Hi, everyone. I hope you had a great first day at the conference. Welcome to our first faculty panel of the conference. We will do this four times and this is a chance for us to answer some questions for us for you that you put into the chat during the presentations. Things that we did not get a chance to respond to during the talks are things we wanted to be able to go into in a little more detail. We have all of our first day presenters and we will go in order. Everyone is going to just highlight a few of the questions that were submitted so I will pass it to Petros Levounis first. >> Thank you, Abigail and it's wonderful to be back at the review course even if it's virtual, we are delighted to be here. Most of the questions that people asked have been answered already in the panel but there are a couple I would like to take. One is, can you talk about the anti---and how it evolves during the course of addiction? It seems like first of all, the pathways are the most complex and the least well understood and that is a very, active focus of research in 2021. The American Journal of psychiatry in the fall of 2020 , it essentially introduces the idea of by directionality , that a lot of things from genetics to trauma to developmental issues, medical issues , that can possibly get the brain in that situation of feeling the discomfort and the malaise and the anxiety of the dark side, as well. It can very well lead to the initiation of drug use of addiction in general but behavioral addictions, as well. But then, the very use of the drugs, the addict state of the brain can also lead into hyper could to feel that discomfort. I very much like that word . So there is this by directionality between the classic self-medication of addiction of where people start using drugs in order to self medicate and sometimes under appreciating, underdiagnosed but then the other side of it is addiction itself leading to the sites react-- psychiatric comorbidity. All of this by directionality to be specific, how does it evolve over the course of addiction? It seems in the earlier stages that the reward pathways, the pursuit of pleasure under reward on the --and will mask the award pathways but as the addiction progresses over the period of several months, they take over and become the center part of the addiction. The patient who comes to me and says I worked all week so I can make as much money as I can and buy as much cocaine as I can so I can finally feel at home and is actually talking about ways of addressing the pain of the anti-reward pathways of the brain. The second question, is there more to suppress or promote from the different signals? It is another cutting-edge area of research in the neurobiology of addiction. We are talking about that we are pretty sure this is a decision mechanism of what is salient and not salient and what should or should not come through in a patient 's final action of using a drug or not using a drug. In a classic sense it is a gateway mechanism but it may also very well promote some of the somatic signals that people feel. The cravings and the need to smoke a cigarette and we talked about this before, wanting to go to the bathroom. The room is too hot, all these somatic signals integrate and finally decide what is relevant and what is not. Adam going to pass it over . Thank you so much, I know there has been a long day but I appreciate your patience and I know at least in my lectures from the hospital I couldn't connect and had to cross the street to a café. I was able to answer some of your questions . In these 10 minutes that I have we will be able to navigate some of them . Let's see if I can unify some

questions regarding Sica form at treatment for alcohol use disorders. Some ask me about the frequencies of what .

