Female: 2017, 2018 program. This year's overarching topic is A New Look at Some Old and Not So Old Drugs, future programs will focus on cocaine, opioids and heroin and mood synthesizers, synthetic drugs. Not only do we have people in the audience here at DEA Headquarters in Washington DC but there are folks watching through a live webcast around the country and we hope around the world if people want to get up in the middle of the night to watch this. Dr. Mark Gold [PH] who put this panel together for us is watching from Yale and we thank Dr. Gold very much for his work on bringing these esteemed people to our stage today. I particularly want to welcome the Texas Museum of Science and Technology in Cedar Park, Tex MOST is hosting **[00:01:00]** our traveling exhibition drugs cause and consequences and their staff jumped at the chance to simulcast this program at their museum today. A pleasant reminder, turn off your cell phones please.

With marijuana in the news both with state level legalization efforts and research on its effects on the body and brain, we have four renowned international researchers providing updates on these issues. Our moderator today is Robert L. DuPont a national leader in marijuana policy, drug policy and treatment, he was the first director of the National Institute on Drug Abuse from 1973 to 1978 and was the second White House Drug Czar from 1973 to 1977. In 1978 Dr. DuPont became the founding president of the Institute for Behavior and Health and in 1982 he and former DEA Administrator **[00:02:00]** Peter Bensinger founded Bensinger DuPont & Associates a national consulting firm. Dr. DuPont is a fellow of the American Society of Addiction Medicine and a life fellow of the American Psychiatric Association, he was the founding president of the Anxiety Disorders Association of America and currently maintains a psychiatric practice in Maryland specializing in addiction and anxiety disorders. In addition to moderating today's discussion Dr. DuPont will consider the question, where is the science for a 0.08 blood alcohol content equivalent for cannabis, Dr. DuPont.

Robert L. DuPont: That's a very generous introduction and I'm very grateful, the only problem with it is it's used up nearly half of my 10 minutes too. I'm going to just say a couple things by way of background, I believe I'm the only person who has personally known all **[00:03:00]** 17 White House Drug Czars all 11 heads of DEA and all 5 heads of NIDA, and I'm very proud to say that. My professional life has been devoted to the problem of addiction and I just say a word about how that got started. When I finish my training I went to work in the DC Department of Corrections because I wanted to help criminals and that's when I discover the connection between crime and heroin addiction, and that's when I got into drug treatment as they say the rest is history. But I want to get that background with you because there's a misguided view in drug policy discussions that the choice in drug policy is between treatment or law enforcement. Do you believe in prison or do you believe in treatment, and nothing could be farther from the truth?

What DEA is doing, I'm very proud to be here because of DEA because of what DEA **[00:04:00]** does and what DEA does is essential to the nation's public health. I want to emphasize that in two ways, one is in terms of supply reduction but also providing an avenue to recovery for millions of people when -- great example of that is the immediate past Drug Czar Michael Botticelli who got into recovery because he was arrested for an alcohol cause accident, so that's by way of background. Now, also taking a long view on this the -- this is the third time in the last 45 years that drugs are front and center in the nation's attention. The first one was the heroin addiction related to crime in the early 1970s, the second was the crack epidemic in the late 1980s and this is the third time. And right now there are two big issues that are dominating the field, one is the **[00:05:00]** opioid overdose problem and the other is marijuana, and the marijuana is what we're talking about today.

In many ways I think that's the more important issue for us to deal with and it's going been going on for 40 years in thinking about what -- how marijuana -- what it is, what it does and how do we respond to it. That is the fundamental question in drug policy because marijuana dominates the picture of use level of drugs not just in the United States but in the world outside of alcohol and tobacco. And what we're doing in this country now is making a third legal drug. I think my bond to you is at our apparel. Now one of the key questions and it's directly relevant to what we're talking about today is what are the consequences of Marijuana use and the way the policy debate **[00:06:00]** is going on is around the sense that marijuana use is harmless or even therapeutic. And the essential element in the public discussion about marijuana policy is to understand the effects of marijuana so that we can have a policy that it fits the needs of the country including obviously the public health needs.

And I'm going to give you my sense of where that needs to go, and that is to recognize that the public interest is to reduce the level of marijuana use because of the negative consequences of it. And the debate about policy to me is a question of how you do that and there's plenty of room for discussing that but I think having that picture is very important. Anyway here we're going to talk about science, we're going to **[00:07:00]** deal with the -- we have with us very distinguished scientist I'm very proud particularly proud to introduce the first speaker Dr. Bertha Madras a professor of psychobiology at the Department of Psychiatry and chair of the Division of Neurochemistry at the Harvard Medical School. Harvard University, Cambridge, Massachusetts in 2005 President Bush nominated and in 2006 the senate unanimously confirm Dr. Madras as the Deputy Director of Demand Reduction for the White House Office of National Drug Control Policy.

Dr. Madras's research focuses on the relevance of dopamine signaling and addiction biology ADHD and Parkinson's Disease, she owes 19 patents a novel brain imaging agents and candidate therapeutics. She had delivered over 250 public presentations

[00:08:00] globally and developed a museum exhibit and a CD license by Disney with the Museum of Science in Boston, she's recipient of the NIH MERIT Award and NIDA Public Service Award, American Academy of Addiction Psychiatry Founder's Award and others. Her brain imaging agent was listed with a better world records as one of 25 technology transfer innovations that change the world. Dr. Madras speaking on marijuana's risk and adolescent brain development. And one last thing before she comes up here she is a hero of mine, right now we have the Christie Commission studying about the opioid problem and making national recommendations, Dr. Madras is on that commission and providing leadership in that. And I'm so proud to introduce to you my colleague and good friends Bertha Madras. **[00:09:00]**

Dr. Bertha Madras: Thank you Bob, with that introduction you cut into all my time, so I have no time left to say anything. What I'm going to try to speak to you today about is marijuana risks and adolescent brain and development. The -- it's going to feel like you're getting a drink of water out of fire hydrant as they say because this is too intense a discussion to be -- to be dealt with in a very short period of time that we have. These are my disclosures, the world the United States, many other nations are at a crossroads in terms of drug policy. There are many different opposing points of view on what we should **[00:10:00]** do about drugs and what I think should be driving the policy to some extent is the science, also are values and what is in the public interest.

These are some of the topics I'll try to cover very quickly the adolescent brain and its development, marijuana in the adolescent brain, marijuana and opioids and marijuana's medicine. Each one of this can take two hours of discussion and as Bob wasted all the time telling silly things about my background I'll try to move very quickly. Many brain disorder start during adolescents, it’s a period of very rapid brain development. Impulse control disorder, substance use disorders, anxiety disorders **[00:11:00]** mood disorders, schizophrenia and psychosis, all during this very critical period when the brain is undergoing very rapid development. The teenage brain has a number of changes associated with this period, it reorganizes circuits and function, it prunes unneeded connections, it grows in size, it wires cortical dopamine circuits. And dopamine is critical in terms of reward, motivation, learning and memory, and it's strengthens connections.

The reason I underline the wiring of dopamine circuits is in the last few slides you will see some of the research that we are doing which is compelling and drives further investigation of the effects of some of the cannabinoids in marijuana on this issue. When I say it reorganizes circuits, if you give a teenager a **[00:12:00]** photographs of anxiety or emotional -- excuse me, emotional context you will see that they light up the amygdala the area of the brain that is critical for assessing, addressing and generating emotional feelings. The frontal cortex which is the area of the brain that's involved in self-regulation in judgment and reasoning and problem solving is very quiet. If you give

the identical scenarios photographs of anxiety and stressful and emotional drawing episodes the adult brain will light up a completely different part. The frontal cortical areas which as I said are involved in judgment, reasoning **[00:13:00]** and impulse control. And the amygdala the emotional part of the brain is almost silent.

And what this illustrates very effectively, this was done by Yurgelun Galen Todd, is that the brain is reorganizing circuitry during this critical phase. The teen brain also prunes connections, connections that are not needed, without the pruning there is a vast array of connections that could in fact interfere with appropriate signals. The teen brain also thickens the insulation around the wires between neurons. And this thickening enables connections between nerve cells -- the communication system to operate at a much faster rate so the teen brain is developing very rapidly. Now, if we bring this up to the level of behavior we don't have the perfect **[00:14:00]** connection between the brain development and behavior. But what we can identify is that adolescents are much higher risk for addiction as well as other psychiatric disorders, that is a critical period.

