, but not pain. His primary medications were Ativan and Ambien, and he said he was using Oxycodone for sleep, but since he had no pain, I had him discontinue that at bedtime and add in a dose of THC at bedtime. And he wanted an edible during the day, so he had a chocolate bar with about five milligrams serving. And his wife reported with the cannabis he is more lucid and cognizant. His caregiver reports it keeps him calm and he is smiling more. He says it relaxes him and helps his anxiety. And he said to me, "I'm wondering why everyone is not using cannabis." Research on the effects of cannabis on sleep began in the 1970s, resulting in mixed findings, supported by a recent review reporting that overall, the varying of doses, small sample sizes, lack of validated outcome measures and failure to control for other variables limited conclusions. The National Academy's report in 2017 concluded that there was moderate evidence for small improvements in sleep quality and sleep disturbance across eight trials. These trials primarily used the (unint.) smalls and sleep was not a primary outcome in the studies reviewed. CBD, meanwhile, has not been shown to alter sleep architecture or have significant impact on other sleep outcomes when it was given at 300 milligrams. In other studies, CBD has been shown to be alerting at low dose, and so in my practice, I don't typically use CBD for sleep because THC has been shown to modulate sleep architecture in a beneficial fashion. In one study for obstructive sleep apnea, they were given -- subjects were given 2.5 and 10 milligram doses of THC with 10 milligrams associated with greater satisfaction, reduction in the apnea-hypopnea index and improvement in self-reported sleepiness. In clinical practice, sleep improvement is a common report to us and associated often with reduction in the use of other sleep medications. Definitely need for a better controlled and a larger-scale and longitudinal trial to give patients more information about this. But meanwhile, a potential pitfall for patients is another unsubstantiated claim, such as this advertisement of CBN or cannabinol, which is a degradation product of THC. And a friend of mine did a recent review of this evidence and there is no evidence to support this claim. So this may just be an attempt on the part of manufacturers to get rid of old and degraded cannabis. Another indication for cannabis in cancer care patients is suppression of aversive memory. PTSD is common in patients with life threatening medical diagnoses, and is comorbid often with panic disorder. And PTSD has been associated with low endocannabinoid tone or reduced levels of AEA and 2AG compared to controls and thus impaired stress resilience. This manifests as high anxiety, hyperarousal, avoidance of cues such as not wanting to think about their cancer, their next scan or doctor visit, intrusive thoughts, nightmares. And agonists at CB1 receptor have been shown to have value in suppression of these aversive memories and the anxiety that coexists. A recent review of 22 studies suggested that THC when used in low dose or in combination with CBD is without significant adverse effect and interferes with aversive memory processing, facilitating aversive memory extinction. So now we're going to talk a bit more about botanical cannabis, the minor cannabinoids and terpenoids. The minor cannabinoids have yet to be studied for mood altering effects in humans, but there are potential mechanisms such as cannabigerol or CBG as an agonist at the alpha-2 adrenoceptor or a blocker at the 5-HT1A receptor, which may be a strategy for augmenting other antidepressants. It's also been shown to be a partial agonist at CB1 and 2 receptors. And one study found it to inhibit anandamide reuptake. And despite evidence of efficacious dosing or outcomes in humans, the marketing of CBG has already begun in earnest. Cannabichromene or CBC was reported to be a CB2 receptor agonist. So this could be a very interesting approach for treating anxiety through anti-inflammatory pathways. The first in vivo data on these minor cannabinoids was recently published using the classical tetrad model developed by Billy Martin's group here where they added on the open field maze as a measure of anxiety-like behavior. And this data illustrates -- if you look in the first graph, the green line is the effective THC compared to the other minor cannabinoids. You can see that they had significantly less robust effects on this arm of the testing than THC did. The cousin compounds to the cannabinoid class are the terpenoids or the essential oil component of the plant. Terpenes and terpenoids are volatile, odorous secondary plant metabolites. They're found across aromatic plants and used in botanic medicine and aromatherapy. These compounds are generally recognized as safe by the FDA as flavoring agents with some exceptions, considered to have high bioavailability when inhaled or applied topically, but their bioavailability is reduced when ingested and have significant first-pass effects. This is a representative certificate of analysis from a THC predominate cannabis chemotype showing myrcene, caryophyllene, linalool and alpha humulene as the primary terpenes analyzed. Patients report this chemotype to be anxiety reducing and mildly sedating when inhaled using a vaporizer for raw plant material. The benefits of this delivery are the rapid effects and direct delivery of both the terpenes and cannabinoids and avoiding first-pass effects. The terpenes synergized functionally with cannabinoids through receptor targets that are not cannabinoid receptors, such as myrcene, which has been shown to have muscle relaxant