Let's say that when we have patients with alcohol disorders and we think that person is a candidate because let's say the liver can tolerate the medication. We check them on a baseline the first time that we see the patient, and later if you have doubts you check it 2-4 weeks after and then if things go in the right direction you can check between three and six months. The question is, when is it appropriate to prescribe it? And how much to not go in that direction. As a rule of thumb, not just the number but the way that you feel clinically that the patient is responding, I will say you can open between three times to five times in the way that you can prescribe . With the questions, remember I tried to explain this in the lecture . It is key to identify if the person can maybe be a better candidate for, let's say a--? Let's say you have a person on the tracks. maybe the patient continues drinking heavily and you want or how to assess that patient. Maybe you are really concerned about the presentation and you want to assist the patient was something else . Some of you , okay, let's talk about the nonapproved medications. I don't want to confuse you. Remark him-- remember that -- big doubts because it is 333 mg and you need to take 2 tablets tablets three times a day, six in total and then the alternative is naltrexone that some people even go higher . Right now, it can be extremely useful for this population and the opioid use population. Talking about other possibilities, something we know that we can use. Remember you need to start slow. Every other week go up to another 25 until you reach a level of 150 mg twice a day. The only situation , not the only, but important situations to monitor is the fatigue that some of these medications can cause. As an addendum that will be reviewed, and-- can be helpful actually for stimulant use disorder . The other medication that some people are using a lot is gabapentin. remember that gabapentin has an interesting mechanism . Nobody knows exactly how gabapentin acts but it is related to the regulatory index a Tory , and then in the case of alcohol use disorder you can use average 300 mg TID . Some of you said, or asked, by the way we need to be careful with gabapentin and one of the questions was to be need to be careful with gabapentin? Of course that we need to be careful but let's say in the arena of how you are practicing, how careful you are with refills, I don't see a problem with giving it either with alcohol use disorder or sedative use disorder . It's a matter of law not prescribing, let's say, 900 mg with five refills. You are monitoring the patient, following the patient, and that's kind of the addendum with the non-FDA medications. Trying to match the two, there are points that are similar. People are asking about phenobarbital used in the treatment of alcohol use disorder versus benzo use disorder. In the last lecture I tried to cover this aspect on benzo use disorder , but some people are really feeling comfortable using it for acute alcohol detox . I would say probably I will move in that direction when you have refractory cases . The Europeans have more experience than other parts of the country are here but again it is something that I encourage you to do in the patient setting. Maybe some of you are prescribing phenobarbital but I will be cautious managing phenobarbital outpatient . These days, internal medicine and ICU people are using it for alcohol withdrawal, and actually you use a dose of 10 mg per kilogram. Even you can reach a level to 1000 mg through the course of, let's say, how we can call it? Like

maximizing the effects of the phenobarbital. It is definitely a very interesting topic that needs to be explored more and hopefully we will have the chance to have more randomized studies with phenobarbital. Let's see if I can diversify things here. People are asking about, can we apply this to monitor ? Do we have another thing to check for for the withdrawal? Remember that these days it's a 22 to check for withdrawal and has some similarities but that is a skill that you can use. There's another one called benzo withdrawal symptom that if I remember correctly it has 40 items and you check for withdrawal and you can use that.

Another question was related with , I mentioned briefly , we all need to be prepared for the genetic component of addiction and other areas in our field but before asking specifically about the OPR and , the gene provides instructions for making a protein . At some points some studies were showing us that it was related with alcohol use disorder but recent studies are showing maybe it is not an association with the genotype or alcohol consumption, or sensitivity to of the individual. But, it is an interesting topic we need to pay attention to. People were asking what did you use here? Screening, referral and treatment plan. That's kind of the public health approach and with the experts the most important thing is I gave you skills to actually assess and in five minutes you can do it. May be it is time for the psychopharmacological approach that you will have with this population. And then you start referral in preparation but that's pretty much what I will say. I don't know if it is my interpretation from outside these days but I sense that when I review the topic of Enzos and how interesting it is to see the kind of the-- prescribing it. I think all of us are capable to prescribe that . The most important thing is how we prescribe it to whom we prescribe it. In what conditions we prescribe it. Based on that I would save it's not that we cannot prescribe it. I'm not against prescriptions, or opioid treatment with pain killers when it is necessary but in what we reviewed, it was a key element to releasing your profile, how to prepare someone that has not been on benzo's. Maybe it's an indication because that person has panic attacks or maybe with some medication you will clarify that at the beginning you will prescribe for one month or so. But, it is a matter of integrating knowledge and integrating, let's say, the knowledge of the consequences in the long run. As we review in the morning elderly populations and that we need to pay attention for the high risk of car accidents, fractures, and when we see person 30 years we aren't going to start tapering that patient but we need to do a report of the risks and benefits of keeping that person and see if we can taper off in a way that we reviewed this morning. Let's see if I'm missing something else here. Let's see. The topic of what medications, the importance of what tools to manage symptoms-- sorry. Pretty much you have a --of medications but to give you more details, we have gabapentin, and melatonin. Those are 4 medications that you can consider, or there are studies done, to manage withdrawal symptoms from benzodiazepines and again, average. Some people use between 200 mg and 800 mg a day in divided doses. With gabapentin, with alcohol you use 300 mg TID in some case reports have been describing dosages between 600 mg and mine 900 mg pewter and, you can also handle dosages. Here we go again with the question. Can we use phenobarbital for withdrawal symptoms? Absolutely yes but I don't want to repeat myself. Trying to be cautious and try to accept limitations. Let's see my personal scenario , I think I would not

feel comfortable prescribing it for the purpose of what we are talking about. I would prefer to do that in an inpatient setting. But of course, the most important thing , or the message to be clinically oriented, would be the evidence-based medicine that we have. For now, I will say we covered most of the questions and I really appreciate everyone. Thank you again for these report's.