So the percent of people who become DSM-5 abused dependent on marijuana and alcohol is much higher if drug use is initiated at the age of 15 or younger compared to if use is initiated between the ages of 18 and 21. And this higher vulnerability to addiction is true not only for marijuana and alcohol, but for nicotine, inhalants, stimulants, cocaine, opioids, hallucinogens, and anxiolytics. So a prevention **[00:15:00]** message would be to discourage the use of all drugs by youth. What about marijuana in the adolescent brain. Marijuana affects short and long term, brain changes that have been documented addiction, cognitive deficits, Amotivation, psychosis and safety issues. Marissa Silvera at McLean Hospital which is my home base currently, synthesized all the magnetic resonance imaging studies that were done in adolescent marijuana users. And she found there about 46 MRI studies and the majority of them show changes in the brains of marijuana users. These are complex to interpret because some are cross sectional studies, very few longitudinal studies so **[00:16:00]** there are or always caveats in interpreting the data.

But in most cases there was a discovery of marijuana related brain changes, more robust in the adolescent initiator or marijuana. And a few of these studies were associated with impaired function. The prevalence of cannabis use disorder is shifting, the old data that reassured you that it's only about 9%, 10% is no longer -- is no longer accurate. There are two studies that came out very recently one ushered in by Deb Hasin from Columbia the other Wilson Compton and collaborators at SEMSA that showed much higher addition rates especially Deb Hasin's which claims that of cur0rent marijuana **[00:17:00]** users approximately 30.6% have a cannabis use disorder, Wilson Compton's data are about 11.4%. What's most important and interesting in this shifting target of prevalence is that the use -- daily use of marijuana has gone up dramatically and so has the potency, and this could be driving the higher numbers. We also know

these are old data that the initiation in mid-teens is associated with much higher prevalence than an initiation in adulthood. And daily use is clearly a very high risk factor for a substance use disorder for cannabis use disorder.

Marijuana effects brain function acutely, it impairs learning and memory, verbal IQ, in terms of error rates, word associations **[00:18:00]** perseveration it impairs motor function acutely and it impairs decision making. All of these are short term effects of being under the influence of the drug. Madeleine Myer published landmark study, this has been replicated in the number by several other investigators recently that early persistent marijuana use is associated with reduced memory, with reduced IQ and memory impairment. There've been caveats to this, if you only study a 13 to 18 year old timeframe or 13 to 21 year old, you don't see robust data in fact you don't really see a difference. You have to wait until the individuals are much, much older and have cumulative effects of long term use of marijuana. And under those conditions by the time in her study at the age of **[00:19:00]** of 38 with steady use of marijuana and early initiation this IQ lost was robust. It was about 8 points, what does 8 points mean? Some people would say it's trivial, but if you are losing 8 points and your IQ is a 100 which is average and you're down to 92, that puts you in the 30th percentile of average IQs opposed to the 50th and that could be disadvantageous.

And what we see as a function of the amount of marijuana used as a teen the number of times used from never up to 400 uses plus that the probability of graduating from college, the probability -- it declines the probability of being on welfare and unemployed increases. **[00:20:00]** And this also has caveats associated with the data because what if these individuals use marijuana were predisposed to begin with in terms of being attracted to the drug for some underlying pathology in their own system. But what's so interesting is in terms of this Amotivation issue is -- a recent study that was done by Mark Seidel [PH] just published in the past year an imaging study in which they were trying to understand what are the brain changes that could give rise to a reduction and natural rewards -- reduction in motivation. And so they put a person into a -- an MRI imaging system but also offer the monetary rewards to play a game. And they **[00:21:00]** found that when these monetary rewards were offered the person's nucleus succumbence the -- one of the sites of reward mechanisms lit up, dopamine was released in vast quantities. But they did the same study with a person smoking marijuana the nucleus succumbence turn silent and dopamine was not released.

And so they conjectured that the brain region that anticipates and may interpret reward was blunted with heavy marijuana use. And this process could drive Amotivation and compulsive drug use, and intriguingly when they did the same study with people who are heavy alcohol users they did not find there's difference. It seem to be unique in the comparison of the two drugs to marijuana. In terms of psychosis **[00:22:00]** there is a growing body of evidence that marijuana is a causative agent of psychosis but even if it

does not produce psychosis in adolescents or trigger it or precipitate it there is accumulating evidence. And this is a very interesting study showing that as a function of how many years in adolescent uses, they are going to manifest more bizarre thoughts if they use between 1 and 2 years to 3 years to 4 years more paranoia, more hallucinations and have more symptoms of preclinical psychosis even if they are not frankly diagnosed with schizophrenia or a psychotic like syndrome. In terms of safety the use of marijuana by parents who have in fact progressed to a marijuana use disorder has a negative influence on child's **[00:23:00]** behavior.

There is an increase in the violent offensive -- of the child and this is a huge study, this had a huge end. And the use of -- the marijuana use disorder in parents had more a consequences to violence in the children than alcohol use disorder, and more consequences to the children in terms of suicide attempt. So there is in some ways as David Sheff the author has stated there is almost the use of certain substances and addiction can become a family disease. What about marijuana and opioids very quickly, this is a data on publish from SAMHSA if you use marijuana the likelihood of using heroin is much higher. And recently this was published by Olson Adoll [PH] in the American **[00:24:00]** Journal of Psychiatry showing that people who use cannabis have a higher rates of prescription opioid misuse, higher rates of opioid use disorder. And if they use cannabis for pain they still have higher rates of prescription opioid misuse and opioid use disorder.

Now very quickly exposure to THC in the -- during adolescents in rodents, now we're going back down the evolutionary scale. And the reason it is so compelling to look at preclinical data animal data is that there are no confounds, there's no stress, there's no exempts, there's no abuse by parents, there's no bullying by friends, these animals are clean other than the introduction of the drug. And we find that if adolescents are exposed to THC this is Yesmin Hart's [PH] work. They are **[00:25:00]** much more likely to seek and consume more heroin as adults, and if they are expose to THC in utero they are more likely to seek and consume heroin as adults. But the most interesting study which needs conformation in humans is that she exposed adolescent male and females to THC, the most -- the psychoactive constituent in cannabis. And then withdrew them from cannabis forever, they never sought again and then they grew up into adults and they were allowed to mate and then babies were born, the babies never had seen THC, only the parents had preconception long before conception during adolescents. And when these babies matured they never sought THC but they **[00:26:00]** sought heroin more and their brains were different than the brains of offspring whose parents had never been introduced to THC during adolescents.

So that is cautionary tale, there's a long way to go before this is accepted. But I think it's a very important one because she also has evidence of epigenetic changes that occur which are probably translated -- transmitted through the germ cells into the -- into

the next generation. We are all aware of marijuana as a medicine taking over state by state in terms of movement, we're also aware that marijuana probably was used for medicinal purposes. This is a gravesite that dates back to 400 AD we know that because Roman coins with emperors **[00:27:00]** at that time were found in this gravesite. This is a 14 years old girl who died in child birth, breach birth and there were ashes that were discovered near her that turned out to be a stable metalloid of THC. And so it was primary evidence that marijuana was used in that case most likely in order to promote uterine contractions, her pelvis was too small by about an inch in diameter and that's why she -- she perished during child birth.

But bringing us back into the modern era or forward into the modern era there is meta-analysis that's been done for a number of diseases with regard to the use of smoked cannabis. Dimension neurological I won't go through all the list I don't like list. But the evidence for medical marijuana **[00:28:00]** as we've heard the vast majority of them, and what is concerning me and brings me into my own lab and my own research is that the THC the CBD ratio in marijuana is rising. It has risen so dramatically that in some cases it's greater than 90 to 1. And what -- why does that have implications for the future? Because THC and CBD have very different effects pharmacologically, THC is addictive it's intoxicating and impairs cognition, it can promote anxiety, it can be psychotomimetic. It can promotes seizures or reduce seizures depending on the individual and it functions as a partial agonist at the CB1 and CB2 receptors. CBD does none of this, in fact in some cases there's growing evidence both **[00:29:00]** humans and pre-clinically that it does the opposite or in fact it may temper the effects of THC.

