Laurie Baty: I'm Laurie Baty the Director of the DEA Museum and this is our fiscal year '18 lecture series. This is the third of four lectures that we're going to have this fiscal year, and this year's overarching topic is to look at some old and not so old drugs. Today's speakers will look at synthetic drugs, and our last lecture of the year in September we'll look at opium and heroin. Not only do we have people here as I mentioned before but there are people watching through a live webcast. We're delighted that CME Outfitters is providing continuing medical education units for this program. They too are streaming online. A pleasant reminder, turn those darn cell phones off or put them on vibrate please. We expect the speakers to take about an hour with questions following all of the presentations. For those of you watching online, there is a link to e-mail questions at **[00:01:00]** deamuseum.org. Our moderator today is Mark Gold the national leader in addiction research. He's Chairman of RiverMend Health's Scientific Advisory Board and among other responsibilities serves as Chairman of the Addiction & Psychiatry Scientific Advisory Board and as the Chairman of the Eating Disorders and Obesity Scientific Advisory Board. Dr. Gold will introduce the speakers.

[Applause]

Mark Gold: Thanks to DEA for another great program. It's a great pleasure and honor to moderate which really means introduce the program, try to serve as a facilitator. This is a very easy program to facilitate because we have really world-class experts, **[00:02:00]** may be one but not specifically in this area. My own work has been mostly to partner with Jean Lud Cadet in methamphetamine and in ecstasy work in animal models, and I'll describe some of that as we go along. It's somewhat unusual to talk about depression and depression like treatment approaches in a DEA lecture but Gerard Sanacora and his colleagues at Yale have helped bring this front and center. Depression is a major public health problem, it's one of the most common diseases. If you add depression and suicide these would be huge problems among young people.

Just in a very recent report this month, major depression was seen as one of the number one health challenges in America today. People diagnosed with major depression are less **[00:03:00]** healthy. They have physical and other problems as well that go along with their depression, and they have overall decreases in quality of life and productivity. They use of way too much in the way of health care services as you can see in this Blue Cross analysis. The diagnosis of major depression according to Blue Cross is increasing and our treatments haven't kept pace.

Gerard Sanacora who'll be our first speaker leads the depression research initiatives at Yale University. His work in ketamine has been called both pioneering as well as the biggest single advance in depression and anti-depressants since the original SSRI invention Prozac and the like. He's a professor of psychiatry and he is going to discuss his **[00:04:00]** work on

ketamine and depression and suicide. In addition to this, ketamine's effect and effectiveness also tells us something very special and unique and new about depression. He can add a great deal to our understanding of both depression and the risks. Ketamine has been on the news, and I know from a DEA trip last summer that it still is a drug of abuse especially in Southeast Asia. I visited with the Hong Kong DEA and found that ketamine was being transhipped in from China Mainland and sold at pennies on a dose and used as a date rape drug. It's a case of profound new medical finding **[00:05:00]** in context of what are the risks versus benefits.

After Dr. Sanacora's talk, we'll have a talk from Charles Conway who is in Washington University in St. Louis where he is a professor and heads the treatment-resistant depression and neurostimulation clinic. Dental patients are familiar with nitrous oxide known as laughing gas, but Dr. Conway's work is revolutionizing our thoughts about nitrous and laughing gas as it would relate to the mechanisms of depression as well as the treatment of depression. People in DEA may remember some dental practices being broken into or lost nitrous canisters. Dr. Conway **[00:06:00]** will help us understand these in the context of his research on safe and effective use in a clinical setting.

Last but certainly not least is Jean Lud Cadet who I may have to fill in for. He has had a chronic back condition and exacerbated it yesterday at work and went home. He's taking medication and bed rest and we miss him terribly. For me, we've worked together since he was an intern at Columbia University. His work on methamphetamine and MDMA, I'll try to do justice to but there's no way that I could adequately replace him because while I'm trained in psychiatry, he is also trained in neurology. Did a full neurology residency and is a double boarded expert as well as **[00:07:00]** doing translational, really pioneering basic research.

All of this could be summarized in a recent article of Wall Street Journal which talks about designer drugs. The DEA must have anticipated this publication because it raised the questions that we're raising today. How can these drugs of abuse that we have a great deal of concern about be so effective? If they are so effective, how we can ensure that they are safely administered, and that's really the work that will be going on here in discussing. Hopefully everybody will get involved, ask questions and we'll have the chance to answer them to everyone's satisfaction. Without further ado, our first speaker is Gerard Sanacora, Professor of Psychiatry at Yale School of Medicine and Director of the Yale Depression **[00:08:00]** Research Program, Dr. Sanacora.

[Applause]

Gerard Sanacora: Thank you Dr. Gold and thank you for the invitation. Very much along the lines of what Dr. Gold was introducing, I'd like to talk a little bit about a drug medication that actually has actually been out since the 1970s, received an FDA indication as an anesthetic drug back in 1970. More recently

meaning over the last decade or two, has really stimulated interest in its potential benefits for patients suffering from depression and that being ketamine. I do have disclosures, I consult several companies and I also have research funded by some industry contracts, and also have a patent and hold shares in **[00:09:00]** Biohaven Pharmaceuticals. Let me just give a brief overview. The first thing I'd like to do is to try to convince you that there really is a great unmet need for new antidepressant treatments. People say there's already over two dozen antidepressants currently FDA indicative for the treatment of depression, do we really need new medications out there?

The second thing I'd really like to do is to cover the data that is available suggesting that ketamine and similar drugs may have a unique robust rapid onset of antidepressant effects that may have real clinical benefit. Obviously, I want to highlight here that neither ketamine nor any of the other ketamine like drugs I'll mention currently has FDA approval for the treatment of depression. Throughout this what I'd really like to do is to make sure that we keep it in balance so that we really highlight the limitations of our knowledge and really try to think about **[00:10:00]** what's a productive and responsible path to move forward with these treatments.

First, Dr. Gold already laid some of the groundwork. For those of you that may not be familiar with depression and the impact that it actually has on the society. The World Health Organization has labeled depression one of the leading causes of disability and a major contributor to the global burden of disease throughout the world. Dr. Gold mentioned that despite our progress in many of our existing disorders and illnesses, and actually decreasing mortality rates, suicide which is not completely secondary to depression but in large part related to depression, has not really, we have not made much of an impact at all over the past five or six decades. In fact, some of the evidence suggests that over the last two decades, the rates of suicide are actually increasing.