Thank you, Ricardo. I also want to thank everybody for joining us today during the conference and am happy to address a few questions posed during our earlier discussion focusing on opioids. The first question is what can we do to get it deemed a dangerous drug? So it is in a very unique regulatory environment that advocacy expressing concerns about risks , that's a really important step both from a national perspective but also from local state chapters as well as local city and county municipalities as well. The reason for that is related to crate him , we see synthetic substances , the DA classifies kraton as a concern, not a controlled substance. In 2017 HHS recommended to the DE the kraton be scheduled as a controlled substance but it is not happened yet. There are various regulations depending on what state or city you live in. Some states have banned it out right so there are at least six states that have banned kraton. At least five have a formal regulation . There are other advocacy groups not just from a health perspective with concern around risk of the medication, but there are groups that advocate for other regulatory structures. I think it's incredibly important to lend our voice to that advocacy. Really now is a great time to advocate on behalf of concerns and per spec dibs. Would you agree that methadone should be available for treatment of opioid use disorder outside of treatment programs? As is done in some countries of Europe.

Depending on where you are, methadone is regulated very differently. In the US as mentioned earlier , since the 70s there has been specific regulatory structure around the use of methadone but we also have another example of an opportunity to advocate for really redoubling our effort to expand the availability of various options. Certainly methadone would be part of that advocacy. Recognizing many of the challenges of the current regulatory structure, some examples would be that all new patients receiving methadone and programs are still required by federal regulation to attend that clinic every day that the clinic is open. No clinic can be closed more than one day a week except for on specific holidays. Opportunities to talk about equity, regulatory changes that would be beneficial, to speak on education efforts particularly around the clinical use of those options, and also safety . Focusing on the clinical availability and access for patients. I think that's another great example and effort that we can participate in. The final question is a little bit longer so I will read it out . This is an example of some challenges initial stabilization on methadone for patients using fentanyl, the initial high doses like given 25 or 30 mg of methadone, that they have moved up in their facility to 50 or 60 mg followed by a long taper. And, they've noticed that has a clinical reduction in those rates and also gives an example of using micro-dosing , helping patients get started . We talked about guidance on initiating methadone. 10 mg up to 30 , the initial process can be complex so judicious, cautious escalation is really important particularly because of the long half-life. But really the opportunity to look at protocols that may exist

within your facilities, separate from initial dosing which, again, we spoke about clearly, some facilities have hard caps on specific doses. We really want to bring our perspective to looking at those protocols and suggest areas in collaboration particularly with opioid treatment programs with the example of methadone and certainly other community providers to ensure that patients receive the right dose, a safe dose, but the right dose of medication while they are hospitalized. We do know that not treating substance use disorders appropriately will lead to increased rates and ultimately poorer outcomes. I will leave it at this point and thank you again, everyone. Next up is Doctor Avery. >> It's wonderful to be a part of this panel with all of these great speakers. What a great group. My talk is on nicotine and tobacco and a lot of questions were around the use of E cigarettes for those who want to quit. We talked about some of the evidence and how it's not so strong a lot of people are saying patients want to try with Juul or other replacements. We are meeting the patient where they are at, trying to taper off using the Juul or the vape they got in trouble with , I think it is worth a shot. the taper with the electronic devices, the problem is which we often learn, people often fail doing this and that often keeps Juul and different pods and disposable things in my office. To demonstrate to people or show them what they are , it is tempting for me not to use it as I look at them. They are so tempting and seductive that it's a little different from gum and patches. It is hard to taper down off of them . You can use them all day, hide them, it can often be stronger nicotine concentrations, as we've talked about. Is much as I have tried to taper them, it is quite hard and often we will try and it takes multiple tries but we do end up going to nicotine replacement ultimate . And it often does the trick and gets rid of some of the behavior that are associated with use. The other thing you will notice clinically is that there are strong advocates and any time I give a talk there's tons of emails with a lot of opinions. I don't get caught up on that but sort of meeting people where they are at . I think the other thing people wondered about were the challenges of nicotine cessation and those with serious mental illness or treating different psychiatric disorders. We talked about the psychiatric side effects of Wellbutrin and a lot of these can be safely tolerated and a lot of people with schizophrenia and bipolar disorder. I think the bigger barrier is that we just don't offer them. A lot of times we still adhere to that approach and often nicotine cessation is the last thing on anyone's list. It's mental health issues or other color occurring substance use disorders and nicotine gets pushed to the end but nicotine and tobacco are really going to cause morbidity and result in a lot of the health problems that shortens one's life. Serious mental illnesses if you can get them going in the right direction. Using a purchase to get them to a point where they are ready to tackle that with you. I think you have to be mindful if you are successful about interactions between cigarettes and medications and may have to adjust them. May have to lower the dose is as people get off of it but overall I think it is a worthwhile endeavor for those with serious mental illness. That is all I had for now and I'm passing it over to Doctor Marienfeld .

