THIS PRESENTATION IS ENTITLED STIMULANTS. I WILL PASS IT OFF TO DR. MIKE BAUMAN TO BEGIN THE SESSION.

HELLO, EVERYONE. TODAY WE WILL BE TALKING ABOUT STIMULANTS AND PEOPLE LOOKING AT THE NEUROBIOLOGY AND TREATMENT ASPECTS of stimulant abuse. This first slide , my financial disclosures. I have none to disclose. The general outline for the talk is a chronology of the stimulant epidemics that we had in the United States over the years, 1980s, cocaine, 1990s, ecstasy, 2000's, methamphetamine, 2010's, bath salts and other research chemicals, and finally a summary of the things we talked about. One point I need to make, all of these drugs are currently available in the drug markets. We are talking about them in terms of their chronology but there actually all present today. Topics covered for each substance, drug trafficking and confiscation of those drugs , formulations and methods of use , the pharmacokinetics and metabolism , desired and adverse effects, chronic withdrawal effects, we will talk a lot about neurobiology since I'm a neurobiologist. And then we will entertain some ideas about treatment and well. We will start off with cocaine. Cocaine is a plant-based alkaloid previously on the left-hand side, you will see a picture of a cocoa plant. It is grown in the Andean region of South America for the most part. Here you see chemical constituents extracted from the leaf. This is the chemical structure of cocaine and in terms of its chemistry, it is a phenyl tripping. Cocaine from the Andean region of South America is traffic on a global scale. Pretty much all the cooking that comes in the world comes from Bolivia and other countries there in the Andean region. If we look over here in the United States. A vast majority of cocaine coming in is tracked by Mexican cartels and coming across the southern border. This is a figure of some confiscated cocaine bricks, a large Caesar of cocaine a large seizure of cocaine. Confiscation remains relatively stable. There are a couple of slides like this in the talk and so I want to orient you guys to what we are looking at. This encounter, this is an acronym that stands for the national forensic lab system. It records each time that a drug has been encountered. This is a repository of information about confiscated drug material from local, state, and federal law enforcement. All of the issue at the database, this is a snapshot of the database. I will show heroin and all of the slides to give you the comparison. We see since 2008, the amount of cocaine has gone down and it has remained relatively steady. The last data point I have here is in 2019, actually in 2020 it looks like there is an uptick in cocaine. There are quite a number of confiscation, we have over 150,000 encounters. One thing about the data is the encounter, we don't have the regularity to say whether it is a gram or a kilogram. That is one caveat to the data, nevertheless it does give us a snapshot of how much cocaine is out there. Formulations and methods of use, cocaine freebase or crack. The freebase does burn. So it is smoked, a hydrochloride salt is soluble so it is used for intravenous injection and needle and syringe. Cocaine hydrochloride is what is snorted . From metabolism , it is important to note that smoked drugs, whether it is cocaine or at the drug reaches the drug within seconds. The drug that is taken intranasally reaches the brain. Oral, even slower time course. The metabolism of the drug is predominately ester hydrolysis to not bioactive. A good place to introduce the rate hypothesis of drug