The third, and this gets back to the fact that we already have two **[00:11:00]** dozen antidepressants out there, do we need others? Suggests that these large studies like the STAR*D that was sponsored by the National Institute of Health show that our current treatments are pretty good, we do well, but there's still a significant amount of patients that don't respond. More importantly if they don't respond to the first two types of classical antidepressants which are all fairly much based on the same hypothesis targeting the monoaminergic system which is really serotonin or epinephrine and little bit of dopamine. If those drugs – if the first two don't work, the chance of the third or the fourth having success drops dramatically, so it leaves a large percentage of our patients that don't achieve a satisfactory response to our current treatments. Interestingly, even when it does work so in the classical antidepressants in this case in SSRI from the STAR*D study, citalopram. Even looking at **[00:12:00]** all the people that do get at least a 50% improvement meaning that they have a response to the drug, it takes them about six weeks for the average person to get there. It takes a month and a half

of treatment before they're achieving that clinically meaningful benefit. There clearly is room for improvement both in the percent of patients that we can get better, and also the speed that we can get people better.

As I mentioned for the most part, our existing drugs were based on what is called the monoaminergic hypothesis, which is the hypothesis that there is some abnormality in serotonin or norepinephrine in the brains of people suffering from depression, and the existing drugs have really tried to target those systems. Work over the past, two and a half, three decades have shown us that there's probably a much more complex **[00:13:00]** neurobiology associated with depression and other mood disorders, and it's not simply serotonin or norepinephrine being high or low. It probably involves neuroplasticity in general and the way that the neurons in the brain are actually communicating with each other. Some of the work suggests that from animal models largely that the glutamatergic neurotransmitter system, so glutamate is the major neurotransmitter in the brain and it's responsible for the majority of neuronal excitation in the brain, suggests that with pathology especially associated with depression, this system seems to be disrupted.

We have other work that really lets us know a lot about the pharmacology. It's a very complex neurotransmitter system, and there's a very rich pharmacology that allows us to target different receptors and create a lot of novel potential therapeutics. One of the main receptors **[00:14:00]** for glutamate in the system is a receptor that's called the NMDA receptor. I won't go through the whole name for these purposes. It's a receptor that binds the glutamate and it causes the cell to become activated. It's a very complex system, but there has been evidence to suggest that in animal models, mainly models of chronic stress, that this receptor becomes abnormal in some way and that the whole neurotransmitter process involving glutamate can become disrupted. This has also been shown in patients suffering from depression, so evidence of this pathway may be involved.

Back in the late 1990s some of my colleagues at Yale actually started to look at a drug that they knew targeted this receptor, so it's ketamine, it's the drug I said that has been approved since 1970 as an anesthetic agent. Ketamine binds and actually blocks the NMDA receptor, so it's a drug that had **[00:15:00]** specific effects on the NMDA receptor. The goal at the time was to see if you targeted this receptor, would it have effects on behavior? I think to everybody's surprise, there were some early papers coming out of the NIH that suggested also that this receptor may have a role in depression and that if you could target it, you may get an antidepressant response in rodents. This was really the first study showing in humans. If you look to the slide on the left, the figure on the left, it shows a study that was done at the West Haven VA almost 20 years ago now where patients with depression came in, and one week got a single dose of ketamine at a subanesthetic dose range 0.5 milligrams per kilogram or just got a placebo saline. Then they measured the severity of their depression over time.

If you look at the Hamilton Depression Rating Scale **[00:16:00]** that you see on the left is a measure of depression severity, so going down means that you're less depressed. You could see the days that they got the placebo infusion, there was really no change in patient's mood, but the really unique thing was after getting the ketamine, within four hours there was large marked improvement in patient's depression that's tended to continue to increase over the next three days. Gradually their mood came back, but remember ketamine itself has a very short half life. The drug is only in the system for a few hours at most and then it's completely metabolized and gone from the system, but yet this antidepressant effect tended to grow over days and be sustained for days after. That study was replicated a few years later by the National Institute of Mental Health showing almost an identical response in a little bit larger sample. You can see these are very small sample size. It's less than 20 people in both of those individual studies. **[00:17:00]**

70%, over 70, 71% of the patients and these are patients with treatment-resistant depression, these are patients that didn't respond to classic treatments, had a response meaning they felt 50% better one day after getting a single dose of ketamine. It's not while the drug is still on, the acute effects that they get from ketamine are long gone, usually within an hour those acute effects are washed out, but the antidepressant effect tends to grow over the next day or so. Just for comparison, you can see on the far right what you would expect to see with some of the classic antidepressants after eight weeks of treatment. You could see within one day you're achieving levels of treatment to response that we typically take eight weeks to achieve with the standard antidepressant.

Since those two original publications, there have been a multitude of replication studies and all very consistently showing this rapid onset **[00:18:00]** of antidepressant effect after a single dose of ketamine lasting for a few days. You can see this is a study from an APA a meta-analysis from an APA Task Force showing that the odds ratio of having a response to ketamine versus the placebo at day one was about tenfold, which is extremely high for an antidepressant even at one week. After getting a single dose of ketamine and then waiting one week, there's still an odds ratio of almost 5, 4.6 that you'll have a maintained response or a sustained response to a single dose of the medicine. This really sort of shook the foundation of how we think about depression. It actually made us think a lot about the neurobiology of depression but also how we treat depression. We've always had this idea that you need a medicine, and for the most part it was always targeting either serotonin or norepinephrine, and it was a continuous treatment and it took a long period of time to work. **[00:19:00]** This is a very different drug, this is a drug first that was targeting primarily the glutamatergic system but possibly other systems, but seemed to have a response within hours. Even after the drug washed out it still maintained the response.

This is the study that was sponsored by Janssen Pharmaceuticals that was looking at what about repeated dosing, because what I showed you is that you

get this response lasting a few days. Then the patients gradually tended to drift back up over a period of several days or weeks. This was the study one of the first done looking at repeated dosing. What if you gave ketamine either twice a week, which is what you see on the left or three times a week what you see on the right, could you sustain that response even further? This you can see in the orange up on top of the patients that got placebo, which was a saline infusion versus that got ketamine, the 0.5 milligrams per kilogram given IV over 40 minutes what all those other studies had used. **[00:20:00]** You see that the response can actually be increased with repeated dosing and that it could be sustained for at least two weeks if you continue dosing either twice or three times a week. I think a major point of this is that we could show that dosing twice a week had just as much of an effect as dosing three times a week, so it suggested that more frequent dosing was no more effective in this sample.