I'm going to be talking about some of the questions on cannabis. I have already answered most of them, I think , during the session but I will go ahead and try to confirm or explore, flesh out some of my responses. There was a question that came in after the presentation so I will try to

address that. In states that have legalized marijuana for recreational use, young adult adolescent use has increased and they perceive no harms. I wouldn't say none but definitely less. I think the person is referencing that even medical students contest that it is safe and not associated with addiction. Any thoughts on how this is being addressed? This is not the review course and I think it is easy end of interest to understand and participate or contribute to various efforts . It does not always necessarily apply to course review content. This is going to come up on the exam. Having said that I think it is helpful to have these kinds of conversations so as physicians we are always in this battle of trying to update information with what we know in a way that people can use because if the information is constantly changing, there is a weariness or a sense of, we don't know what we are talking about and can clearly see this with Covid and the battle of science or not. We are trying to update ideas and see how things go with that. Sorry. For this in particular, I think there are organizations with a lot of different players. Advocacy groups-- groups , pro-marijuana , medical organizations, politicians, popular press folks like Michael Pollan who has been talking more about psychedelics and things like that he is a prominent person who writes newspaper articles and books, et cetera. So there's a lot of people vying for your attention. As physicians I think we just have to keep trying to reiterate the points about what we are learning, how we are learning, what we do not know and how when we do know things we need to update opinions on it. For adolescent use in particular I think we have reasonable date of that adults with cessation from cannabis use, pretty clear effects that we see on cognition, focus, concentration can resolve within about a month or so of abstinence. With adolescents the data is unclear and it is somewhat controversial, the ideas of whether or not somebody can , whether or not we have good data on adolescents. Just looking quickly at some questions, we have various periods where at my clinic I will have a bunch of people who have it. I don't see it for a while, it is typically a motivator for people who may not have previously had any insight that cannabis may have been causing them problems. It's one of the reasons they may present for treatment , and then sometimes I find that's a great opportunity to have a window of abstinence from marijuana in order for them to see the impact on their lives and potentially how much more functional they might be , potentially improvements in anxiety and move mood with cannabis cessation. Aside from treatment, cessation is the best treatment. Acutely, if someone is not doing well , a hot shower seems to work anecdotally and through what I have seen data -wise. Some questions I have already answered so I'm going to pass it over to the next presenter. Thank you very much for your time. >> Hey folks, thanks for hanging in there. had many questions, some of which I answered during the chat but there are a few that I did not answer and a couple that I did but I want to speak in a little more detail on. I will him to handle three specific questions. What are your thoughts and advice that we should give to patients related to the coal ingestion of cocaine and alcohol leading to coca ethyl information? Is this commonly seen? The vast majority of people who use cocaine go in just alcohol so these substances are commonly used together. The problem with that is that coal ingestion inhibits the metabolism of cocaine so that you have higher blood levels of cocaine, so you enhance the effects of cocaine and additionally, you generate a unique metabolite called cocaethylene which is very similar in

the ability to block the dopamine transporter. The synergism, all these things happening will prolong and perhaps exacerbate the effects of cocaine so most people do use cocaine in the presence of alcohol and this issue is an important issue to consider.