and sedative effects, but in fact may produce anxiety at higher doses. We have beta-caryophyllene, a sesquiterpinoid common to many cannabis chemotypes and considered to be a dietary cannabinoid found in oregano, cinnamon clove and black pepper. It's a CB2 receptor agonist that has been looked at for its anti-inflammatory action and in animal study suggested to have anti-anxiety effects. Linalool is found primarily in lavender species shown to potential GABA A currents. When inhaled, it has produced anxiolytic effects in mice and taken orally in humans that had a 36% linalool component, reductions in the Hamilton anxiety scores of the participants. So lavender oil in itself may have some therapeutic benefit. Humulene or alpha-caryophyllene is found in abundance in hops, clove, and ginger, thought to be antioxidant, but also some data suggesting a chemo preventive and anti-proliferative effect. There are other terpenes, mono-terpenes with potential mood altering effects. Terpinolene or delta-terpinene has been shown to have sedative and anti-hyperalgesic effects in mice, proposed to be mediated by the 5-HT2A receptor. Limonene is a mono-terpene with high bioavailability orally, shown to have anti-depressive and anti-stress effects in mice with potential mechanisms at GABA A receptor or by increasing serotonin levels. One study in hospitalized human subjects demonstrated improvements in depression with limonene was infused into their hospital room. The so-called whole plant preparations may be a misnomer as various extraction processes will extract, change or potentially lose some of the compounds. Here are results from a super critical CO2 extraction of cannabis showing the loss of mono-terpenes in this extraction process with the exception of linalool. These were five different cannabis chemotypes. You can see there was increase in the potency of the heavier weight terpenes and about a four-fold change/increase in the cannabinoid fraction that's now shown here. So the current practice in the industry is just to add these terpenes back in. You can purchase these terpenes online individually or in mixtures that are called after the name of a chemotype. But there is a potential pitfall for these patients when terpenes are added back, such as this one, which is actually labeled to be essential oils, a mixture of different essential oils that have had THC and CBD added at an isolated compounds. These products can be highly sensitizing to older patients, patients who have had chemotherapy and radiation and the safety of ingesting these large amounts of essential oils is not demonstrated and in fact can be toxic. So how should cancer patients utilize cannabis? Does the type, administration form matter? In this follow-up study to the two previous studies on cancer use in cancer patients from Israel, it's described how 108 patients arbitrarily chose their products and the researchers compared effectiveness at one month. There were basically three chemotypes available. They could be used via inhalation or oral administration, and they found that those using THC dominate chemotypes were more likely to be inhaling while CBD dominate or mixed chemotypes were used orally more often. At one month, they measured significant improvements regardless of the chemotype or administration form in weekly pain intensity using a numeric pain score, sleep quality and duration using the Pittsburgh Sleep Quality Index and distress using the Memorial Symptom Assessment Scale. Their conclusion was that there was a lack of differential effect based on the chemotype or the administration form, and that there's really no added benefit or therapeutic value for having more THC except potentially for sleep duration in the group using the high THC dominate chemotype. In her book *Dying to Get High,* Wendy Chapkis documents what she calls the messy terrain of people living and dying with cancer and using cannabis to navigate. In direct quotes from some of the subjects they report, "A present-tense focus. May not feel altering so much as enhancing in the context of terminal illness." "It produces a positive shift and I can go on to something else." "It stops the fear. It stops the worrying." "I don’t think there's anything wrong with dulling the reality of my situation." So might we conclude along with Dr. Chapkis that this consciousness altering property of THC is actually directly related to the medicinal value. So perhaps when patients are finding these brief flashes of being in the present moment, of relaxing and forgetting or what might be considered euphoria in a healthy subject is simple a sick person coming back to baseline, experiencing a moment of gratitude, which has been described by the psychologist David DeSteno as allowing us to notice symptoms less, enhance well-being, and reduce the stress of chronic illness. So in conclusion, about half of people using cannabis for therapeutic purposes are reporting anxiolytic benefit. There's been a long documented history of this use. THC has dose dependent effects on anxiety with low dose being anxiolytic while increasing doses may generate anxiety. CBD has some anxiolytic potential not yet studied in non-healthy subjects, but the dose required may limit its use in cancer patients. Minor cannabinoids really we need data on these, especially for dosing or any potential efficacy in humans. The terpenes are bioactive, acting synergistically and may be contributing to the overall effects. And low potency THC cannabis is serving cancer patients well. Thank you for your attention today. This is my email address if you're interested in any of my references or have any further questions.