reward. This simply states that the routes of administration that delivered the drugs rapidly and to very effective means to the brain will be more addictive. That means that such as smoked, and IV will give to the brain quicker , you get much higher levels in the brain and this is associated with higher abuse liability. The faster rate of drug entry into the brain, you get an enhanced subjective and rewarding effects and this will enhance the abuse liability of the drug. By contrast, intranasal or oral routes , slower rate of drug injury and reduce the effects. Why do people use cocaine? There are many desired effects including enhancement and euphoria, increase attention and alertness, decreased need for sleep, appetite suppression, sexual arousal. High dose administration or repeated high dose of menstruation or binging can lead to adverse effects including psychosis . It can be indistinguishable from schizophrenia. Things like feeling bugs on the skin . Tachycardia, arrhythmia, heart attack. A lot of cardiovascular complications. Hypertension, stroke, hypothermia , multi-system organ failure. Tolerance. Some of the effects of cocaine exhibit acute tachy for Lexis or a first dose tolerance where and after you have been exposed to the drug, subsequent administration is blunted. These include cardiovascular effects , euphoria, sexual arousal or. Interestingly there is no long-term tolerance. If you have time between the bottom of cocaine use, you can reestablish the initial effects that you got from the drug. These acute effects are sometimes known as first dose effect and it is mostly in the clinical literature , controlled administration of cocaine shows a blunted cardiovascular effect on subsequent administration in the same session. That is the classic example. Sensitization is the opposite. The classic example of this would be cocaine -induced seizures and cocaine induced psychosis. For example paranoid delusions, and these are virtually indistinguishable. From a clinical standpoint, it is important that folks that are under the issue and influence of cocaine and have been binging on high dues cocaine , the drug detoxifies in the baseline mental state , these cocaine binges and acute psychotic episodes. Withdrawal effects includes the ability to experience pleasure , depressed mood, increased appetite , nourishing and fatigue, unpleasant dreams. And these withdrawal effects and this can be a driver of continued drug use. We will talk about the molecular sites of action and the monoamine transporters. That is dopamine transporters and serotonin transporters. And additionally cocaine interacts and this is the numbing effect that you get from cocaine. This is actually used to clinical use of cocaine . Here is the main site of action that is involved and that is the dopamine transporter. I will show you what is the normal functional role of this membrane protein, it is a member protein responsible here is a cartoon, you can see that the transporter takes dopamine back up into the presynaptic terminal. Any drug that disrupts the function of that will increase dopamine and these increases are perceived as rewarding. Here is a cartoon showing how cocaine works, cocaine is the triangle. He will see cocaine blocks the permeation poor of the protein and it inhibits dopamine uptake. This is cocaine's action on the molecular level. We can look at this with preclinical models. Here is a slide that shows some microdialysis data for rats and here we are actually able to measure cellular dopamine in the brain while rats are behaving in the arena. At a one milligram per kilogram dose, we see an increase in dopamine that is induced by cocaine administration. We get a larger dopamine with a higher dose. Here we see a twofold increase. These are

super physiological uses. What cocaine does, it takes to normal rewarding effects of dopamine and magnifies them greatly. In the rodent models, one of the things we show, as we increase the dopamine, they run around, but they move in the commission . Another model we have in the preclinical world and this is the use liability is self administration. This is the number of those folks, animals will get an intravenous administration of cocaine. We compare the active Weber, where it gives an infusion of cocaine versus inactive that has no consequences. You will see acquisition day one is acquisition day one so there are 10 days of acquisition. It doesn't take very long by day three because there is a pronounced lever press were animals are getting drug versus where they're not interested anymore. We have maintained substantial self administration of cocaine in this essay. E stands for extinction as we take the drug away as we see a decrease because the animals are no longer being reinforced. This is a preclinical model. What about treatment for cocaine dependence? As of yet, there is no FDA approved medication. All treatments are psychological. His most effective treatment in my opinion is cognitive behavioral therapy. There are other types of therapies including community therapies and twelve-step programs. Even though there are no FDA approved medications , a recent review article in 2020 , they get a meta-analysis looking into the all the studies that use prescribed stimulant medications to treat cocaine. They found that indeed there is some favorable outcomes prescribed medications. Without going too deeply into this data set, the line that you see over here , this line here , any treatment effects to the right favor the stimulant over the placebo and you can see the actually do some benefit for using stimulant medications, particularly ones that contain amphetamine. This would be an example of what is known as replacement therapy. Nevertheless, none of these medications are FDA approved. 1990s, we are moving to the next drug. MDMA is a synthetic drug in contrast to what we saw with cocaine. MDMA is a synthetic drug , it is made in the laboratory. It is a ring substitute amphetamine analog. In fact it is an analog of methamphetamine. There is the ethanolamine . Here we see MDMA which is methamphetamine with a ring substitution here. This ring substitution is dramatically affecting the pharmacology of the drug , as you can see. This affects the serotonin system. What about the confiscation of MDMA? We see data so much what I've showed you for cocaine but here we see many encounters and when we compare that to heroin, we see that MDMA confiscation is very very low when compared to other drugs like heroin or cocaine . Formulations of abuse. Drugs are typically found as powders, capsules, and tablets. Oral ingestion is the most common method of use. There is some intranasal and intravenous use but tablets. This is pumped through repeated intermittent dosing. When you take the dose and it wears off, you bump with another dose and you can continue to do this in many cases where kids go to these all-night dance parties. They will take the drug whenever it will wear off , it will take another dose. This can continue for hours. Stacking is little bit more dangerous because there is some tolerance developed and what many users wind up doing is they take more drugs to overcome the tolerance. One way to overcome tolerance is dose escalations and stacking, taking multiple doses at once. We will see why this is problematic. This often leads to binge and crush cycles and we have seen some cocaine and methamphetamine. What about the pharmacokinetics and metabolism. After oral ingestion, takes about two hours for the drug to reach maximum effect. But you can get nonlinear