Now, in terms of psychosis THC can produce suspiciousness, paranoia, conceptual disorganization and perceptual alterations. And there is a small but growing body of literature that CBD will oppose these -- some of these effect as well as cognitive impairment. In our own lab we decided to interrogate this issue by -- in non-human primates by looking at the effects of THC alone or THC combined in a very similar ratio, and I can get into it. And we were looking at a few specific targets, one of them is DCC **[00:30:00]** which guides adolescent dopamine cortical wiring. It is required in obligatory ford, and what we found is that in the prefrontal cortex which is critical for cognitive function for psychosis, we found that THC up-regulated this gene that's critical for dopamine wiring and up-regulation is in fact a bad thing to happen. The excess amount is not healthy for brain function and CBD in combination with THC reduced it down to zero.

We found the same type of responses with a number of other parameters in the brain which we don't have time to get into. So I'd like to close by just saying that from my perspective **[00:31:00]** we're not waging a war on drugs, we are in fact defending our brain which is repository of our humanity. And supply reduction which is what the DEA

focus is on to some extent is a form of prevention because if you prevent, if you reduce supply you're prevent to use to some extent, thank you very much.

Robert L. DuPont: Thank you Bertha, it's a delight to listen to Bertha who is always inspires me. Our next speaker is Arpana Agrawal a professor of psychiatry at Washington University in St. Louis, Missouri. Her research focus is on epidemiologic and genomic approaches to the **[00:32:00]** study of substance use and addiction funded by the National Institute on Drug Abuse, she is studying how genetic and environmental factors work together to shape our liability to use cannabis and become addicted to it. In addition, she is the co-project investigator of the substance use disorders working group of the Psychiatric Genomics Consortium PGC. The goal of this working group is to identify common genetics variance that are related to liability for alcohol, nicotine and cannabis and other drug use disorders and further to relate this low-psy to the genetic risk for other psychiatric traits, example personality and disorders for example, depression. Her topic today marijuana exposure in young people increases the risk of schizophrenia, depression and anhedonia, thank you. **[00:33:00]**

Arpana Agrawal: Thank you very much Bob and thank you to the DEA for inviting me to come here and share with you a brief update, I'm going to get this into presenter mode in a moment. So what I want to do today is give you a brief update on the science surrounding cannabis use and mental health. And the challenge that I hope I will be able to outline to you is we know that there are clear associations between cannabis misuse and mental health, but we struggle with where those associations and how those associations arise. So what do we know, we know that individuals with psychiatric illness those who are suffering from a psychiatric disorder across their lifetime are significantly more likely to use substances, so alcohol, tobacco, certainly marijuana **[00:34:00]** as well as other drugs like cocaine. And they're also significantly more likely to be dependent on those substances.

For cannabis the most salient associations are with psychotic disorders like schizophrenia with major depressive disorder and with suicidal ideation and attempts and this partially overlap with depression but are also a feature of a number of other psychiatric disorders. Now notably absent from this slide of comorbidities are the other addictions, as you might well imagine individuals who have a cannabis use disorder also more likely to have a history of alcohol dependence, to experiment with cocaine or heroin and are also more likely to smoke cigarettes and developed dependence on nicotine. In fact in the United States subsequent to Australia we're witnessing what is commonly known as a reverse gateway, the idea that youth actually initiate their substance use trajectories or substance if you -- with marijuana and then **[00:35:00]** work their way back to nicotine. And some of this may just have to be -- to be associate with the way we use these drugs, but I will not be talking about the other addictions nor

will I be talking about childhood deviancy and conduct problems which are very highly correlated with the use and the maintenance of cannabis use.

So the question here is we know from large studies that there is an association and that the association is strong. But what are the origins of these associations, they do the causal factors or perhaps do we need to account for common predisposing influences, and I'm just going to give you a very broad overview of what the science suggest. The most interesting perhaps association that cannabis has with the psychiatric disorder is with psychosis as Dr. Madras just outlined. In 1987 Adreasson and colleagues publish this first study that kind of turn our attention to this very strong **[00:36:00]** correlation. And what they did in the studies they looked at about 45,000 young men who are Swedish conscripts and they gave them a questionnaire before they were conscripted. And this questionnaire included an assessment of how much marijuana they've used. They also had a psychiatrist evaluate them for their history of psychopathology. And 15 years after this first questionnaire was administered they actually merge their data with the medical registers and what they found was quite surprising for the time. They found that of those conscripts who have reported prior to conscription over 50 or more instances of cannabis use, they were at a relative risk of 6.0 so it was 6 fold increase likelihood of having schizophrenia 15 years later or in that time period.

This analysis actually accounted for their own smoking and drug use, their family history of alcohol problems **[00:37:00]** whether they would ever run away from home when they were young which is a marker of a conduct problems. And the point here was that there seems to be a very interesting and unique connection between heavy use of marijuana and the onset and maintenance and schizophrenia and other psychotic disorders. So the idea that cannabis use or even daily cannabis use directly causes a psychotic disorder does not seem apparent. If it was purely and simply causal you would expect that everybody who uses cannabis on a daily basis would have some form of a psychotic disorder and the prevalence's just don't line up. However, researchers began to explore the possibility that there are subset of individuals who are genetically vulnerable to schizophrenia who in the context of early and heavy exposure to marijuana may actually have an onset of their schizophrenia or psychotic disorder.

And one of the first explorations of this hypothesis **[00:38:00]** from a genetic perspective came from Caspi and colleagues. What they did is they looked at a single marker in our DNA in the COMT gene catecholamine-o-methyltransferase gene this codes an enzyme which actually degrades catecholamines including dopamine. And therefore it's very critical in our studies of the neurobiology of marijuana but also in schizophrenia which has a dopamine energy basis. And what Caspi and colleagues found was this interesting pattern in the dark bars here, they found that individuals who carried one or more of the [inaudible 00:38:35] one of the forms of this marker in our DNA were more likely to report schizophrenia by the age of 26 if and only if they had

used cannabis during adolescence. So it wasn't sufficient to have the genetic susceptibility and it wasn't sufficient to use marijuana at an early age, it was a concert the interface of these two risk factors **[00:39:00]** that actually led to an increased vulnerability. And this was a fascinating example of what we call a gene environment interaction where you have an environmental provocateur of genetic vulnerability.

This specific polymorphism has been replicated somewhat sporadically, but about a decade later investigators in Canada actually took a somewhat different approach. They said we don't want to look at one polymorphism, all of these disorders and phenotypes that we're studying are highly polygenic contributable to the small effects of a number of very large number we're talking in the thousands of markers in our DNA. And so they said let's just aggregate add up these tiny effects of multiple variants across the genome that shape our liability to schizophrenia. And so what you're seeing here on the X-axis is actually a genomic score for individual's vulnerability to schizophrenia and we all carry the score at some cut point on the score perhaps along with other **[00:40:00]** environmental factors we perhaps begin to exhibit schizophrenia, so it's a genetic susceptibility.

And they found that this genetic susceptibility the schizophrenia as it increased these youth began to show cortical thinning, the thinning of their cortices which has been associated with schizophrenia as well as a number of other psychiatric disorders but only in the presence of adolescent marijuana exposure. So again this interface between genetic liability aggregated across our genome and early exposure to marijuana and this effect in this study at least was only significant in boys. And so they kind of put another spin on this gene environment interaction model and they said well indeed exposure to marijuana acts as perhaps an environmental trigger of our genetic, our aggregated genetic vulnerability to schizophrenia. But the point along the pathway where it acts is not in fact schizophrenia directly but this intermediate neurobiological marker of cortical **[00:41:00]** thinning and that's fascinating.

One of the challenges that we've encountered with all of these studies that involve the interrogation of our genome is that ideally we would like to understand and Dr. Madras alluded to this what are the common genetic underpinnings to using marijuana heavily on schizophrenia. So the heritability of schizophrenia is about 80%, the heritability of heavy marijuana use and problem use is about 50%, so 50% of the variation and the population to the extent that we use marijuana is attributable to genetic factors. The traditional way that you would capture that correlation would be using twins, identical twins who share all their DNA versus fraternal twins who don't share all their DNA, they only share 50% of their genetic background. But the prevalence of schizophrenia is so low that you'd be hard press to find a sample of twins where you'd get adequate numbers of individuals with schizophrenia. So this seem like a real challenge until recently when genome **[00:42:00]** wide association studies this approach of

interrogating your entire genome for association with disorder became very common. And what they led to were these aggregated genetic scores that I've been telling you about the addition of the small effects of variants all across our genome that contribute and shape our quantitative liability genetically to a disorder.