>> Thank you so very much, Michelle. So if we can please have Dr. Carey Clark. Thank you.

>> All right. Wow. So excited to be here and honored to be able to talk about the clinicians' role in medical cannabis care. I have probably logged hundreds if not thousands of hours talking to nurses, particularly oncology nurses and holistic nurses about their role in medical cannabis care. But my plan for today is also to really focus on advocacy. So I'm going to try and relate a lot of what I do to our role as advocate, and it's super important. Our oncology patients need us to act as advocates. All of the patients that could benefit from medicinal use of cannabis need us to act as advocates. I'm also going to talk a little bit about education, particularly some of the research I have done with nursing students and what they know about medical cannabis and what we could do differently. And then I will jump into issues around practice and what do we need to consider as clinicians when we're out there in the practice setting. So next slide, please. All right. So conflict of interest. I wasn't totally sure these are conflicts of interest, but close enough. I'm the editor and author or a book called *Cannabis: A Handbook for Nurses.* It's actually being published by Walters-Kluwer. It's coming out in January 2021, and in that book, we cover the six essential areas that all nurses need to understand in order to work with medical cannabis patients, and we're super excited for that to come out. Part of the proceeds of that book go to American Cannabis Nurses Association where I'm the immediate past president. It was a labor of love to bring that forward, and it's a book for nurses written by nurses, but we also plan to use it in our medical cannabis certificate program at Pacific College of Health and Science where I'm the chair and I helped to develop the majority of that curriculum, which now we have several hundred providers from nurses to doctors to pharmacists to -- we even have a track in the medical cannabis certificate program now that if people do not have as much of a medical background, they can also look to getting a certificate as well. So next slide, please. All right. So yesterday, hopefully you were here yesterday, and you've been able to absorb so much of this great information that's being brought forward to us. The Pergam et al. I really this is a seminal article that came out in 2017. It was great to hear Dr. Pergam speak yesterday. But in this study, they looked at over 927 patients, so a big study, and it was in a major medical center. So it was in Washington State where they have both legalized medical cannabis and adult use cannabis. So patients had access to cannabis. And what they found was that 74% said they wanted information about cannabis from their healthcare providers. That's you. That's me. We're down there working with them in oncology settings or even in primary care settings, but only 15% are actually getting information from healthcare providers. Oh, dear. And the study goes on to look at how did patients actually use cannabis. And I'll let you read that for yourself, but I want to say that we are ethically obligated to educate ourselves so we can educate and support our patients towards safe and effective use of cannabinoids. And why do our patients turn to cannabinoids anyway? We've been hearing all about, well, we've started to get some research. There's a little bit of evidence. Maybe the evidence isn't that strong. We know it's strong around pain, but maybe it's not that strong around chemotherapy-induced nausea and vomiting. Well, they were using because they are not satisfied with their emetogenic care and their palliative care. So one thing to think about as clinicians is palliative care begins when? It begins with diagnosis, right? So when they have these really intense treatments that they're going to be getting, we don't want to push palliative care off toward the end. We need to start it upon diagnosis. Even considering that, about around 80% of chemotherapy patients will experience some adverse effects. That number is huge. So patients are turning to cannabis because they perceive anyway, and who knows? As we've been discussing today, the true effects until we really get those really great RCTs, but they're perceiving that it's helping them. And that's another thing I would say is we need to have really patient-informed evidence-based practices, right? So we have these great trials, but we also need to be listening to patients and seeing what works best for them and considering that to actually be evidence. There is so much data out there on patients' experience, oncology patients' experience with use of cannabis that strong points toward effectiveness for palliation. The problem is is that we tend to call it anecdotal data. It's out there. It's on the Internet, right? But we call it anecdotal data, and in some ways, to me that sort of belittles the patient experience. I really appreciated hearing from Stacy yesterday and her sharing her experience to bring that in. But we need to be, I think, really careful about, you know, calling data anecdotal data and that maybe it's not that great. I prefer to call it qualitative data. That's the patient experience data that's out there. It's qualitative in nature. We just need to be able to analyze it a little bit better. But we also know that there's a lot of clinical costs to poorly controlled chemotherapy-induced nausea and vomiting and other related chemotherapy adverse effects like we heard about today, the peripheral neuropathy issues. And these poorly controlled symptoms impact patient adherence and completion of their treatments. So they're very costly in many ways. Okay. So that kind of sets the stage for us to really start advocating for education of providers. So you're here. You're probably, if you're a provider, you're really interested in educating, coaching and supporting your patients towards success with use of cannabis to palliate their oncological treatments. But we also need to advocate that every provider that's interacting has this sort of information. So let's go onto the next slide. All right. Here's a book I'm going to recommend. So one of the challenges that I see for clinicians around advocacy of course is prohibition and then there's also a major issue that is coming to light with systemic racism. This is a book that we use in our program at Pacific College. It's by Johann Hari. It's called *Chasing the Scream*. It's about the first and last days of the war on drugs, that failed war that you've probably heard so much about. Okay. So some things to consider here as we are advocates. This book will help you understand how we got from cannabis being truly a first line treatment, and Dr. Braun (ph.) talked a little bit about this yesterday. But you could go down to the corner pharmacy and get your cannabinoid medicines and you could use them for that headache or for nausea and vomiting, or whatever reason that you had to use them. And as the prohibition era started about a hundred years ago, obviously that became no longer true. So this book really walks you through it in a way that's really readable, in a way that brings human aspect to it, that provides the stories and also provides you the content that -- it may also motivate you to be more of an advocate and to make sure that patients have access to medical cannabis regardless of whatever zip code they're in, right? So there's patients right now in Idaho that have access to no medical cannabis legally, no CBD. They may be going over to Nevada or down over across to California, right, to access their medicines, because patients are going to use cannabis whether or not it's legal. Okay. So that's one recommendation I have for you to really have a good basis, and I do see that oftentimes people miss this basis of prohibition and really understanding it and the systemic racist roots around prohibition. Another good recommendation I have for learning more about racism and addiction is Dr. Gabor Mate, and you can find his books and his great stuff on YouTube. And I really think that these two things should be accessed by everyone who is interested in working with medical cannabis patients. I think both of them also bring forward the question of what is addiction, right? I saw in the chat earlier Dr. Bonnie Goldstein mentioning that