The other interesting point that was noted by several studies, going back and looking at the data was people -- some of the investigators were noting that the patients that had suicidal thinking were specifically saying that that thinking disappeared very quickly after getting a single dose of the drug. This is meta-analysis that we did in collaboration with several of the other groups, in fact all of the other groups that had published the data **[00:21:00]** to this point where we're able to look at the individual patients that had suicidal thinking. This is a 167 patients, and go back and look and see how rapidly and what that improvement was like after getting ketamine versus the placebo, the control. You could see on the left, this is using a clinician rated, it's a scale that has allowed us to use the different studies and bring them all into one. You could see a very rapid improvement within one day of people's suicidal thinking that is maintained over a period of a week after a single dose compared to placebo. If you look at the figure on the right, those are actually showing you the proportion of subjects without suicidal ideation. These are people that started having suicidal ideation and then after one day in the blue bar, more than 50% reported no longer having suicidal ideation if they got the ketamine compared to about 20% if they got the placebo. You could see **[00:22:00]** even going out two, three, and up to seven days, that response seems to be maintained. After a single dose, people are maintaining this effect where they're reporting no longer having suicidal thinking, so very interesting and promising data.

With that, there's been this real uptake in ketamine, both from the media in general it's been portrayed in very positive light. People have really highlighted the potential benefit of this drug. Pretty much all the major news outlets at one point have run a study highlighting the benefits of this which is really stimulated patients. I can't tell you how many calls I get every week for patients looking for this treatment, it's -- for people that haven't experienced the depression is really a terrible illness. After you've tried a few treatments and there's no benefit, **[00:23:00]** people really become quite desperate for whatever they can do to achieve benefit. When they see stories like this coming out, there's quite a bit of interest in it. The real struggle has been how do you balance the benefit, these

are all small studies to date. If you could see along with the interest from the patients, there has been growing interest from clinicians to provide this treatment.

This is a survey that we conducted going back almost two years ago now when we started collecting the data, looking at the growth of clinicians around the country that are offering ketamine for a treatment of psychiatric disorders. You can see that this has grown rapidly over the years, and I can promise you that if we look for 2017-2018, this curve is continuing to go on basically a logarithmic growth curve. There's widespread **[00:24:00]** availability of this treatment at different centers around the world, academic centers, clinical centers, private practices, so it's increasing the use. The struggle as I mentioned, is really balancing where we are, the real benefits of this drug the data seem to be very consistent, it seems to be highly replicable but still mainly small scale studies that haven't gone to look at long-term efficacy and safety. The unique part of this drug is this hasn't ever gone through what we would typically look at as an FDA phase 3 trials, the large scale studies for safety and efficacy. In large part that is that the drug has been out since 1970, it's not so easy taking a drug like that forward.

One of the things that has been done is Janssen Pharmaceuticals has taken **[00:25:00]** the enantiomer, so I'm not sure, I don't want to get into the organic chemistry here too much, but drugs usually exists with a stereoisomer. You can either have a sort of a mirror image of the drug either an R and S version at different spots. This is using just the S enantiomer which is half of what was given in all of those other studies, but it seems to be the half that is most potent at acting at the NMDA receptor. It allows you to reduce the actual volume that you're using and to be able to give it as a nasal spray. The other studies that I talked about primarily have been done using intravenous treatment. This is a treatment that allows and ensures nasal use. This is just an example of a phase 2 trial that was sponsored by Janssen and run that actually starts to do more of the classical drug development that we're used to going through FDA phase 1, 2, 3 studies **[00:26:00]**. This is recently published data looking at intranasal ketamine for the treatment of depression, and again not very large sample sizes in this phase 2 trial but showing that there may be some evidence of a dose effect, but all the doses of ketamine seem to have an effect over the placebo. Then looking over time it seems to be that for the people that would continue into an open label phase, you can maintain this to some level.

Now, I can tell you actually today at the American Society for Clinical Psychopharmacology in Miami they're presenting very similar large scale, the phase 3 studies are reading out so you'll be able to hear about that very soon. Now, we're looking at much larger numbers that are being studied with this medication, and there are also recent reports at the Society for Biological Psychiatry looking at the phase 3 trials with esketamine. Finally, I just want to talk a little bit about a study that was recently published using **[00:27:00]** esketamine again sponsored by Janssen Pharmaceuticals for acutely suicidal

patients with major depressive disorder. I showed you before the data that were in patients that had some suicidal thinking, but those were not patients that were imminently suicidal. Those were patients that came into research studies and they said, well, yeah I do think about suicide at times. This was actually a study where patients were specifically recruited mainly through emergency rooms when they presented either with a suicidal attempt or were deemed to have imminent or deemed to be at imminent risk for suicidal behavior along with their depression.

This is a study looking at the ability of esketamine to reduce the depressive like symptoms is what you see in the upper left corner over a period of two days, which is in four hours and 24 hours out compared to a placebo, but it's not just the drug itself. This is actually giving the drug compared to the best treatment **[00:28:00]** that we can give. This was done at many of the academic sites that do a lot of treatment-resistant depression work, Yale and several others. They got the best treatment we could give them basically and then on top of it, they were randomized to this study. You could see over those first two days there was evidence that the esketamine can have a rapid antidepressant effect.

If you look at the graph to the right of that, it seems that with repeated treating twice a week for a period of four weeks that effect can be sustained over time. You can see that we do pretty good with our standard of care treatment, it just takes a little bit longer to get there, but we do pretty good, but it really does look from this again phase 2 study. You can see the sample size is there it's in the 30s that we can get a more rapid response that is sustained. Then the colorful figures are a little bit complicated, but I think the main way to think of this is if you just look at **[00:29:00]** the blue and the red, that means that the patient is saying that they feel that they would be better off dead and that there's a real risk of them, they feel that there's a real risk of them acting on that. You can see how that drops very rapidly. The esketamine is to the right each time and the placebo is to the left. You can see very quickly there's over 70% of the patients very quickly report that they're no longer at that level of having suicidal thinking within four hours of the dosing. Then you're getting over 75% within one day saying that.

Then if you look at the red where it's more the burgundy, the [inaudible 00:29:51] frequency distribution. Those are looking at, if you look at the red, those are patients that were assessed to be requiring inpatient stay for their **[00:30:00]** suicidal thinking. If you look over time from baseline, pretty much all of them require that. Within four hours, those getting the drug was down to 64% and then within one day only 50%. 50% basically 49% were now reporting that they no -- that the physicians reporting that they no longer felt the patient needed to be in the hospital for their suicidal thinking after getting the treatment. You can see that's compared to about 35% of the patients that didn't even get the treatment, that got the standard treatment. Very interesting early phase data suggesting that this is a potential, a very important treatment for patients with imminent

suicidal thinking and there are phase 3 trials going on looking at this in a much larger sample that would be able to tell us more about the efficacy and safety.