And this study was actually published on Monday right -- brand new and what they find here is fascinating, and I'm going to show you a couple of examples of this. They found that individual aggregated genomic liability to schizophrenia in patients who had schizophrenia was also correlated with their past likelihood of daily cannabis use. So this is a very interesting and new perspective in that it suggest that there are common genetic underpinnings to using heavily and misusing marijuana **[00:43:00]** and the susceptibility to schizophrenia. Now you might argue that in a sample of schizophrenics genetic liability to schizophrenia use would be high. So to counter that argument at least two studies have looked at this genetic susceptibility to schizophrenia which as you know we all carry to some degree on this continuum was associated with cannabis use in the general population.

The first study here where you see the series of red and orange and yellow bars was conducted in a population of Australians where nobody had schizophrenia. And what they found really from these bars is that the height of the bars actually represent the extent to which marijuana use by the individuals in this population is associated with genetic vulnerability to schizophrenia. And the various bars represent the number of markers across the genome that you're adding up so the more markers you add the more of this liability that you're able to explain. And so in a general population sample even not in a sample of **[00:44:00]** of individuals with schizophrenia genetic vulnerability to cannabis use and genetic vulnerability to schizophrenia were correlated. And we're now beginning to guess that this correlation is somewhere in the order of 0.2 which kind of seems small, but remember these are highly multi-factorial disorders with genes and environment all acting together and we're talking about our entire genome.

In another study our colleagues at Wash U examine the association between a variety of substances and genetic liability to variety of disorders. And I want to draw our attention specifically to the cannabis association, so look at the series, this checker box pattern here of hot red squares, that shows that in a sample of cannabis dependent individuals those who are more dependent actually carry a higher susceptibility genetically the schizophrenia as well as depression which we'll talk about next. So across the board we're beginning to think that assessing causality in humans becomes a little challenging because of all these evidence supplier trophy **[00:45:00]** of shared genetic factors. We certainly need to identify what these common genetic pathways are because then we can intervene accordingly. But a possibility is that over and above these shared genetic factors are other factors, this could be environmental factors, they maybe indirectly causal, how do you identify them.

So I want to go back to this analogy of using twins, this is a major component of the work we do. And the strategy we've adopted is to take pairs of identical twins that genetically matched, same in utero environment, take pairs of identical twins where one uses marijuana and the other does not. So this is our dream natural experiment, right, we can't assign people to a use cannabis and a not use cannabis category. But we can leverage the idea that some people naturally pairs of twins one does use and one does not. And you'd be surprise we get a substantial number of twins that varied quite dramatically in where there one twin uses or uses heavily and the other does not. It's hard to study schizophrenia **[00:46:00]** in a twin population but you can study psychosis like experiences, and these are fairly prevalent.

So I want to draw your attention to this set of bars in the middle. What you're looking at here is the prevalence of psychosis like experience and this ranges from I think people are reading my mind too, I sometimes have magical odd eccentric ways of thinking. So quite a range and diversity of psychosis like experiences but the twin who uses cannabis relative to their genetically identical counterpart is far more likely across their lifetime to report more psychosis like experiences, so even matching for this lovely genetic correlation that we've been estimating there appears to be something over and above that correlation. Now whether that is something attributable to the psychoactive aspects of cannabis use or perhaps something that happens along the pathway between cannabis and schizophrenia is something we still need to understand.

Another fascinating **[00:47:00]** approach that genetics has given us towards understanding the relationship between cannabis and schizophrenia is something called Mendelian Randomization. And this is a -- kind of fascinating idea where we assume that all of us at birth are randomized to having a risk genotype or a protective genotype. We have no control over that it's whatever we get from mom and dad and there's a 50-50 chance we'll get one or the other. So if you're randomized to being more attracted to psychoactive substances to being a heavier cannabis user and that genotype is associated with subsequently developing schizophrenia you may begin to think there are other pathways that lead from heavy cannabis use to schizophrenia. And this study here shows that in fact these 10 genotypes that are nominally associated with liability to cannabis use also show associations with schizophrenia. So this could mean that there are common genetic pathways, it could also mean that if you get randomize into the environment or the **[00:48:00]** situation or the personality or the context of cannabis use that may take you down a pathway that may increase your chances of psychosis like experience as in schizophrenia.

These analyses clearly demonstrate that there are more than genetic factors, genetic factors are very important but environment that a person makes for themselves, creates for themselves and is exposed to individually is very important. You know, cannabis use does not occur in a vacuum, persistence cannabis use particularly during

adolescence is associated with lack of achievement of lifetime goals, unemployment. Dr. Madras showed you some of those slides that outline the trajectory that a youth might take if they start using marijuana and use it heavily. So some of these individual specific factors might become really pertinent in making these connections.

One of these factors that we need to keep in mind is actually potency, this is a fascinating study out of the UK in which **[00:49:00]** they looked at first episode psychosis patients. And they compared the extent to which these individuals reported using a high potency form of cannabis skunk in the study really just represented their -- all of their high potency forms versus marijuana or hash which was their normative or low potency forms. And they found that even though first episode psychosis patients did not differ from the control population in terms of how much or whether they use marijuana, they were considerably more likely to have reported using a high potency form. So the take home message from this is that there does not appear to be much evidence for a straight forward causal model. There are some evidence of risk in genetically vulnerable individuals, there's overwhelming support for shared biology factors other than shared biology are likely to be important. And there are some support for increase correlation in the context of high potency use.

So in the next couple of minutes let me just give you a quick overview of a similar relationship between cannabis and depression. This is a longitudinal **[00:50:00]** study that shows very clearly that daily cannabis use is associated with suicide attempt in a prospective manner. Unlike psychosis we actually have a compelling molecular biological theory here the same endocannabinoid system that marijuana acts on. Dr. Madras talked about the CB1 receptors, it's also a target for stress regulation and mood management. In fact in a study we found that individuals who had a variant in the gene that was associated or -- associated with coding the cannabinoids 1 receptor actually was also associated with increased vulnerability to anhedonia in individuals who'd experience severe childhood abuse. And stress really seems to be the activator of the system, individuals who experience chronic persistent and unpredictable stress seek significant modulation of their endocannabinoid system. Some cannabinoid -- endocannabinoids go up some go down and this really modifies the way the hypothalamic **[00:51:00]** pituitary adrenal axis helps us react to stress and modify our mood.

So does cannabis use predict suicidality? Most of the evidence suggest that early on sort of cannabis use may have a minimal effect, we know from a recent study that acute cannabis use occurring 24 hours before suicide attempt is not actually a risk factor but that alcohol is. We also know from a couple of studies that someone disagree with each other that the relationship between medical marijuana laws and suicide vulnerability might also be explained by other policies in the study. Investigators initially found an increase likelihood of suicide and increase rate of suicide in states that had

legalize marijuana for medical purposes. But when you control for other tobacco policies in those states that association went away. What we find is that there is an elevated likelihood of suicidal ideation and major depressive disorder in this **[00:52:00]** twin pair design where one twin uses cannabis very heavily and the other does not. So it appears that there seems to be some kind of association over and above shared genetic factors that could be attributable to individual specific variance and that disassociation for depression and suicide maybe somewhat different. Individuals who themselves do not use marijuana where the co-twin uses it actually are an increased risk for depression. So there might be some kind of environment that your co-twin brings in.

So I want to conclude by thinking about whether preventing cannabis use can reduce mental illness, and I think the answer is yes but the pathway is likely to be fairly complicated and not as straightforward as causation. Without a doubt reduction of cannabis particularly heavy and persistent use will likely assist in recovery from psychiatric illness, it is a major confounding factor. And there are some things we need to keep in mind in particular shared predispositions when we think of the relationship between cannabis and psychiatric **[00:53:00]** disorders. Thank you very much for your time.

Robert L. DuPont: Thank you very much, an excellent presentation. Our next presentation is by Adriaan Bruijnzeel is an Associate Professor in the Department of Psychiatry at the University of Florida College of Medicine in Gainesville, Florida His current research suggest that drug addiction is a chronic disorder that is characterized by compulsive drug taking and relapse after a periods of absence. The research in his laboratory focuses on the development of non-addictive treatments for nicotine, alcohol and opioid addiction. His research group has sown that a corticotropin-releasing factor mediates the negative mood associated with nicotine and alcohol withdrawal and plays a critical **[00:54:00]** role in stress reduction -- stress induced relapse of extinguished nicotine seeking behavior. His studies may lead to the development of treatments that decrease drug abuse in humans and prevent relapse after periods of abstinence. Dr. Bruijnzeel will speak on original brain studies prove secondhand marijuana like tobacco smoke is addicting.