patients that use cannabis medicinally tend to not have cannabis disorder. So perhaps it's not as big of a concern when we're talking about medical cannabis as when we're talking about adult or illegal use cannabis. I would also say though that patients may develop a tolerance to medical cannabis. They may or they may not, and they may actually, even if they're using -- starting low, going slow and then they need to make some changes or they decide to take a cannabis break, they may have some withdrawal symptoms, which generally are about the same as caffeine withdrawal symptoms. If you've ever tried to withdraw from caffeine though, I would not poo-poo those. Those can be really big symptoms, headaches, nausea, inability to sleep, tearfulness, mood swings, all those sorts of things. All right. Let's go onto the next slide. So I want to share the story of Fate Winslow. But first, I'm going to give you some statistics. I'm scrolling down to my statistics on my own notes here. So according to the FBI in a published study in 2018, in the year 2017, so I believe this is the most recent data we have, there was one arrest for cannabis every 48 seconds, greater than for heroin, cocaine, synthetic drugs and other non-narcotic dangerous drugs. Cannabis arrests equal 15% of all drug arrests in the USA. Forty-percent of those are for -- of all drug possession arrest are cannabis related. There was an upward shift. So even as we're moving to this era of ending prohibition, we are seeing huge issues still around cannabis arrests. So there was an upward shift. In 2016 there were 653,249 arrests for cannabis in the United States. And then in 2017, that number jumped up to 659,700 arrests. So even as cannabis is becoming legal in places like Colorado, there's more arrests. And in the USA, 4.5 million people are on parole or probation, twice the number of people incarcerated. So that's a huge population. One-third of these folks will be sent back to prison due to parole violations often related to cannabis use. Now, there are some states like California, Illinois and New York and I think also Missouri who are working to expunge thousands of cannabis convictions from records. There's also the MORE Act, which we heard a little bit about yesterday that would help in that area. But if you take a look at your scope and standards of practice, we are called to be advocates, right? And we are called to advocate for vulnerable populations. And we need to get on the ball with that, right? We need to be doing advocacy locally, at your state level, and at the federal level. And I can guarantee you right now, if you go out there and look at your state medical cannabis laws, there's room for improvement. Almost every state has room for improvement in their medical cannabis laws. And so how do you do that? You do outreach. You align with other organizations, and we can talk a little bit more about that. But I wanted to share with you the story of Fate Winslow, and I'm glad we've had his picture up here for a little bit so that you could see this man. In September of 2008 he was arrested. He was homeless at the time. He had about a dollar in his pocket, and he was looking to get some money so he would have food to eat. He ran into a person who was looking to buy some cannabis and requested $20 worth of cannabis. Fate went to another person who happened to be a white person that was a dealer in the area, secured the cannabis, brought it back to the person that was buying the cannabis for the $20. He went back to the dealer and gave them the $20, and he got a net of $5. Unfortunately, it turns out that that was an undercover cop, and Fate was put into prison. He was tried and convicted. The convicted was ten to two, so ten people voted that he be convicted. Here's the problem now. The white dealer served no time at all, and Fate has been in prison since 2008, serving Angola prison, serving a life sentence with hard labor for this deal of this small amount of cannabis. The reason for that was that he had several prior convictions mostly related to burglary. I reached out to Fate Winslow over the summer. I got to know him a little bit. I was emailing him in prison. He was able to be connected with the Project Innocence group. And he emailed me October/November and he was very, very concerned about COVID in Angola; I mean, frightened. That was his biggest fear and just wanting to get out. And I have some amazing news to share with you. I'm breaking it here. I still haven't seen it in the news yet, but Fate yesterday was granted via video trial time served on his conviction, so 12 years for this $20 worth of cannabis that he got $5 from, and he said he would be leaving Angola this morning from prison. So I'm super excited about all the work that people have done around this. And there's many more people like Fate. So as clinicians, I know you're busy and all that, but let's get involved and let's help those in need and not forget about them, the people that are suffering. So it's super exciting that we have made some leeway with Fate. And you can also -- I guess there's a movie about him. I posted this on Facebook and somebody said Amazon Prime has a movie called *Fate* that came out a couple of years ago, so I hope you'll watch that too, and hope it motivates you as well, that we can begin to end the systemic racism around incarceration, and that is one of our roles as cannabis clinicians and just as clinicians in general because we care for vulnerable populations. All right. Next slide. Okay. So now I'm going to switch gears a little bit here, and we're going to get into the National Council of State Boards of Nursing six essential areas for knowledge for healthcare providers. So I really think these are universal areas. So this is -- although it's nursing, I know many of you here are not nurses, but I also know there's a lot of nurses here as well. These can be applied and should probably be adapted by every professional group out there. I saw the chat yesterday that the pharmacists in California are trying to make it mandatory that this sort of information is included in all of the pharmacy schools in California. That sounds like a great idea to me. So the National Council of State Boards of Nursing published this great article in the *Journal of Nursing Regulation* in 2018, and they said all nurses need to be educated in these six areas. So you've got to know your current state of legalization of medical and recreational cannabis use for your state. You should also have working knowledge of jurisdiction's MMP. That stands for the marijuana policy in your state. The nurse shall also have an understanding of the endocannabinoid system, cannabinoid receptors, cannabinoids and interactions between them. The nurse shall have an understanding of cannabis pharmacology and the research associated with the medical use of cannabis. The nurse shall be able to identify the safety considerations for patient use of cannabis. And here's my favorite one as you may have guessed already from my talk, but you need to approach patients without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms. So whether the evidence is there or not, you've got to support the patient and work closely with them. And, again, as I said, I think these can be adapted for other professions, and so onto the next slide. Now, I have the joy of sharing with you some research that I did with Ms. Rachel Parmelee. Rachel Parmelee is a PhD student getting her PhD in education. She's going to focus specifically on cannabis care education, and she also teaches for us at Pacific College of Health and Science, and she's the current secretary of American Cannabis Nurses Association. And her name is first, because she's doing a lot of the heavy lifting here, and I am guiding and supporting her. But we did a survey, a national survey of nursing students' knowledge, skills and attitudes regarding medicinal cannabis care. We're still in the process of writing this up, because we were also finishing the textbook this year, but we're hoping to submit it for peer review coming up. We have an IRB of course before we did this. So hopefully by January we'll have this submitted. So we looked at all levels of education. We started with a pilot in August of 2019 and finished collecting data in March 2020. Where did we get the data from? Well, we put a lot of stuff on social