Just back to the main point, so we have this treatment that does appear truly to be very effective, at least in the short term, **[00:31:00]** at least looking over a few weeks that seems to offer great hope to people that aren't getting much benefit for the standard treatments for depression. However, we don't have a wealth of data, a large amount of data looking at the safety and efficacy over periods of time, and that's really what we're faced with right now. How do we balance these potential benefits, especially for people that are so desperate for help versus really the unknown, the known risk, especially the substance abuse, the drug diversion risks that we always have to think about, but also the unknown risk of longer term safety. Obviously longer term treatment trials are what we're looking at and those are fortunately data that we should be having in the near-term future. There are several other antidepressant, there are several other drugs targeting other glutamatergic receptors that **[00:32:00]** are being developed at this point, so there are other phase 2 and phase 3 trials that are underway and we'll also be hearing more about that. I'd just like to thank all my lab and everybody that we collaborated with to do these studies. Thank you. I will move on.

[Applause]

Charles Conway: I'm Charles Conway I'm from Washington University in St Louis and my area of work similar to Dr. Sanacora is in treating patients who are highly resistant with severe depression. It turns out as the title of the talk indicates **[00:33:00]** that, that many of the drugs of abuse that you all in DEA and others have been dealing with for years do have potentially therapeutic benefits and one of the more recent ones that has shown up on that horizon is nitrous oxide. A little bit of background on nitrous oxide. Nitrous oxide has been around for a very long time. In fact, it has about 120-year history. It is a naturally occurring compound that can be purified and that's what is used in dental offices and anesthesiologists use. It is a colorless, odorless gas. You might ask how do you -- how is it that we came to use this compound for depression? It turns out that it was sort of a circuitous way that this came about. We at the institution that I'm at Washington University, we, some of the **[00:34:00]** anesthesiology people were doing research. The anesthesiology and psychiatry people were doing animal research on the effects of nitrous oxide, which is a known NMDA antagonist just like ketamine, and it turns out that the ketamine story became hot as Dr. Sanacora indicated about 15 years ago.

Some of them came forward and met with me and said, look we have this compound that we've been studying in animals for years, nitrous oxide. It's a known very potent NMDA antagonist. Maybe we should try this in treatment resistant depression. The depressed people that I work with are severely resistant. Some of those studies that have been done and different treatment

studies that have been done in patients with who have failed one or two medications as you'll see when I show the data later on. The patients that we deal with are patients who have failed seven, eight, nine, ten medications. These are the highly, highly resistant **[00:35:00]** patients. As was discussed earlier, these people's lives are literally in many cases a living hell, and many of these people have been depressed for decades or many years. Anything that we could do to get these people out of this position that they're in clinically depressed stuck position is potentially very beneficial.

The anaesthesiologists use nitrous oxide and have been using it for years primarily in indications where you want someone to have a reduction in pain but not to be completely sedated. It's like childbirth and relatively minor procedures. The biggest danger with nitrous oxide, both from an abuse potential as well as a use potential is that it can displace oxygen and lead to anoxia. If you were to inhale greater than 70% nitrous oxide, **[00:36:00]** you run the risk of anoxia and all the things that come along with that like stroke and organ damage. One of the very nice things about it, similar, not totally dissimilar to ketamine, is it has a very rapid metabolism in the case of nitrous oxide, almost instantaneous. Any of you in the audience who have ever had a dental procedure where you receive nitrous oxide, you know that within a matter of minutes you can drive home. That's extremely advantageous if this were available as a therapeutic compound.

Literally the patients who we see sometimes go back to work, go back to school, and are fully capable of engaging in any type of activity, operating motor vehicles, etc. Like ketamine, it is a noncompetitive NMDA antagonist. It also acts with multiple other receptors in the brain and as was indicated in the previous talk, we don't -- **[00:37:00]** although we know these compounds to be NMDA antagonists, there's a very reasonable possibility that there are things going on further downstream that may be really critical in the efficacy of these compounds and that's still being worked out. The various -- Dr. Sanacora indicated very complex pharmacology. There are other compounds that sound like nitrous oxide that I mentioned here nitric oxide and nitrogen dioxide, but nitrous oxide is something different.

As I indicated earlier, it had medical uses for many, many years actually used in the civil war on a limited basis. It was used in the 1950s when it was first introduced in England, in labor and delivery. It is not a controlled substance, which is interesting, which means that it is as we'll see in a minute, the potential for abuse stems from its use **[00:38:00]** in preparation of desserts, primarily whipped creams and so it's actually under the rubric of the FDA rather than the DEA.. That doesn't mean that people don't take advantage of that as you'll see and that's not a first either, I'm sure, those in the audience can attest to that. The way it's delivered in dental offices is typically through a nasal cannula, which is positioned around the nose, which allows the patient to breathe oxygen through their mouths and then they're receiving the nitrous oxide, typically 50% nitrous oxide through the nose. The way it's done is it's set up like this, there's typically

a tank, two tanks, a nitrous oxide tank and an oxygen tank and a valve which limits the percentage of nitrous oxide to 50%. Generally speaking, as I mentioned earlier, if you go above **[00:39:00]** 70% you run the risk of bringing in anoxic damage to the brain.

Now, this is the part that probably has the most relevance to those of you in the audience who deal with heavy abuses of different compounds. Nitrous oxide has been within the last 15 years it has seen -- there has been an increase in the recorded cases of abuse of nitrous oxide. As indicated here, it's primarily a drug of abuse of teenagers and people in the early 20s as is the case with most inhalants. This was actually news to me because I was preparing for this talk I'm not an expert on drug inhalant abuse. It's estimated that about somewhere around 10 to 15% of the population in the 6th through the 11th grade abuses inhalants, and the most **[00:40:00]** common inhalants are magic markers and solvents, paints and other paint thinners and such.