Adriaan Bruijnzeel: Thank you, so I will talk about the development of cannabis dependents and I will actually start out just talking a little bit about nicotine dependents because it explains our mobile variable. So drug abuse is a major health risk factor, tobacco smoking leads to -- tobacco smoking leads to 400,000 death each year, poor diet **[00:55:00]** and lack of physical activity at the second spot, alcohol consumption is to the third spot. And interestingly a legal drug use is actually really at the bottom so it doesn't means that a legal drugs cause more people to die like, also the legal drugs are very dangerous and lead to a lot of problems in society.

So I wanted to show the slide about cannabis use because I was actually amazed how common it is. If you look at the people who are between the ages of 18 and 25 more than 50% has used cannabis, 30% use during the last year and 20% use during the last month, so cannabis use has just become so extremely common among young people. So the legalization of cannabis is a concern because it might lead to an even further increase. So this slide demonstrates Calls to Colorado Poison Center **[00:56:00]** before and after medical marijuana dispensaries were allowed in that area. And you see like after 2009 when they were allowed you saw many more like calls related to cannabis intoxication. So this seems to suggest that like cannabis becomes legal there might lead to an increase used or at least in increase number of like also poison control center.

So when people develop a drug addiction it's a big problem and they -- because when they stop using the drug they feel very anxious, they become depressed, they cannot focus anymore and depending on the drug they have somatic withdrawal signs. So when you get to this first stage then the problems are not really solved and you deal with the protracted withdrawal syndrome. And this syndrome can **[00:57:00]** can last for decades or basically the rest of your life, so this -- during this periods stressor then use very strong negative emotional drugs trait -- stage in drug users and it lead them to craving and relapse. Also the cues associated with drug use can lead to craving or relapse so let's say somebody has been smoke or using drugs in a certain area and they move away and they don't feel those cravings as much but then they move back and they've been re-exposed all the cues associated with drug use. It's very likely that it uses craving and relapse. And also when you take a very small amount of abused drug or another drug that can lead to craving and relapse.

So this is a slide that they bought from George Cope who has done a lot of work in this area. And it shows that people start using drugs because they -- they think it's exciting they try it they like it, so it makes people feel good **[00:58:00]** they get excited about. But they continue to use drug to prevent negative mood state associated with drug withdrawal. So drug taking starts out as like an impulse control disorder, people think oh should I take the drug, should I not take the drug, they're at a party they don't then call a impulses variable and so they take the drug and they like it. But it gradually develops into a compose disorder, when people don't take the drug they feel very stress and anxious it becomes like repetitive behavior then they take the drug, they feel better and it becomes an obsession so they end up in this loop. So they take it first they like it and they get excited about it and then basically have to take it.

So this is a slide from an old paper by John Cryan [PH]. So he work with animals and the thing is when you work with animals you cannot ask how they feel. **[00:59:00]** So in order to ask our animals how they feel we implant electrodes in their brain. And stimulation of these electrodes are extremely rewarding and we use this technique to --

an indication of the state of the brain reward system. So if you give rats -- you give a drug to the rat then they become more sensitive to those rewarding electrode stimuli. During drug withdrawal they become less sensitive. Here you can see it more detail how to procedure work, so the rate receives a stimulus in the brain of a certain strength, if the rat likes it they turn the wheel and they get it again. Then we gradually lower the current and at some point the rat doesn't like it anymore so then we increase the current, we -- current, we increase the current and we get a brain reward threshold. And this brain reward threshold stays the same for over the life of a rat. It depends on the **[01:00:00]** location of the electrode mainly and how the electrode performs. But in a healthy rat is does not change.

So that's why we can use this model to investigate the effects of drugs of abuse on the state of the brain reward system. So we have mainly done a lot of work on nicotine so I want to kind of demonstrate some of our work. Then we give a little bit of nicotine to nondependent animals, here in the left you can see the brain reward thresholds go down so it means if a little bit of nicotine is rewarding not very rewarding but it is rewarding. If we give too much it's not rewarding it becomes aversive really quick, so you have to be careful how much nicotine you take. Here you see the response latency, this is the time between the stimulus that the rat's receive or free and then they turn response wheel to get the second stimulus. **[01:01:00]** So you see nicotine decreases to latency so that means that like nicotine is a stimulant and everybody knows when you take -- when people take nicotine they can respond quicker it's a stimulant.

So in order to induce dependence we use this osmotic mini pumps. So infuse some nicotine in the pump or any other drug that we're interested in, the implement of the skin and if the dose is high enough the rats become dependent. So what happens when you give like an antagonist to dependent animals they go into withdrawal, it's the same as humans if you have a heroin abuser and you give them a high dose of an opioid antagonist they will go into very severe withdrawal right away, so we see that in our animals too. So the rats are dependent, we give them a nicotine -- antagonist and the threshold's go up off the nicotine rats and this compound has **[01:02:00]** no effect in the control rat. So if nicotine dependent rats, we suddenly block the nicotine receptors and they go into negative mood state. It's only very brief because the drug is metabolize really quick so in half hour or so an hour they are completely back to normal and you can look at the effect of another dose or -- but mostly you wait a few days.

So that's precipitated withdrawal, they can also talk the pumps out that's spontaneous withdrawal. That really models when somebody has being abusing a drug for a long time and they just suddenly stop. So what happens to these people they feel very bad for like three or four days or so, and that's what we see now a model. So you plant this pumps if the 14 days we take the pumps out and for a few days the brain reward

thresholds are elevated so the animals are not feeling so well, but then the thresholds go back to normal. So we can use this model **[01:03:00]** to evaluate potential treatments for smoking suggestion like for varenicline and bupropion they are highly active they -- they prevent this negative mood state associated with nicotine withdrawal.

So then Dr. Gold came along my former mentor and he said, you know, he said smoking is not just nicotine it's about the 4000 compounds in tobacco smoke it's much more than nicotine. So in order to study the effects of smoke on the brain we bought a smoke machine and then we can expose freely moving animals to tobacco smoke. So we can do very low dose system model, secondhand smoke, higher doses kind of to model tobacco smoke exposure and we can use all types of cigarettes, low nicotine, high nicotine. So then we looked at the precipitated tobacco smoke withdrawal on brain reward function. So the exposed animals due to **[01:04:00]** tobacco smoke for few weeks few hours a day and then we suddenly block their nicotinic receptors and then you see the thresholds going up. So this basically means that chronic passive exposure to tobacco smoke can leads to nicotine dependence.

So then we had that model and then we started to think okay what happens with cannabis smoke exposure, does exposure to cannabis smoke also lead to dependence, it was well known. So we prepared our rats which was electrodes in the brain then you expose them to air or cannabis smoke for 50 or 100 minutes per day for 10 days. So it's relatively short amount of time. Then at least after 10 days of exposure we gave them a cannabis antagonist and it's called Rimonabant. We also collected blood samples **[01:05:00]** look at THC levels and so we determine to THC levels. And here you can see the effects of precipitated cannabis smoke withdrawal in brain reward system. So we have our control animals who have not been expose to cannabis smoke, then we have like some rats that have got five cigarettes per day for 10 days and other group got 10 cigarettes per day for 10 days. And as you can see in the -- when we block the cannabis receptors then suddenly the thresholds go up, the threshold of the smoke exposed animals go up. So this indicates that the passive exposure to the tobacco smoke induces adaptations in the cannabinoid signaling system. And these are some early signs of dependence so it basically indicates that passive exposure to cannabis smoke leads to **[01:06:00]** dependence.

So we also looked at the THC levels in those animals. First we look after [inaudible 01:06:08] after the smoke exposure and we were really surprise the levels were very, very low and we were wondering how is it possible that's -- such low levels lead to dependence. But then we looked at different time points and it turns out when you look like 15 minutes after the smoke exposure we see very high levels of THC. So what you see with THC after the inhalation there it's just like a very, very quick drop in THC levels. THC goes very, very quick from the blood into fat tissues into the brain. So it's around -- it's in the system for very, very long time at a very low levels, but so immediately after

the smoke exposure you can detect a high levels and then there's a very quick drop. **[01:07:00]**

So a little summary, so our work had showed that drug withdrawal leads to a negative mood state that is reflected in elevations and brain reward thresholds. Passive exposure to cannabis smoke leads to development of signs of cannabis dependence and this is a concern because negative mood state associated with this drug intake help to maintain the drug addiction. Drug addiction is at least partly driven by the negative mood state associated with drug withdrawal, all right thank you.