media, and then we invested a little bit of money. We had no funding, but we invested a little bit of money and we were able to get access to the National Student Nurses Association. And they sent out our survey multiple times. We actually had about 1,500-some odd that completed the survey or that did parts of the survey, but only about 1,346 had actually completed the survey. So if you think back to those areas in the National Council of State Boards of Nursing, what we asked the participants to do was to rank themselves on their agreement of whether they have knowledge in these areas. So 70% said they have knowledge of the law in their state, and 38% said they had knowledge of their jurisdiction. So I think law also includes federal law as well. Now, some of these numbers are a little bit surprising to me, but I think the next couple of slides might explain them a little bit. So the endocannabinoid system, 31% felt they had some good knowledge; research, 33%; pharmacology, 32%; safety, 31%, and being able to approach patients with that nonjudgmental attitude. As we all know nurses tend to be ranked in very caring and compassionate, ethical approaches. So that was around 93%. Next slide, please. Okay. So here is -- and I just pulled a few things out from the survey. I don't think we would have time to cover everything. But here was the survey question. My nursing school educates nursing students around managing care for a patient using medical cannabis. Strongly agree 2%. Agree 5%. Oh, my gosh. We only have like 70% that really feel they're getting the -- or I'm sorry, 7% that really feel they're getting the education they need around managing care for medical cannabis patients. And 20% said they neither agreed or disagreed. But here we go. Seventy-four percent either disagreed or strongly disagreed that they're getting this information in nursing school. And I'm thinking back to yesterday's chat, and somebody said, "Well, it's not that big a deal, but students aren't really educated around the endocannabinoid system." Of course, that’s their opinion, but I do think it's a [AUDIO DROP 02:07:42-02:07:50] we're not teaching it in school, so next slide, please. So okay. Those two slides didn't quite match up, right? They said they knew about the endocannabinoid system and pharmacology and about the latest research. So where are they getting it if they're not getting it in school? So here's some news. Sixty-two percent are getting it from the media and the news. So that is a problem. And why would that be a problem? Well, there was a study that [AUDIO DROP 02:08:21-02:08:33] with Twitter data, emerging topics and social bots. And that was in the *American Journal of Public Health*. And they found that there's many unfounded claims regarding the health benefits of cannabis. These gets posted regularly on Twitter and other social media platforms, but oh-oh, it often happens to be bots that are posting misinformation. But this is where patients -- sorry about the video there. Okay. Hopefully my video is showing. If not, it will pop back. This is where it becomes very concerning. A lot of this information looks really legit. It may not be. Forty-five percent are getting information from research articles, which is great. Twenty-eight percent are getting information from patients. That's good. We want patient-informed practice. But where are patients getting information from? They're also getting it from the Internet. So it's very concerning that there could be a lot of misinformation going on. We can see as we go down here, none of the above, and then they're getting a little bit maybe in clinical or class lecture or an assignment or required reading, but they're just not getting the information they need. I'm very hopeful that having a textbook available for nursing faculty will help to support them in including this information in their curricula. All right. Next slide, please. Okay. So I want to talk a little bit about moving forward and that whole role that I promised that I would talk about. So there is an article that I wrote that is in *CJON,* the *Clinical Journal of Oncology Nursing*. It's called "Medical Cannabis: The Oncology Nurse's Role." Sorry about that, and patient education about the effects of marijuana on cancer palliation. I believe the publishers wanted me to call it the M word. So that role really gets specifically into the nursing process. The nurses here, if you haven't read it, read it. Anyone else who is interested, read it. I talk a lot there about this process. So what do we need to do when we assess patients? So we need to firstly use motivational interviewing and coaching. So what is motivational interviewing? It's an evidence-based approach where we partner with the patient in a change process, express acceptance of them. Doesn't that remind you of the NCSBN requirements? Communicate with them. Listen, guide them, and empower people toward change. We ask open-ended questions. We affirm them. We give them, you know -- we recognize them as being strong people who can make changes, and we reflect back to them. Another technique to use when working with patients is coaching. So coaching provides a sense of accountability, right? They have someone they're accountable to. It provides a connection. And, again, back to that belief and that person. And someone who kind of -- I'm a runner, and I've had a lot of coaches back when I was younger. Someone that runs alongside you on this journey, that's what a coach does. And they educate and they support and guide you. So during assessment, we want to look at their current palliative regime. Of course, things like do they have drug/drug interaction potentials. What is their past and current cannabis use and experience? Have they had cannabis use disorder or other distinctions? What are their finances? This is so important. Cannabis is an expensive medicine. I've talked to families. I met a nurse at a conference once. Her family was spending $900 a month supporting their loved one who was on hospice with cannabis use. So do they have a baseline knowledge of cannabis and the endocannabinoid system? What kind of support systems do they have in place? Do they the knowledge of the holistic modalities that upregulate the endocannabinoid system? And this is one thing that, you know, I emphasize so much with nurses. It's we are not just cannabis care nurses. We are holistic nurses. And in order to support patients to use the lowest amount of cannabis that will be effective for them, they also need to be doing things like acupuncture, massage, osteopathy, changing their diet so that they have more flavonoids, have a better balance between omega-6 and omega-3 fatty acids, and all the other things that diet implies. A great article on all those holistic things that upregulate the endocannabinoid system is the Partland et al article that goes into the care and feeding of the endocannabinoid system. So what are they doing around that to upregulate that? Spiritual concerns. Cannabis is one of the few things that we have out there as a plant medicine that can actually help to support our spiritual needs and our spiritual healing. And I don't think I've really hard that mentioned yet in this conference, but that is something we should be discussing with our patients. And, of course, knowledge of the law and process in their state and how to get a recommendation. But in the assessment process, we also want to be using motivational interviewing to assess their goals. One goal we hear a lot is, "I want to feel better, but I don't want to get high," right? So if that's one of their goals, we need to be supporting them with that. In nursing we then set a variety of nursing diagnosis, which can include everything from sleep pattern disturbance to pain to knowledge deficit and spiritual distress. We need to then support them with a plan. If they don't have the recommendation yet, how are they going to get it? How are they going to access medicine in their state? In Maine there's multiple different ways for patients to access medicine. They can go to medical dispensaries. They can grow it themselves, or they can have a caregiver grow for them, and every state is different. So they need to have a plan around that. Again, the finances. How are they going to manage any side or adverse effects? And how are they going to track their medicine?