The fourth most common one is nitrous oxide, and the way it's done not to make this instructional but the way it's typically done is kids will use whipped cream containers. They can actually take whipped cream containers that are available in the store and they don't shake them because that mixes the gas with the whipped cream and they just inhale the gas that comes out before the whipped cream comes out. They joke that if you go to a grocery store and you're going to buy whipped cream make sure that you spray a little bit out first to make sure somebody didn't get to that can before you did. When it's abused -- the biggest danger with abuse in kids and younger people is that it typically -- the gas that remains in the can **[00:41:00]** and there's also commercially available small cylinders called whippets sometimes referred to colloquially as whippets is that you're inhaling a 100% nitrous oxide and there's all sorts of negative sequela to that. In addition to the fact that many kids who do this do it frequently, so you run the risk of -- there's collective affects of frequent nitrous oxide use. We don't know how much we have to take for how long, but we do know that it leads to B12 deficiencies both acute and chronic and we'll talk about that in a minute.

These a picture of -- couple pictures of commercially available -- I just went on – I think it's Walmart and Amazon.com to get these pictures. As you could see, actually I think one of them is Target, as you could see these cylinders are available. You don't need any special license, you don't need to show evidence that **[00:42:00]** you're a restaurant worker or that you're in the restaurant business. These are available to anybody who wants to purchase them. These are a 100% nitrous oxide cylinders, and they're very small so they're easily transported and easy to hide from potential people who are trying to stop you from abusing these. In addition to these whippets there's also larger tanks of nitrous oxide which are commercially available that often times kids will take and fill balloons with and take them to parties or take them to concerts and the use or abuse comes from that as well.

The short-term abuse of nitrous oxide has more to do with what we've been talking about the anoxic and hypoxic damage because you're displacing oxygen in the bloodstream with nitrous oxide. It doesn't take very **[00:43:00]** long for this to potentially do damage to the brain. This is certainly true with other inhalants, especially the more combustible inhalants. The fatality rates -- there have been cases of fatalities due to nitrous oxide abuse usually in instances where kids have used very large doses or at least believed to have used large doses of nitrous oxide. Probably as dangerous or more dangerous in some instances is the acute delirious effects that high dose nitrous oxide can lead to which has been associated with motor vehicle fatalities as well as sexual assaults and other types of injuries that occurred while people are intoxicated on nitrous oxide.

The chronic effects, this is not very well studied because there aren't that many people who are serial users of nitrous oxide. At least there hasn't been any case series reports to **[00:44:00]** my knowledge, but what is believed to be occurring is the nitrous oxide actually binds to the cobalt ion in vitamin B12 and essentially renders it inactive. It's useful I think to know that things that have typically been associated with B12 deficiency, chronic megaloblastic anemia, or low blood counts. Also as you could see that there's a whole range of both motor and sensory deficits which occur as a result of B12 deficiencies including seizures and chronic meaning many months to years abuse of nitrous oxide could potentially lead to a condition called subacute combined degeneration, which involves a sensory and motor loss in the primarily the lower extremities. That's the bad **[00:45:00]** part of the story the nitrous oxide abuse.

The good side of the story is that we were beginning to see that potentially nitrous oxide has some significant benefits in depression. What I'm going to present to you is a study that we published in biological psychiatry a couple of years ago. This is the first study, double blinded study in which we gave patients with severe resistant depression just one dose of nitrous oxide, and since this time we've moved onto some different ways of delivering nitrous oxide and we're looking at different methods of delivering it. As Dr. Sanacora went into great detail on, the NMDA antagonists, especially ketamine have become very significant players in the resistant depression arena in the past 15 to 20 years. It is out of that **[00:46:00]** line of reasoning that this idea of using nitrous oxide in patients with treatment resistant depression. This study was the first of its kind and it involved 20 patients with treatment resistant depression. Each patient got -- they underwent two sessions, one in which they received 50% nitrous oxide via face mask over the course of one hour's time. Then the other type then one week later they came back and received -- the same patients received a placebo which was essentially 50% air mixed with 50% oxygen. Then we looked at the improvements using standard depression scales. It's what we call a crossover design. Every patient in the study got every treatment in this case either nitrous oxide or placebo. The patients did not know what they were getting and the raters who were assessing them didn't know what they got, so it's double blinded.

Nobody knew what **[00:47:00]** anybody was getting, which is sort of the ideal situation when you're trying to prove that something is efficacious.

As I mentioned, this is the demographics of this population. This is a very, very sick population. On average they had failed eight medications so that the most of the ketamine studies, the patients have failed two or three medications. These patients -- this is sort of the end of the road population. These are the people who typically get ECT and many of these patients had received electroconvulsive therapy. On average I think the age here is about 48 and on average the duration of depression these people would had was about 19 years. These are very, very chronically and severely ill individuals with depression.

These are the results of the study. On top is the HDRS **[00:48:00]** stands for Hamilton Depression Rating Score and the blue bar is the active treatment, in this case nitrous oxide, the black bar is placebo. Over the course of one treatment, we -- similar to the ketamine studies, we are well aware of the fact that nitrous oxide, like ketamine has acute euphoric effects and we didn't want to confuse depression with euphoria. We intentionally chose as our endpoint 24 hours. We're far enough away from the acute effects where you could say that if there's a bonafide antidepressant effect that by 24 hours there shouldn't be any euphoric effects of nitrous oxide left. As you can see from the top graph at two hours we had about a four point drop, a four point on average greater drop in the active treatment group. Then in the lower bar you see the score change and over the course of 24 hours is about a **[00:49:00]** 5.5 drop in the depression scale.

When you look at patients who responded versus patients who – at least a 50% drop of these 20 patients, four of them in the active treatment group had a response and one of them in the placebo group had a response. Then when you look at those who were essentially depression free at 24 hours, there were three of the four responders were remitters. This is interesting because one of the next -- I'm going to skip a slide and then come back to that. One of the things that we were – this is completely unchartered waters we ran so we didn't' know what we're going to see. We didn't know how long we had to space apart the two treatments. One of the things we unknowingly discovered was similar to what Dr. Sanacora was talking about with ketamine is that [**00:50:00**] one of the fascinating things about these NMDA compounds is that they enter the brain and they exit the brain but their effects persist well beyond the time that the compound is active in the brain which is probably very different than our other antidepressants, which if you stop taking antidepressant I think in general the potential for the depression coming back is pretty high if someone who is acutely depressed. What we found was that the patients receiving nitrous oxide for depression actually maintained their effects well beyond a week. Some of the patients who were coming back for placebo who started out in the active treatment arm were still better and we didn't expect that at all.

This is a heat map showing in this case red is depression, blue is response to depression or reduction in depressive symptoms. As you can see those who receive -- this is just the people who got nitrous first **[00:51:00]** on the left, and the people who got placebo first on the right. You can see there's a significantly greater amount of blue on the left than there is than on the right. Now other interesting things, again similar to what was presented earlier, is when you look at the depressive symptoms, the three bars on the left here are nitrous oxide. The three bars on the right are placebo. As you could see there is a significant percentage of expansion in the groups who are green, which is what you want. That means minimal depressive symptoms, the white and the green and yellow, and you want to reduce the red and the kind of pinkish color there.