Robert L. DuPont: Thank you Adriaan. I want to make a couple of points before I get into my own presentation here **[01:08:00]** first of all I want to notice that Adriaan talked about Mark Gold who is unfortunately not able to be here. But Mark Gold put together and extraordinary group of researchers and clinicians in addiction at the University of Florida in Gainesville and has made a tremendous contribution to our country by what he's done in his own work but also the team that he's put together that continues to produce absolutely outstanding work as Adriaan is a great example of that, I want to emphasize that. And the other thing is I'm a psychiatrist and if you look at mental disorders, it's hard to find animal models for that but you don't have a problem with addiction, it's very interesting to think about this. And for all the struggle with understanding about risks of addiction, but when we're talking about the brain effects of the chemicals now that's different from the behavior of addiction **[01:09:00]** which has all kinds of other determinants but just what the brain is doing. Notice that it doesn't have to do with an old rat or a young rat, a female rat or a male rat, a black rat or a white rat all the kind of things that we think about as effecting drugs. And when you look at the animals it does have anything to do with what's going on, and that's very important to think about the vulnerability to drugs in terms of what that brain effect is.

Okay, so now I'm going to change to a really very different level of thinking and think about a social problem of major significance that is related to cannabis or marijuana use and that is highway safety. Everybody who comes to this question wants to find what the level is **[01:10:00]** of THC that is now as to the 0.08 which is the per se standard for alcohol impairment. And when they don't find it they think they need more research, and I'm going to show you why they don't find it and why more researches not going to help them find it. Now first of all the problem is very large and it is growing, and here are some examples I'll show you several examples of this, this is a National Roadside Survey. You'll notice this 2007 survey found 16.3% were drug positive of the weekend nighttime drivers and that time period was picked because that's more likely to be associated with alcohol and drug use. So to -- it was interesting in that, but that number was so surprising that it led to the White House Drug Czar at that time Gil Kerlikowski **[01:11:00]** to define drug driving as a major national priority in the federal strategy for the first time, so this is a good example of a survey that had a dramatic effect on public

policy. Now this is fatally injured drivers and you'll notice in 2005 28% were positive, 2013 40% were positive for drugs, and we're going to look at some of the --what the drugs are but the biggest one in all this is marijuana.

Now I'm not going to go through this, these are some of the effects of marijuana use on driving related behaviors. And they are very large and they are additive with alcohol and we're going to see that there's a lot of cannabis and alcohol together. Here is the National Roadside Survey's **[01:12:00]** samples of THC showing a dramatic increase that has gone on in these -- among these drivers. Traffic fatalities in cannabis increased in Colorado, you see the data here and all traffic fatalities also increased in Colorado over that period of time. And here is percent of all traffic deaths from the farthest data associated with -- that show marijuana and you see the significant rise over this period 2006 to 2015. Washington State shows similar data about the cannabis related **[01:13:00]** driving problems.

Okay, the hope as I say is this look for this level and several states have adopted levels particularly likely to be taking is the five nanogram and Adriaan made a point a moment ago about what happens when a person is -- or an animal expose to cannabis, and that is there's a very rapid increase in the blood THC level and a precipitous fall. And that's because as he said the THC goes out of the blood but it stays in the brain, and you will hear all the time people say well they had a highway study and they show that there was carboxy-THC a metabolite of THC but they didn't find THC. Therefore, that's not related to the cannabis, that's the sort of logic of that. But what's missing of that is that the metabolite **[01:14:00]** the carboxy-THC is quickly eliminated from the body through the urine, it does not stay in the body. If there is the metabolite carboxy-THC in the urine there is THC in the brain. You can argue about whether it's enough to make a difference that's a different question but it's really important that you take away the next time somebody tells you well that's just the metabolite in there. Remember that metabolite is a marker of what's retained in the brain which is the THC.

Now, the reality is that people say well marijuana is an odd drug, somehow alcohol is a normal drug in terms of these issues. And the answer is no it's not, it's alcohol that's the odd drug not marijuana. And problem is that there is a profound effect of tolerance **[01:15:00]** on behavior including driving behavior. And so the level of a THC that is associated with impairment in a tolerant person is orders of magnitude different from a non-tolerant person that's also true for alcohol but it's much less true for alcohol. It is true that many people at 0.08 or much higher pass the field sobriety test because of the tolerance the alcohol whereas many drivers at 0.05 are severely impaired by it, but that is very important. And I just use the example of the opioids a simple factor in this -- understand impairment the sort of ultimate impairment is death. And if you take opioids and take methadone, a methadone dose of 40 milligrams with non-tolerant person is lethal. A 100 milligrams shows no impairment **[01:16:00]** in the tolerant methadone

patient. So what's your blood level going to be the 0.08 for methadone, that's the problem.

Now here's data from Sweden that's very striking about these numbers to look at drivers. Now, these -- all these drivers were arrested for impairment just with marijuana, so they've been arrested for being impaired and then you look at their blood levels. And this is really what shall I say sobering to look at this. The THC 43% had concentrations less than 1 nanogram not 5 nanograms and 90% had concentrations that's what shows how stupid the 5 nanograms standard is that is going across this country right now.

Here are some data from Washington State about this, I'm going to kind of rush through some of these slides because I'm **[01:17:00]** concerned about our time. But the data is here for people who want to look at it. The -- here is one of my points that I really want to make sure you understand, to get a drug test in a highway setting you have to first be arrested as impaired, now think about that. There's a decision made by the officer that this driver is impaired that's why the test is done, it's not just every driver driving down the road and that's really important to think about what this is, that's true for alcohol also. A driver who passes the field sobriety test is not giving an alcohol test, you have to fill -- that's why the average alcohol level of person failing field sobriety is 0.15 it's double **[01:18:00]** because you got to fail that test first before you're getting tested -- before you tested. And also showing that the chronic marijuana use has measurable impairments three weeks after the last use, so this is a lot more complicated.

And also here's something very important poly substance use is a very big problem in this sample that it's not so often to see either just alcohol or just marijuana but there's also other drugs as well as those that are very commonly part of this. This has change overtime in Washington State, and you'll notice the items the things that are going up THC is going up, THC with alcohol and you'll notice those very big numbers while alcohol alone is going down over the course of that period of time. **[01:19:00]**

Now I'm going to just spend a few minutes on what can be done because people get -- when they hear this they think well then nothing can be done, no that's not true. We know that more research -- I'm trying to find a 0.08 cannot solve the problem, I have a great belief in research I'm all for research, on this point you're not going to come up with an answer to that problem. So there's idea that somehow down the road we're going to do this, it's not going to happen. But there are lots of good ideas for what can be done. The simplest one is all drivers who are arrested for impairment to test them for drugs as well as alcohol, we don’t do that now but that would make a huge difference in terms of identifying this problem.

Second thing is when a drug is illegal like heroin let's say, do you really want to have a heroin level in the highway setting, I don’t think so. If it's an illegal drug **[01:20:00]** the

per se standard is then -- then that -- that meets the standard of drug driving. And the same thing can be done with cannabis in the many situations where it is illegal to do that. The third thing to emphasize is that focus on the multiple drug use and have a separate category for that that you don't have to get to the same level of alcohol or marijuana if you got both of them together in terms of legality. And point here about administrative license revocation, this is an immediate step that is done when the person fails an onsite evidentiary test for the drug rather than waiting until this is finally adjudication. We need to standardize procedures and oral fluids testing is a great step forward **[01:21:00]** because it could be done easily at the roadside and it is only going to be positive for relatively few hours after cannabis use, you'll miss a lot of cannabis that way but it's a big step forward it's something that I think we really need to do. We need to standardize our databases particularly in fatally injured drivers and its trauma centers and educate the public about this.

Now, I want to end this by just emphasizing a couple of points. First of all I want to make sure you understand that this is a major battleground about marijuana, it is some ways the Achilles heel of the marijuana movement to legalize marijuana. And so it is very important that we work our way through a complicated problem but come to practical solutions that will **[01:22:00]** work to decrease this problem. So let me end my remarks there, thank you very much and I will ask the group, the other participants to come up and we're going to answer questions from all of you. So thank you very much.

[Informal Talk/Indistinct Voice]

All right we got two microphones in the audience. And I'd like anybody here to ask any of the three real experts or me a question and we will answer -- I'm going to pass the microphone **[01:23:00]** to the other folks come up here. So who would like to start us off with something that you're interested in about marijuana and research or whatever that you'd like to ask about.