>> And Carey, we're going to need to wrap up soon.

>> Okay. Great. So using a cannabis diary can be really helpful with that, and teaching them how to use that. And then continuing to work with them as they start using the medicine and continuing to address all of those things. Some challenges we have moving forward, and then I will wrap up is with self-titration and selection of delivery methods and some of those other things. I really like the MacCallum and Russo article from 2018. It has a very clear structure on how to start low and go slow with medical cannabis. I like Dr. Sulak's website, healer.com. It has great information for how patients can start using cannabis safely and effectively. We need to do more research around prohibition issues. We need to address this of lack of qualitative analyses of the anecdotal data that's out there. And we need to make sure that patients aren't misinformed and that other caregivers aren't misinformed. And then the last slide, please. These are just some references. It does give you that link, which you can download for free for the NCSBN guidelines. And it looks like everyone's doing thank yous. So I want to thank Pacific College of Health and Science where we have the medical cannabis certificate program and their belief that such a thing was possible, American Cannabis Nurses Association, all of my friends and colleges there, my co-research on the student data, Rachel Parmelee, American Holistic Nurses Association that's hosted me at multiple conferences to spread the news amongst holistic nurses, and there's actually a chapter now in the newest edition of that holistic nurses handbook that I co-wrote about sacred medicines, Oncology Nursing Society that brought me out to start teaching oncology nurses starting about 2017 and I've been doing it ever since. There seems to always be a need for it. Walters-Kluwer for publishing the textbook. Dr. Dustin Sulak for setting me on this path and getting me informed about the endocannabinoid system and all things medical cannabis, and then Dr. Alexis Bakos for inviting me and the whole committee for inviting me. Thank you.