The next question. Many were related to MDMA which unfortunately I cannot answer and I think because part of this is that MDMA is in another land where many investigators are starting to use this for PTSD and other types of indications. It looks like it has some clinical utility under certain circumstances. In the biology of addiction lecture they showed slides of dopamine increases caused by various drugs. Have there been similar studies with drugs like MDMA where you do not have the same level of repeated use when you use it compared to opioids and alcohol? This is a great question and it is related to the issue of the dopamine hypothesis of addiction. MDMA does cause profound elevations in dopamine. The critical issue is, these effects on the dopamine system are eclipsed by an increase in extracellular serotonin. So ecstasy increases extracellular serotonin to a much greater effect than dopamine. The end result of that is, the effect tends to dampen the dopaminergic effects which means it is less addict give addict give .

Based on mechanism, one would think those treatments work. >> I'm not aware of the use of SSRIs for the treatment of MDMA use disorders, but I will say there are potential problems with the use of MDMA in the presence of SSRIs and this is classic drug interactions. They are very important-- potent inhibitors. Cytochrome 2-D six is the enzyme responsible for the metabolism of MDMA so in the presence of a drug like this, anyone getting into dose escalation can get into trouble because they are not able to metabolize the drug and there are instances where you increase the risk of serotonin syndrome and other types of toxic insults when you take MDMA in the presence of an SSRI because of this interaction.

I'm going to end right there and hand off to Doctor Abigail Herron so I hope that she's ready. >> Thank you, Mike. Thank you again for everyone sticking in here. We are at the very end of a long day. I had a diverse group of substances to talk about and a diverse group of questions but I'm going to put them together into some themes. One thing that people asked about was the use of talk therapy for inhalant abuse. As I mentioned and you were correct to point out, there can definitely be challenges because of the cognitive deficits that can be associated with long-term inhalant use. I will add that another things that were shared is that they are less likely to be encountered. Patients with use disorders are less likely to present to care and particularly with steroid use disorders, this is often going untreated and is not necessarily flagged the radar unless there is significant physical consequences. You will not see a lot of patients participating in treatments for inhalants and steroid use disorders and there can be challenges. A reminder of course that there are no approved pharmacological treatments for these substance use disorders at this point so we can be a really difficult disease to have if you're trying to look for treatment options with patients that have cognitive impairments. >> Then there was a series of questions around the use of hallucinogens, particularly ketamine and silicide been in clinical practice or clinical

trials for the treatment of refractory depression. This is certainly something that has changed dramatically over the past several years. When I was first doing this course we were not seeing this being used at this point. We still have ongoing research. With ketamine there's a form that has been FDA approved for the treatment of depression and can only be done in a monitored setting . And then there is ongoing research of silicide been and its use combined with intensive talk therapy for, again, treatment-resistant depression. I think these are promising and I can say anecdotally I've had a couple of nations. I have had a couple of patients that have received ketamine treatments and done well. Setting is very important . Managing expectations and being in a safe and comforting environment have emerged as key factors into the potential for success. I urge everybody to keep watching the science and look at the clinical trials. When you see this out in practice, take it with a grain of salt in that there is a lot of variability in the process for some of these boutique practices doing this. Some work extremely closely with psychiatrists and therapists and members of the team and others are more commercially focused and may not have this stringent of standards. >> The last area of questions that I wanted to address was talking about , someone asked about the capital receptor being dysphoric and there is a theme around , why do people want to use things like hallucinogens and dissociative's? I would say the group of substances that I talked about are not as commonly used as most of the other drugs that we spend most of our days thinking about and treating. It is a certain type of person that is reinforced by the experience of dissociation or hallucination. So, there are some potential analgesic effects as well as people using these substances in order to seek the dissociative experience. That is not something that would be universally appealing , it is something that for a certain subset of the population, it is reinforcing.