What's also interesting similar to what was presented earlier with ketamine is that we're also seeing a profound decrease. In fact, one of the driving symptoms in the depression scale that lead to statistical significance was suicidal thinking **[00:52:00]**. Again, we don't know why this is but it's a recurring theme in the ketamine literature and it occurred in our nitrous oxide population too. In fact, we were fortunate enough to receive a grant from the American Foundation of Suicide Prevention to study nitrous oxide in acutely suicidal hospitalized inpatients and we're currently looking at that. Now the story is not perfect. There are some side effects to nitrous, the most common side effect that we've seen is the development of nausea and vomiting. The vast majority of the patients tolerated though very, very well.

One of the things that we're contemplating now, we're actually doing a study looking at dosing nitrous oxide. The animal studies that have been done by Dr. Zurowski and Mennerick at Washington University demonstrated that the effective dose of nitrous oxide to lead to NMDA antagonism **[00:53:00**] is probably around 25%, so 50% is probably overkill and 50% probably leads to more frequent side effects too. We're going to try to -- we're currently doing a study, where we're taking patients and giving them a series of 50% space it by a month 25% and space it by a month and 0% to see if there's a dose -- an optimal dose for nitrous oxide in depression. The obvious limitations, this is very, very new. I would not bet the house on this. I'm from Missouri, so you have to show me. I tend to be skeptical of things that are too good to be true and this data I think is promising. I think there is a real effect here, but this is a very tiny sample size and granted it is a very, very sick population. I think we're still -- because it is such a novel concept of **[00:54:00]** immediately acting antidepressants, we don't have very good measures for this. Our standard measures like the Hamilton are kind of clunky scales that are intended to measure depression over months or weeks.

My final slide, these are -- we've sort of expanded into multiple different areas of looking at nitrous oxide. One of the potentially very interesting areas is what is -- what exactly is this doing to the brain similar to what's being done with ketamine now. No one really fully understands what are the effects of these compounds

on the brain? We were fortunate enough to land a NIMH funded study to look at functional connectivity pre-post nitrous oxide. Both the normal controls because nobody has even looked at that and in people with severe depression. Then as I mentioned that the dosing study and the suicide study, and then also milder forms of depression, **[00:55:00]** because this is very safe, it had relatively limited addiction potential and it is something that can be used and not cause a disruption in a person's life. I think it has potential therapeutic effects. I think that is all I have. Thank you.

[Applause]

Mark Gold: Well, it was just great, thanks. I'll fill in for Dr. Cadet as best I can and catch us up on time. His work has been in thinking about psycho stimulants and here we are with the DEA museum right next door. In there is the American Disease by David Musto and Musto a famous Yale Drug Historian said that every opioid epidemic **[00:56:00]** is followed by a psychostimulant epidemic. If he were here, he'd say look for cocaine to follow or look for methamphetamine to follow. Both are following as there have been more seizures of methamphetamine and more seizures of cocaine, more production of cocaine, more trans-shipment of both, more consequences of both. As we said at the last educational event, cocaine deaths have moved up to number two on the drug death list.

Quickly, Dr. John Lud Cadet and I had studied the effects of methamphetamine and also MDMA, and how it might be like a traumatic brain injury. Literally, you reminded me of this when you were talking about **[00:57:00]** biological psychiatry because we got the chance to make a cover of biological psychiatry and had a hammer because the animal model was hitting a rat over the head with a ball-peen hammer and comparing that to MDMA and then comparing it to methamphetamine. Through neuropathological studies it was shown pretty clearly that methamphetamine and high dose binge use is like a traumatic brain injury, is like a hit over the head and MDMA less, much, much less so and very much localized.

The same neurotransmitters are always seem to be targets. Psychostimulants are structurally similar to dopamine, and dopamine has been the focus of methamphetamine and MDMA work, as well as you can see the abnormal pathway activated for methamphetamine where both vesicles are squeezed out into the synapse and then trapped in there. All of that causes **[00:58:00]** oxidative stress and relative damage in these systems. So much so by the way that methamphetamine in chronic use could cause dopamine system abnormalities, and even produce Parkinson's disease, another dopamine system, not one that's the target for euphoria but a clear dopamine system in the brain. There are these discrete systems as well. While psychostimulants have these dangerous effects, Dr. Cadet would remind us that they've been wondrous drugs in helping children and young people with attention deficit hyperactivity disorder and returning them to a normal function in the classroom and normal learning.

Nora Volkow would say having additional protective effects once treated as far as drug abuse.

Without going into all of the available analogs I'll just point out that in the list **[00:59:00]** dexamphetamine being used in binge eating disorder an amphetamine derivative and then Adderall and all the drugs that you do hear about. There's considerable abuse, considerable use for performance enhancement for studying, test taking and these are considered performance enhancing drugs in Silicon Valley for people who work around the clock and not have time to even think about eating. Dr. Cadet lists all of the clinical trials and evidence that show these medications when prescribed are safe and effective. At the same time, there's the negative effects for abuse, global abuse and everyone here at DEA knows all full well about crank and crystal and the museum has this displayed as well. The short-term effects and the long-term effects of inhaling, smoking, snorting, and injecting and the high dose repeat use, **[01:00:00]** binge use so common and endemic in other areas.

MDMA would have a different proposed theoretical used. Part of its effects are unknown, and maybe there's some empathic affects generated, but all of them interact with monoamines in a way that are not quite straightforward and likely to cause some changes in long-term use that are untoward. Acute effects of MDMA would be empathic and hallucinogenic and the club drugs as a result of that, with effects on dopamine, serotonin, and other symptoms as well. You can see the widespread effects, the longer lasting effects summarized by him, but most recent use has been proposed in a combined psychological and **[01:01:00]** pharmacological treatment of PTSD. They're highlighted as a safer alternative to both the disease as well as the existing treatments of a military veterans, firefighters, and police officers summarizing these studies. The slides will be available on the web, and also we have Dr. John Lud Cadet and I have a current review in current psychiatry volume 16 this November of ‘17 that you can refer to as well. Amphetamine analogs are mostly discussed in terms of abuse liability but they have considerable benefits. They can be administered safely and effectively. They are administered for ADHD safely and effectively in MDMA as well. I thank you **[01:02:00]** and we miss you John Lud Cadet.