>> Thank you so very much, Carey. I'd like to bring all of the panelists back up again. Thank you very much. So before we address some questions from the audience, I'd like to ask each of our presenters on this panel, now that you've heard an overview of the current science on the clinical management of symptoms and treatment side effects, what do you see from your own perspective as a major challenge, and how do you think that this could be addressed? So maybe I'll start with you first, Mark, since you led us off.

>> Sure. So I think it's clear that we need more research in cannabis and cannabinoids. And one of the roadblocks is the regulations. So we need to change regulations to allow more research. But there's also the challenge of -- whenever I speak on this topic, I get questions. How do I dose this? How do I use it in my clinical practice? It's difficult for me to give recommendations when they're outside of California, because due to the federal regulations, it so highly variable from state-to-state that I really can't give them. Okay. I don't know what your source of cannabis is. So we need new regulations to allow more consistency across state lines so we can know what we're giving our patients.

>> Thank you very much. Jose?

>> Yes, thank you. I think, you know, after reviewing and listening to all the talks, I think that a major challenge remains, you know, to do a well-designed clinical trial that can advance the field and provide, you know, evidence-based data for practitioners out there. And that would include taking into account the standard of care for whatever indication we're talking about, being anorexia, pain, nausea and vomiting and looking carefully at this specific population that we're looking into it and of course paying special attention to safety and drug interactions.

>> Okay. Thank you very much. Aminha? Oh, I think you're on mute still. Thank you.

>> Okay. Thank you. I think that's a great question, and I acknowledge that really any type of clinical trial has its challenges regardless of what the focus would be, regardless of the intervention. But I think that under these circumstances, if we have patients with cancer who are using these agents or who want to use these agents, I think it behooves us to do the research. And as Jose was saying to actually think about it and design a really good trial and to move forward. I mean, patients need the information. They need the data so they can make their own decisions.

>> Thank you. Excellent. Carey?

>> Hi. Thank you. So I agree so much with everything that's already been said. Again, I've got to put a plug in though for more qualitative research for our patients and their experience so that we can really have, you know, a practice that's informed by the patient as well and not forgetting about that patient voice. And really being able to gather that data and analyze it I think is really important. And then, of course, you know, truly ending the prohibition era. So moving into a stage where we have access to high quality medicine and can do the kind of trials that are being done in other countries, but also that I think we could do really well, and of course, patients having access. So right now, it's zip code dependent, what kind of access you have, and that really needs to change.

>> Okay. Thank you, Carey. Michelle.

>> So I agree with what Dr. Wallace and Carey have said. I think that the wide availability for many patients, of just a plethora of preparations makes it really challenging for researchers, number one, to reproduce maybe what we're seeing clinically, because we don't have the access to the same products for study, and also that they're out there self-experimenting. The wild claims being made by these producers and manufacturers that are not really being censored I think could bring harm to patients. And also I really agree with Carey also about using patient-reported outcomes. I think cannabis is a powerful botanical medicine that has really important implications for palliative care and that the patients should be who we are listening to.

>> Wonderful. Thank you so much, Michelle. Thank you all of you. I'm now going to go to some of the questions that have been posed to the panel. So, Aminha, the first question is for you. This question is, "What are the side effect profiles of the Megestrol Acetate and Dexamethasone and the side effect profiles of cannabis comparatively speaking?"

>> You know, in our study, the Dronabinol study that I mentioned, the adverse event rates were quite low, at least those adverse events that we could directly attribute to the intervention. And it was really in the range of less than 10% of patients had a major adverse event. I mean, you know, Megestrol Acetate, it's sometimes known for causing blood clots, but really the rate is quite low and, you know, similarly with Dronabinol. The dose that we use, there was a lot of concern about patients getting confused, especially as we were likely going to be recruiting an older population, and we really didn't see that. And we did check for that, and we did look for patient-reported outcomes on these adverse events, and we didn't see it. So actually both were fairly well tolerated.

>> Okay. Excellent. Thank you. This next question is for Jose. "To understand this, could you please talk about and say to" -- I'm sorry. "Tell me, what do you say to a patient to whom you prescribe an antidepressant?" They start with which dose. They determine the initial dose without any information about doses, and they want to understand -- the person who poses this question wants to understand your method of prescribing.

>> Yes, thank you. So my practice is probably different than most of the practice in the U.S. in the sense that I work at a VA hospital. And so we have mental health providers embedded with each team. And a lot of our patients already have a mental health provider, a mental health diagnosis, and so I traditionally do not prescribe antidepressants myself. I refer them to the mental health provider on the team for them to manage this. Oftentimes, I do have to take into account the potential side effects of the other medications that I have prescribed, and how they can potentially interact with antidepressants. And so I usually reach out to the other mental health providers myself if I have a question as to whether they need a dose adjustment, for instance, or if a potential side effect of my intervention -- so just to give you an example, a patient with a history of bipolar disorder who may experience now euphoria and will that need, you know, a closer follow-up to make sure that I'm not precipitating something that is underlying, like a manic episode. So that's my personal approach.

>> Alexis, I'm going to ask Michelle, because there seems to this whole -- there's been a lot of comments on access and -- Michelle, can you share with the audience, because California has a quality control system set up with the Bureau of Cannabis Control. Can you share with him what you do to assure patients are getting what we want them to get and the dosage that we want them to get?

>> Well, I mean, there's no 100% assurance. I mean, many states have required quality control testing, and this is above and beyond any testing that occurs for any other dietary supplement or botanical medicine. So cannabis is being scrutinized much more highly than other, you know, supplements people are buying over the counter. You know, that's one thing I explain to patients, that it is being quality controlled tested for contaminants, pesticides, microbial fungal contamination, and then the potency. So to the degree that we can feel confident in the laboratory analyses, which I know in California, you know, they have taken steps here to ensure the competency of these cannabis analysis facilities, as well as in other states. And so they are supposed to come accurately labeled for potency. And so really all we get is the THC/CBD potency. It is really confusing for patients though, because sometimes what the label says is very inaccurate in terms of dosing. For instance, saying take this every two hours when it's an oral, you know, compound. And so at two hours, they may just be starving to reach a T max level, and you really wouldn't want a patient to be dosing again in two hours. So this is where it becomes very frightening, I think, for our patients when these products are being allowed to be sold, but they don't have to comply with other types of labeling for supplements. So on the one hand, we have better scrutiny, but in terms of the labeling, not quite as good.