[Informal Talk]

Dorothy: This is really not a question I'm just concern. My name is Dorothy and I work for the Diversion Control in Chemical Evaluation section here at DEA. And I was really focused when you talked about the ALR the license revocation, what would it take to put something like that in place I mean is it something that had to go through legislation.

Robert L. DuPont: Yes it would have to as I understand it but is become fairly common place for alcohol. And so you use that as a precedent of it absolutely. **[01:24:00]** Yes that's what I would suggest, and it just look up administrative license revocation and I think you'll find pretty good things. I'm not an attorney but it is widely used now and I think it can be used because it's very important, otherwise what happens is the person,

you know, gets their license and goes on driving after they fail the drug test and that's not a good thing. Yes.

Male: Dr. DuPont thank you, picking up on your last point about impaired driving and I'm sure you've heard this argument from the other side, I'm curious how you would respond to it. There were those who would say wellbeing having THC in your system doesn't mean anything when you're driving because you could have smoke say days ago week ago and the effects are all gone. So what responds would you have to that?

Robert L. DuPont: Well first of all you're not going to get tested unless you fail **[01:25:00]** a field sobriety test, you got to have somebody -- somebody's got to make a judgment to get you tested and you've -- the officer has made that judgment, so that's the first thing. The second thing is to think about that that the -- there's a lot of confusion about marijuana -- both the THC and the carboxy-THC. Now, what you hear is that you can smoke marijuana and be positive for a month or two months, that's not right. At a standard urine test, after one or two joints 50% of the people are negative 24 hours later, all of them are negative within three days. The people who are positive for the long periods are the heavy users and that's true. You can be **[01:26:00]** if you're a daily smoker and you stop you can be positive for two or three months after that and that's because the tissue is -- your brain tissue and all your fat tissue is saturated that's right. But a person who's smoking intermittently is going to be negative pretty quickly, now not -- they're not negative in six hours but that's another reason to go into the use of the oral fluids test which just gets people in the last six hours pretty much for an oral fluids test positive.

[Informal Talk]

Male: Dr. DuPont I believe I heard you say that legal marijuana in Colorado has killed people on the highways, is that correct?

Robert L. DuPont: I wouldn't say it quite that way, no. I think that the -- there has been an increase in **[01:27:00]** deaths in Colorado as I -- I -- just go back to my slides I'm not sure what exactly that said. But I think that that is true, but I don't think the legal marijuana is the issue, I really don't I think it's the marijuana use that's the issue whether it's legal or illegal.

Female: All right, we have a question from a web viewer for Dr. Madras. Is marijuana an effective treatment for opioid addiction, and does marijuana use reduced opioid overdose deaths? The pro-marijuana lobby uses these arguments to promote medical marijuana legalization.

Dr. Bertha Madras: I think the answer is that the data is not available yet. You know, just looking at state overdose deaths and comparing that to legalization or to

medicalization does not give you a specific **[01:28:00]** view of what is happening to an individual in an individual basis. We also have to remember a very important thing and that is a lot of people who use psychoactive drugs opioids and marijuana use them for pain but we have to remember that both those drugs have other effects that are what one could call psychological calming in terms of depression, in terms of sleep disorders, it's a very complicated issue. And I think that what we have to really look at is interrogate which people are using opioids for what reason, are they using them because they've been prescribed them or are they using them because they have **[01:29:00]** to -- have access to diverted opioids and is there bonafide pain, is there not. This is still a very early time in the studies that would try to look at a relationship. The data from Colorado are not promising, heroin overdose deaths and use disorder are soaring in that state since legalization has occurred. So we do have some journal articles that claim that there's an inverse correlation. I think that that is so premature that to make policy based on those articles which are not specific they're just population studies are inadequate.

[Informal Talk] **[01:30:00]**

Female: It is such a treat to have all four of you here at the same time, and I have a couple of questions for each of you but I'll be respectful of Dan and cut it down. I'll continue with the -- the highway and the driving impairment discussion with you. Would it be simplest to match the blood alcohol level principle by simply picking a threshold that is very low in those states that have chosen to allow marijuana use?

Robert L. DuPont: No the problem is you can't defend it **[01:31:00]** because you got people who are impaired at very low levels and people who are not impaired at high levels.

Female: But isn't that the case also with alcohol as you mentioned?

Robert L. DuPont: Well it's less of the case but it is the case with alcohol too and we don’t think about it, we just accept the 0.08 when people say well, you know, who's impaired? They say well that's 0.08, well no. I want to back up though because this is exactly -- extremely important point. When I was the first director of NIDA the first research paper book we ever publish was about drug driving which is sort of amazing to think about. And I wrote the introduction and I was certainly naïve about everything but including this, I said well why worry about testing why don’t we just test for impairment. And if a person is impaired it doesn’t really matter whether it's because of alcohol or marijuana or anything impaired you don’t want to be who drive, and if they're not impaired you don’t mind they drive whether they're taking marijuana or not **[01:32:00]** seem clear to me. Well that was even more naïve than now because you don’t have any test of impairment and that's very interesting to think about that because it's logical

you think that's a good idea but you get very interesting thing. The General Motors had a test in that early era of an interlock where you get in the car and turn on your key and a group of numbers would come up on a screen and you would have two seconds to introduce those numbers, that was going to be the test of impairment, seem good to me, what did they find? A whole lot of drunk people could do it and a whole lot of sober people couldn't do it. And it's a serious problem because you get an overlap, I sort of use the example from in that era of basketball and you get -- Michael Jordan can put it in when he's falling down **[01:33:00]** and I can't get it in when I'm sober. And that's the problem with testing for impairment. Bertha you guys ---

Dr. Bertha Madras: Sure, when Richard Compton at NetSA [PH] did the initial studies that determine the 0.08 blood alcohol level he used a very simple empirical correlation that is at what point in alcohol do you get a steep rise in traffic accidents. And you see alcohol blood level's going up very, very incrementally and then at 0.08 there's this sharp steep peak and that was the empirical data that was used to develop the cutoff point. With regard to marijuana and many other drugs alcohol is unique as Bob said very eloquently because it defuses across everything, it's lipophilic it's hydrophilic. So it will be in **[01:34:00]** water, it will be in fat at the pretty similar concentrations. With regard to THC the hydrophilic to lipophilic ratio is very different, and I'll give you an example of that. When I was studying -- we were working a brain imaging agent that was quite lipophilic and it was very -- it was hot, it was radioactive it was labeled with iodine.

We could not detect one radioactive molecule in blood, we ran the iodine detector over the entire animal it -- there wasn't one blip above background. When we went to the brain it went off-scale because it just accumulated and stuck in the brain, not even the periphery **[01:35:00]** in terms of peripheral fat which was quite surprising. So that ratio of brain to blood is really critical, and I think that it's something that plagues the whole field of drug policy in terms of highway safety. But there are people who are working on alternatives to it, there's an excellent investigator at the Mass General who has developed a device that monitors it's sort of a portable MRI device that monitors parameters of brain function in people under the influence of cannabis, and which she's also correlated that to neuropsychological deficits. And I think that's where the field is going to very state of the art devices that may **[01:36:00]** help us circumvent this whole -- from my -- from my perspective blood levels, plasma levels are meaningless. And I'm reiterating what Bob said but I think device development may in fact be able and devices that can detect certain brain parameters that are correlated with cognitive in capacity or driving in capacity may help us enormously.

Robert L. DuPont: Let me just mention one thing that I am the president of a nonprofit organization the Institute for Behavior and Health and we have a website www.stopdruggeddriving.org and you'll find information in there about Administrative

License Revocation and other things too for anybody who's interested in this discussion. I'm less saying when --and Bertha is about this test but give you -- but it is exciting and I've been wrong about a lot of things I could be wrong about this too. **[01:37:00]** But another test that is very exciting is a test of eye movement using very sophisticated measures. And one of the nifty things about it is it gives a nice readout of what the finding is that can be used in court case, and that's very good. The question is going to be how well that's correlated with the parameters of driving impairment and that will be a very good -- very important question. I wonder if we want the two people -- this the heavy duty scientist here to say something I'm worried about Bertha and me especially me doing all the talking.

Female: I have a question for Dr. Agrawal.

Robert L. DuPont: Thank you.