I will turn it over to my cochair and final presenter for the evening, Erin Zerbo.

Thank you so much, and I'm the very last person so thank you all for hanging in. it is a long day and it's hard with virtual lectures but really great to have everyone here. I had a few questions I was going to cover. There is some research on Alcoholics Anonymous. There have been a couple of studies done and as we've seen it's difficult to do research because of the anonymity and the way the groups are structured. I did find a review that looked at a couple of studies. I think it was around a dozen different studies, they looked at them altogether and what they found was inconsistent. Some studies showed benefit using it entirely on its own or a combination of formal treatment and medications but other studies showed no additional benefits. So right now, I've noticed this with patients, I think that twelve-step groups are very helpful for some patients but are honestly not for everyone. Some people get triggered by going into groups and will describe that there is an idea of the drunk monologue where you are talking about stories or using so sometimes they can be triggered. so I like to educate people on it and let them figure out for themselves if it's going to work or not but I think it's important to make people understand that this is considered an adjunct treatment. It is not formal because you are not getting personally assessed and evaluated. But that said GA is incredibly helpful for a lot of people.

What percent of persons suffering from gambling disorders or with other STDs suffer from gambling? It was hard for me to find numbers for everybody , how many people have a gambling disorder. I do think the number is pretty small but the other direction is a bigger correlation. Usually around a quarter of people with gambling disorder will meet criteria for alcohol abuse. Around 17 have 20% , they will meet the criteria for another disorder that is not alcohol. Compared to the general population which would be 1.4%, we can see this is a big jump so if you have a disorder you are more likely to have an alcohol use disorder than someone in the general population. It is interesting because the substances we see most often are alcohol, cannabis, stimulants, and tobacco. We don't tend to see opioids as much so those are kind of the 4. And alcohol and tobacco are by far and away the number one substances we see with the gambling disorder. >> There is a question about --is a compulsive disorder? That's a great question. There is very small literature. I saw a randomized virtual trial but could not find the results. There are some key studies for single patients where it was shown to be beneficial and was listed as a potential treatment that people are looking to study so I think like many things we don't have enough studies or data but it looks like there could be some promise. If you have a patient that you have tried naltrexone and it's not working or you want to add on top of it, I think it would be reasonable to give it a trial so it is something that people could consider. Another question, why does help with late onset but not early-onset alcohol use disorder? Keep in mind this is data that has been replicated several times showing that if you have a substance use disorder that begins before age 25, that those patients are much more likely to do worse if you put them on an SSRI. The study looked at something specifically but we think they are for all of them and as someone develops a substance use disorder afterwards than it is much more likely to treat depression and anxiety and actually reduce cravings and assist with their, kind of, recovery. We actually do not know the reason for this and it is something we. we found out, they think it has to do with the changing neurochemistry so when people use substances early, obviously that is when you are feeling out and fully forming your biological connections so it seems like it's going to be incredibly disruptive to that biology and if for some reason you add an SSRI to that ideology it increases cravings. I think it is that they have disrupted circuitry that looks different than those who get addicted after 25. And just a reminder those before 25 have multiple addictions, where is over 25 you see less severe addiction and more common with one substance so we are talking about two types of people with substance abuse disorders.

The last question I wanted to mention was what about hoarding? That is really interesting so I did not include that in my presentation. Right now, in 2013, the text revision was brought out finally is an independent disorder and is a DSM 5 put under obsessive-compulsive and related disorders so thinking of it on the compulsion spectrum. There are some researchers and authors thinking about it as a behavioral addiction and talk about the pleasurable component that can happen with collecting and saving items. People get a lot of pleasure from that so there's definitely some conversations about how it can be related to other addictive disorders but there is less research on hoarding than a lot of

other disorders and right now is classified under obsessive-compulsive so it's not technically a behavioral addiction but that can also change with more research

I will go ahead and stop there. thank you so much. >> Thank you. With that we have reached the end of day one. Thank you so much for your time and attention. We will start back tomorrow morning at 9:15 Eastern time. There is an informal network opportunity and we will start lectures at 9:50 Eastern time so have a good evening and see you tomorrow. Take care. >> [event concluded] [Event Concluded]