>> Thank you, Michelle, and thanks for that as well, Mark. Jose, someone has just chat in I think just to stick with you for a little while longer. The question is, "Are you able to prescribe cannabis to your patients at the VA?"

>> Right. I was actually responding to that on the chat, so thank you for (unint.).

>> We all want to hear it.

>> So the VA facilities are considered federal facilities, and so I do not prescribe cannabis at the VA. I can prescribe the FDA approved cannabinoids, but not cannabis per se.

>> So let me just make a comment on this issue of prescribing. It's actually against federal laws to prescribe cannabis. Now, there's a difference between prescribing and recommending. So we as physicians give medical recommendations. However, now, what we're doing at UC San Diego, are we crossing the line, because we're actually telling them this is what you ask for, what ratio. This is the amount you take every four hours. We're giving them all of this. And I guess we're even writing it down, but the only difference is is a prescription is when you prescribe it, you write it down, they take it to a pharmacist, pharmacists dispense. Well, we're writing it down. They're taking it to the dispensary, and the dispensary is saying, "Yeah, okay, this is what you want," and they go to the shelf and they give it. Am I right, Michelle? I mean, sort of? I mean, we can't be 100% sure that the dispensary is giving them what we're telling them, we're writing down for them, but I think we're getting close.

>> All right. Mark, there's a question here for you. I'm going to try to read this as best as I can here. So "What are the basis for self-titration?" It says here, "We physicians are not doing this with any other treatment, even though we take into account patient's information about how the treatment goes. Is it because prescription as you say is under federal laws and you haven't still legalized it at the federal level, perhaps because we still have not enough substantial or conclusive evidence about the efficacy related to ranges of doses for the majority of potential indications or any other reasons?"

>> Yeah, I answered some of that in my last one about the prescribing and things. So I think I want to make it clear. When we were talking about self-titration, the point I was trying to get across is that in medicine, when we do therapeutics, when we use pharmacological therapeutics, there are therapeutics that we don't allow self-titration. We say this is how you take it, on this schedule, and you do not increase it until we see you back in the clinic. And then there's therapeutics that we say, okay, this is a range of doses and frequencies that we will allow you to titrate, but don't go outside of those ranges, and then they come back. So my only point being is we consider -- because a lot of people say, "How can you let somebody titrate cannabis when we don't know what the dose is and it's not safe?" My point being is that we feel that it is safe to put medical cannabis in the self-titration category, very low risk. So we can let the patients self-titrate within dosing limits. So when we tell them, we say, "Okay, you're going to take this much of a dropper full every four hours. If after 24 hours or 48 hours you're not having side effects, okay, then you can go up to this dose and that dose and that dose and that dose." And then I'll see them back in four weeks, and I kind of get an idea, "Okay, what are you taking?" So this all goes into the patient's medical record too. So when Dr. Sexton sees them in her office, she sees their medical record in my office. So we can communicate that way, and we document it as a part of their healthcare.

>> Thank you. Thank you, Mark. And Carey, just along those same lines in terms of self-titration, can you talk a little bit about your use of, you know, patient reported -- you know, their symptoms and the use of their diaries? Can you talk a little bit about that in terms of getting at that self-titration?

>> Right. So I think there's a bunch of different things online that patients can use. In the nursing field, April Hatch has a publication on Amazon that is a cannabis patient diary that really allows them to also reflect on their experience with using the cannabis. So basically what you want is similar to a pain diary, right, so the time they took the medicine, what kind of medicine they took, the dose if they know it, how soon effects started to happen, and did they have any side effects or adverse effects from that experience. And, you know, they can customize it to like, you know, rate that product that they used. So it's really important that they're doing this as they do the self-titration process, but also as they're selecting their chemo bar, which we used to call chemo bar strains, so that they're able to use a medicine that really works for the condition that they have. And that is one of the challenges that I think we haven't talked a lot about, but many patients out there, you know, they spend a few minutes with a practitioner and they get a recommendation, and then they're out there on their own trying to figure out what medicine do I use, which chemo bar, which ingestion method, what's going to work best for me. So the more that we can support them around that, do that kind of coaching around how the different ingestion methods work and how they might be beneficial or not beneficial and the challenges and drawbacks for each one and help them with that decision-making process. So the cannabis diary is very similar to a pain diary and very helpful when working with patients, one, for them to kind of take responsibility, but, two, for that coaching relationship with them to ensure that they are actually getting, you know, the benefit, avoiding the side effects and the adverse effects.

>> Wonderful. And I think we are just at time. So I'd like to applaud my speakers on Session Four panel, and thank you, all, very much for the time that you've taken to put very thoughtful presentations together. And I guess this concludes today's symposium.

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