Female: I have followed closely the discussion in the literature on the relationship between early marijuana use and the development of schizophrenia and psychosis. And **[01:38:00]** all this anxiety about the -- neuter and nature interaction that you've mentioned as environment and stimulus relationship, that exist in every disease, right, and yet on the pack of every cigarette we don't dispute that smoking cigarettes causes cancer. Would -- if we were to look into cigarette smoking and as much granularity or maybe a disease that has a lower incidence in the general population than cancer, something that has an incident closer to that of psychosis and schizophrenia. Would we get in our own way in the same way by saying oh maybe the stimulus on its own does not cause the disease, would we be as cautious. I fear that we sometimes are too cautious with marijuana **[01:39:00]** both in establishing thresholds and in establishing a causality because we look in such a granular fashion in the science. We look so deep and we create so many caveats, it's like burden of proof is amplified compare to all other diseases and all other risk taking behavior in public health, what do you think about that?

Arpana Agrawal: Now that's an excellent point, I think we do in fact a very high standard when it comes to human studies. And I think the reason for that is these are complicated disorders I think from a geneticist perspective we call them complex traits or complex disorders. They're not simple genetically you will think something like schizophrenia which is very straightforward from the context of having a clear neurobiological underpinning, we've identified what 200 genetic markers that are associated with that, we know there are thousands more. And these markers interface **[01:40:00]** with each other constantly. So I think the question is less whether cannabis use or heavy use is correlated with it. The problem is the pathway that underlies that association is more challenging to determine and it's because you are studying humans. So I think by doing translational work, so looking at animals where you can control for

some of those confounds, you can kind of chip away at pieces of the puzzle, but it is still a more complex puzzle. And I think that you can look at cancers or you can think of even a normally distributed trait like height. With psychiatric disorders, there is an incredible level of polygenicity, it is more layered and I think as Adrian very nicely pointed out you can't ask an animal do they think the government is reading their mind. It's the mouse model, the [inaudible 01:40:50] model is an aspect of human behavior. So you can carve away at aspects of that mechanistic pathway, but I think being **[01:41:00]** very specific about causation is challenging in humans, you can kind of get at whether there is evidence for it but in my opinion proving causation in the human model is very challenging just because there are these confounds, and they are real confounds I think what – and it's again a challenge with population based studies people that are different they are so much heterogeneity why five individuals end up on a pathway to cannabis dependence are so different from five other individuals. So I think that that complexity is somewhat implicit in the human design.

Dr. Bertha Madras: I would just like to weigh in on this. I always – we always try to be cautious, but there are few areas in cannabis research in humans that I think are worth highlighting. One is that in normal people without any history who are just lab subjects and that their administered THC, this is studies done by **[01:42:00]** [inaudible 01:42:00], what they do is the THC induces symptoms of psychosis acutely without any background, without any concern about genetics. You just take Bob and you take myself or any member of the panel and you give them sufficiently high doses of THC and we are going to be able to self-report that we have paranoia, we have possibly delusions, depersonalization. So it can trigger symptoms of a psychosis acutely that's number one. Number two, dose dependence, the higher the dose the more likely there is listed symptoms of psychosis. Number three, duration of use, as we saw in the study that I **[01:43:00]** reported done by others in adolescent the longer they use the more they develop increasing levels of symptoms that are associated with schizophrenia, but not necessarily diagnosable schizophrenia. So the evidence is mounting very significantly. There are a number of people who try to define what are the data that are needed to prove causation and one of them is biological possibility, the second is dose response, the third is sequence, in other words, did the schizophrenia arise before or after the cannabis.

Number four, are symptoms of psychosis exacerbated with the use of cannabis. The evidence is overwhelming in that as well **[01:44:00]** because people with schizophrenia who use cannabis have much higher relapse rates, greater numbers of rehospitalization and greater self-reported symptoms of psychosis. So there are number of criteria that have already been met, and biological possibility because hypo dopamine levels in the frontal cortex are associated with early onset schizophrenia and cannabis use after long-term reduces dopamine release in the frontal cortex. So these are all interesting

and very important data points and more and more people are beginning to say that the evidence is pointing in the direction of causality, but what is missing is as you have so **[01:45:00]** eloquently pointed out is the precise biological pathway. And I think the co-registration of polygenetic propensity to develop schizophrenia and to develop a cannabis confounds the picture but the other data that I summarized is pretty straightforward.

Robert L. DuPont: Did you have a question for Adrian?

Audience: I do.

Robert L. DuPont: Good.

Audience: [inaudible 01:45:34].

Robert L. DuPont: Let's have one for Adrian.

Adriaan: Okay thank you.

Female: Actually I have another web question from the viewer. I don't know who it's for, but the question is in the treatment field we are seeing an increase in marijuana used disorders with co-occurring stimulant used disorders **[01:46:00]** usually related to an ADD, ADHD diagnoses. What are the special issues that need to be considered clinically when treating teens and young adults with both of these disorders? Does continue to use of prescribed psychostimulants create vulnerability to relapse generally?

Robert L. DuPont: Wow, okay. That's a very, very, very good question. I want to backup when answering it. We are talking about the opioid problem nationally, it's a big focus, but there are almost no patients addicted to opioids who are not using other drugs, usually many other drugs. So, for example, in the Florida Studies of Opioid Overdoses between 95 – about 95% of the opioid overdoses have multiple drugs average two to four at the time of death **[01:47:00]**, and this is true, this was a clinical question about when you see a patient with any addictive disorder they are likely to be using multiple drugs, and it's weird that our diagnoses the DSM 5 is substance specific, well the disease is not substance specific, the disorder is not substance specific. And that gets us all mixed up I think about our understanding of things and example here is the marijuana users and the use of stimulant drugs used to treat ADHD. There is a big question in the addiction treatment field about the use of control substances or for that matter alcohol and marijuana in a person who is in recovery. The person who has had the problem should they stop, if they have an opioid problem, do they just stop opioids, do they have to stop drinking, do they have to stop marijuana use **[01:48:00]**, ADHD medicine, benzodiazepines.

I think the simple standard I am a big proponent of the recovery movement of alcoholics anonymous and narcotics anonymous those people are experts at this recovery business from my point of view and they have a clear answer don't do it, if it's a drug that stimulates brain reward don't use it period all of them. Now it's not all the experts go along with that but that's the place to start about this. So I would say there is a risk, does everybody who has a marijuana problem who then uses ADHD medicine is that a problem for every person? No, it isn't. But it is a risk factor and I think you will have to be very careful about it.

Female: We are well over our time. We are well over our time so one question and then **[01:49:00]** if you didn't have your questions answered or queried our panelist will be available after we stop this session so one more question.

Audience: Alright this question is for Adrian.

Adriaan: Oh –

Audience: This is the basic science question.

Audience: Yes I actually have a basic science question. I thought you gave a very good present – all of you gave a very good presentation, but I thought it was interesting that you said that the rodents experience, the dependence or withdrawal syndrome from passive exposure to the marijuana smoke or even the nicotine smoke, and I was wondering if you could expand on that. And then I also noticed that you used five cigarettes or five joints and 10 joints as your dosages.

Adriaan: Yeah.

Audience: If you could explain that with respect to human relevance.

Adriaan: So we are actually just starting out this type of work. So we are really kind of guessing **[01:50:00]** kind of basing our tobacco war how much smoke we have to give. So we kind of hope to get up to a level of like 100 nanograms per mil into our cell. So yeah these were some early studies and we did just we smoked one cigarette at a time and we did five, we exposed them to the smoke from five cigarettes. But basically the machine allows us to we could burn like 10 cigarettes at the same time so we can change all the settings, we can change the airflow to the chamber. So there are lot of different things, we can change a lot of things on the machine, we can like – it's just kind of a starting point, we just had – we very did not know what kind of levels we were going to get. So it was kind of the first experiment. We have more experiences in tobacco smoke exposure **[01:51:00]**.

Audience: Just a follow up, have you thought of nose only exposure because it sounds like you are using I believe it's a dynamic chamber exposure?

Adriaan: Yeah we do whole body exposure. We are a little bit – I have lot of experience than any more behavioral studies and I am just a little bit concerned about the restraint and the stress that it causes, but you see this whole body exposure. Animals are most very calm, doesn't seem to bother them too much so I think from a behavioral standpoint and the view of the study stress systems, you don't have to introduce like an additional stressor like restraining the whole animal that's actually a big stressor. So we prefer that the animals can move around in a home cage during the sessions.

Audience: Thank you.

[01:52:00]

Female: I just want to thank everyone for being here and anyone viewing the webcast and thank our wonderful panelists for really thought provoking information today. So thank you all very much.

Male: Thank you for making it possible.

[Applause]

[Music]