[Applause]

Laurie Baty: That was definitely speed slide reading. Thank you all very much for your presentations today. I'd ask the three of you to please come up on stage. We have microphones I think on either side. I know there's a ton of people out here. Again, a reminder that you can post questions via deamuseum.org. I also ask that one, I mean not a large audience, I realize but we asked out of respect for everyone, please ask only one question. Depending on how our time is, we may get to let you ask a second one, but if there are more questions please come up and talk to our host, our guest speakers at the end of the presentations. Thank you.

Mark Gold: **[01:03:00]** I got some questions from the web. Anybody who would like to answer would, can you take a depressed person and give them ketamine and have them become manic? Is that a problem for you in your practice, and use clinically?

Gerard Sanacora: I'll start by saying there have been a few reports of manic – sorry. There have been a few reports in the literature of the manic switch actually a very few. There isn't much evidence of this occurring above baseline rates, but that being said there haven't been many large controlled trials that would be measuring this over time. I don't -- it's a little bit of -- absence of evidence isn't necessarily evidence of absence at this point.

Mark Gold: You mentioned a little bit about the ketamine like drugs out **[01:04:00]** there and someone had specific question ---

Gerard Sanacora: Yeah Memantine is -- Namenda is the brand name, it's been out for quite a while. It's actually an FDA approved treatment for cognitive impairment associated with dementias and Alzheimer's disease. It is another NMDA receptor antagonist. It has different pharmacologic properties in some way than ketamine. The few studies that have been done have been mixed. The probably best studies done at the NIMH did not show it to have a large antidepressant like effect. I think at this point it's the evidence which suggests that there isn't great evidence of Memantine having that antidepressant like effect but I think the jury's still out.

Mark Gold: Do you -- both of you could answer this. **[01:05:00]** Do you think there's a category of FDA approval that separates depression treatment from treatment for suicide? Like could you get approved or ketamine be approved just because it has an instant effect on suicidal ideation?

Charles Conway: Yeah, this might be better answered by Dr Sanacora but to my knowledge to-date no drug has yet received FDA approval for the use for acute suicidality. I think one of the things we're seeing with the FDA in the past 10 years is that they are starting to divide up their approvals or to sort of subdivide their approvals for more specific indications like treatment resistant depression and use of compounds as adjuncts in treatment of resistant depression. I think – I don't **[01:06:00]** know if anybody is pursuing that, so I'll hand it over to Dr. Sanacora.

Gerard Sanacora: I think what Dr. Conway says is correct. I don't think there is a path as of today for approval. I don't think there are any drugs approved. In fact, there's very little evidence of pharmacologic agents having anti-suicidal effects. There's evidence for lithium and clozapine, but these are really retrospective type analyses.

Mark Gold: Both of you presented data like that. The patient shows up in the emergency room or they're on a psychiatric unit and they're acutely suicidal and the psychiatrist might have to order 24/7 round the clock nurses. They might have to order almost emergency shock treatment. They might have to put the person in a locked psychiatric unit, and both of the treatments that were proposed seem to be alternatives to that.

Charles Conway: Yeah, I agree. I mean the goal is to have an alternative. I think we're still not quite **[01:07:00]** at the point that we're saying we have that yet. There are studies, there are several studies underway. The ones that I'm aware of at this point are – all but mainly within an indication, so it would be suicidal behavior in depressed patients, and the indication would still be linked to ---

Mark Gold: Depression.

Charles Conway: --- an existing diagnosis whether it'd be depression or bipolar. I think the plan down the road would be to broaden that to include people with imminent suicidal ideation and behavior trends diagnostically.

Mark Gold: When you think about -- you are mentioning that there's been a rise in practitioners using ketamine off label. You could look at ketamine provider, are there guidelines that you have or recommend people to look at for off label **[01:08:00]** use or how is this being done?

Charles Conway: That is -- in my mind one of the concerns is that there really isn't any standardized treatment approach, and in large part I think that's because there hasn't been enough data to really issue formal guidelines how to do that. I was fortunate enough to be part of an APA Task Force that try to at least develop a consensus, and that was published last year where we tried to at least get a consensus statement on not so much how the treatment should be used if it should be used at all. If it is going to be used these are the issues that you should be very concerned about. At the time we wrote that, that was almost two years ago, that was based on the strongest evidence based data that we had and trying to really just highlight **[01:09:00]** what the concerns were. If you are going to do the treatment and we really were not making judgment statements on whether this is the right treatment or not to do, but if you are going to move ahead, what should you really be concerned about?

Mark Gold: What should they?

Charles Conway: There are several things. I mean one is ketamine does have some more acute effects that could be worrisome. There's effects on cardiovascular function, there's increases in heart rate and blood pressure that could cause problems for some people. There's definitely the acute behavioral effect, problems with cognition and perception and anxiety that are very closely

tied to the dosing of the medication which are real issues. The fact that there weren't at the time long-term data suggesting efficacy even or effectiveness. There is even animal data suggesting that high dose over a long time could be neurotoxic, and we know that people that abuse ketamine have -- it can do damage **[01:10:00]** to their bladder. There are a lot of concerns that need to be addressed if you are doing this and if you're planning on doing it long term. Those were some of the issues that are within a patient that concern. Then obviously the substance abuse liability is a real concern, and if it is been given for take-home use, the risk of drug diversion is another real risk that we need to think about.

Female: Hi, my question is for I believe it was the gentleman sitting to your left there. You, yes sir. I forgot your name I'm sorry. You were speaking about the ketamine and the intranasal sprays, and you mentioned Janssen and Ron, are they researchers or is that a pharma lab?

Charles Conway: No, that is a company Janssen Pharmaceuticals.

Female: How far along are they with that particular **[01:11:00]** study?

Charles Conway: There were a phase three trials that are being reported literally as we speak. These phase three trials are being completed.

Female: At what point along the course of that – those studies do they get to the FDA and they get on the market. I'm looking from the perspective of investments, etc.

Charles Conway: I can't speak for the company or ---

Mark Gold: Is that Johnson & Johnson?

Charles Conway: I believe it is a subsidiary of Johnson & Johnson, but that depends on the FDA filing and how long the FDA will review it. I can't say much more than that, except for the fact that I can say within the past month, several of these phase three trials have been reported, and several others are ongoing, especially ones looking at its effects on a suicidal ideation in people with depression.

Mark Gold: You know **[01:12:00]** it's for older person working in the field and you know what I mean, I started in the 70s, early 70s. The idea that an antidepressant could work in a period of time shorter than three or four weeks is quite remarkable and unexpected. The idea that a medication might have some specificity for self-harm and suicidal thinking and behavior would also be really remarkable. The idea that a dose, one dose might have an observable effect for a long period of time long after that disappeared would be heresy, because in the old days we used to have blood level response relationship so that the

medication would have a level in the blood to work as an antidepressant and you would have to sustain that for weeks. Very often **[01:13:00]** the patients would give up. I just think it's worth noting that both of these kinds of new treatments and others that target the same area will change the textbooks on what depression is and how to approach it. That I think is, I mean I'm not sure whether you said it was the biggest thing since Prozac but one of those articles did.

Gerard Sanacora: Yeah I would agree completely with what Mark is saying. I think this is a potential revolution in psychiatry, and it's very exciting. It's also -- there's a lot of unanswered questions in terms of where -- how long do patients take these medications, how long – because one of the things we know about treatment-resistant depression is it's a nasty beast and it comes back and it doesn't – it figures **[01:14:00]** out a way to get around your treatments. We don't know if someone's on ketamine for two months, three months. If you stop the ketamine does the depression come roaring back? Is there or are there long lasting or potentially negative effects to chronic administration of ketamine? To my knowledge, except for perhaps in pain patients, I don't think it's been used in that capacity for years in patients. What we know about treatment resistant depression for example, electroconvulsive therapy and vagal nerve stimulation and other therapies is that most of these people, their brains are unfortunately geared towards depression. If you stop the treatment, like if their vagal nerve stimulation device, I've seen this numerous times, their device battery fails, the depression comes roaring back. Is that going to be the same story with ketamine or is it maybe perhaps changing **[01:15:00]** the biology of the individual such that they don't need to be on ketamine perpetually or maybe just booster sessions? There's a lot -- in many ways, there's more questions than answers at this point, but it's definitely an exciting time.

Charles Conway: I can add a little bit of information that these studies like randomized withdrawal studies are being presented in the very near future. We're going to have a lot of this data, and I mean in the very near future like in the next few weeks it will be presented, and we'll have a lot more of this randomized withdrawal to look at. There's also data coming out for longer term use up to a year for some of these treatments. We are going to have a lot of that data readily available.

Mark Gold: You know what it is, you just can't say it because they're in press or in papers. If someone were to ask you, you would say that there's most of the **[01:16:00]** things out there are supporting the notion of safety and efficacy.

Charles Conway: I'm very reluctant to say much at all, but at this point I think there is good evidence for sustained response in certain patients going on. The evidence what we're really worried about are these big red flares of having evidence of cognitive impairment or having bladders that are really being damaged, we're not seeing that generally.

Mark Gold: Yeah, we reported the toxic bladder effects in a paper in Hong Kong and so forth. The dose differences are just so dramatic that -- and I do think it'll be the same thing in your nitrous work that when you get down to the lowest, safest effective dose and a route that's safe **[01:17:00]**, that's the hope. I mean if you think about it if you have depression and you're suffering, you'd like to have access to a potential treatment in the same way that people who have cancers are asking for access to new cancer treatments.

Charles Conway: I mean I think that's the point that gets lost to people -- depression unfortunately is a term that is so widely used, and it has such a broad spectrum of meaning. Unless you're really treating patients that are severely ill with depression that stopped eating, not sleeping really are willing to end their lives because they're in so much pain. When I talk to them about the risk benefit ratio, it's hard to put that in perspective when I say this could have some negative effects, and they're coming back to me and saying, well, if I don't **[01:18:00]** take it, I'm going to kill myself.

Mark Gold: Go ahead in the audience.

Male: I think you referred to it Dr. Gold a little bit but my question revolves around -- when I think – it was actually when you were speaking, because I didn't want to distract from the other two presenters. I Googled Ketamine Clinics in the area and what I found was they treat depression, PTSD, OCD, and other disorders. It's like there's a dramatic proliferation of the so-called Ketamine Clinics. My question is I guess is buyer beware? I mean, who knows where to go or what the efficacy of any of these clinics?

Charles Conway: It's a great question, and it's one that I don't have a straightforward answer to. The best I could say is the consents paper that was published from the APA Task Force at least tries to lay out what **[01:19:00]** seems to be the most rational approach to making sure you're having a thorough workup. What evidence is available? In fact, one of the things that the consensus paper really very strongly supports and in fact urges is that there's real informed consent given. When a patient is being treated at one of these clinics, there is real informed consent on what the evidence is for any individual treatment that's being given. Clinics using varying doses, but really if you looked at the published data it's really limited for any dose beyond that first one that was published 18 years ago 0.5 mg per kg over time. Using it for indications other than depression, there's limited data. I mean there's two papers that I know of in PTSD and OCD, they're really, really limited data to support that use. **[01:20:00]** I think it is a little bit of buyer beware, but I think it really is incumbent on the clinician. If you're going to be giving this treatment to make sure you're really giving informed consent that you really are explaining what you're doing, where the evidence to support this exists.

Mark Gold: Well, that was really great. If you'd like to say any last words for this program and then we'll end it.

Gerard Sanacora: Well, I just thank you for the opportunity to come and talk to you. Thank you for all the work that you do to keep the street safe. I thank you very much.

Charles Conway: I agree. Thank you very much for the invitation to come and speak here. I know this is a relatively unique way of looking **[01:21:00]** at these old medications that have been out for decades but with very new uses. Also running the risk of having a real abuse liability that getting a chance to visit the museum, you realize that you have to be careful of not letting history repeat itself too often.

Mark Gold: I mean, I'd just like to thank DEA for such a avant-garde and well thought out program and interest in the subject. As we know, most drugs of abuse have a use in medicine and are being used in medicine, even down to cocaine for ENT surgery. That doesn't mean that cocaine is safe from abuse, it just means that we have to ask the question of safety and efficacy, ask for it to be proven, and try to come up with the safest route of administration **[01:22:00]** dose and route form so we can monitor. It is very important to recognize that the American Psychiatric Association put together a document with advice and suggestions and that's worth referring to. I thank you both for pioneering work that's changed the way that people have thought about depression and given hope to people with depression that they might be able to live a relatively normal life again. Thanks again.

[Applause]

Laurie Baty: Again, thank you very much all three of you for being here today and Dr. Cadet, we hope you feel better if you're listening over the Internet. Our next lecture is as I said on cocaine and heroin and it is September the 18th, we don't have the time yet, but that'll be the last of the four this year on a new look at old drugs **[01:23:00]**. Thank you very much for coming.

[Applause]