drug accumulation. That is more than you expect, more drug than what would be predicted by the dose administered. The metabolism is and demethylation to form MDA and oh demethylation visitation to form hydroxylated metabolism. One of the reason why MDA is a dangerous drug or potentially a dangerous drug, here we see the metabolism, it is complex. There are two main pathways. One pathway here causes this dihydroxy compound . The other pathway here , we remove this methyl from the --this is also bioactive. One of the problems with MDMA is that it inhibits cytochrome. In other words, you inhibit the mechanism for disposing of the drug. If you inhibit this pathway , you basically push all of the MDMA this pathway where you get very high levels of these two compounds , both of which are bioactive. Why do people take this? It has the combined effect of a stimulant and hallucinogen , enhanced mood and energy, also heightened and altered sensory perception. These altered perceptions can really lead to feelings of empathy and closeness to others and these are often referred to, ecstasy is referred to impact pigeons . You can get cardiovascular stimulation, appetite suppression . Like all other stimulant drugs, high dose or repeated binge dose administration can cause psychosis, sympathetic simulations such as palpitations and heart attack. Another dangerous syndrome you see with ecstasy they don't often see with other stimulants and drugs like this is five HT syndrome. This is characterized by hypothermia, dehydration and it can lead to multisystem organ failure in the worst case scenario. We treat this with hydration, cooling, sedation. It is important to avoid beta blockers because they could exacerbate the hypertension. Withdrawal. You see anhedonia, depressed mood. This is often referred to as the Monday blues. After taking ecstasy for a weekend bench, people experience lethargy and fatigue for several days after one of these big episodes. Sleep disturbances. There is really no indication for treatment. The withdrawal severity , you cannot really treat it per se but once again as we see with other stimulants, if you have withdrawal, is often the driving force to lead people to get back into administering the stimulants. Molecular sites of action, like cocaine, ecstasy targets these monoamine transporters but in this case as we will see, it targets the serotonin transporter more than others. Similar to what we saw from the dopamine transporter, serotonin transporters uptake actor serotonin. You see it being taken up by the SERTs . SERTs are membrane proteins that are expressed in serotonin neurons that responsible for the uptake of really serotonin. Any drug that disrupts the function of's SERTs increases of five HT. Increases and five HT are not particularly rewarding. They are positive for mood, but drugs that elevate extra serotonin are not self-administered. For example, SSRI. They have therapeutic attributes but they're not necessarily addictive. Here's a cartoon showing the effect of MDMA and it is important to note that MDMA targets the serotonin transporter in somewhat different way than what we saw with cocaine. Here are drug molecules actually going in through the transporter permeation port. I will redo that again. Watch our dime. It not only binds to the transporter but it goes into the transporter and in doing so it disrupts vesicles, it increases the amount of serotonin available for release and it reverses the transporter's direction. This is often known as reports transport reverse transport. The release occurs by reversing the normal direction of flux so that serotonin comes out of the cell through transporter action. We can look at this with our microdialysis preclinical model. It's important to note here that we have dopamine here

in the left panel. This is the percent increase above baseline. Here we have serotonin increase above baseline. As we have one and three milligrams per kilogram of MDMA. A small increase in dopamine. Similar to what we saw for court coming for cocaine. In the same animal, we have a much larger increase in extracellular serotonin with MDMA. MDMA thousand more activity when compared to other stimulants. This is sort of the underlying mechanism for its effect. One of the problems with MDMA , and this may be due to this pharmacokinetic issue that I mentioned earlier , you can get a nonlinear accumulation into the drum . It has that neurotoxic potential. MDMA acutely increases synaptic serotonin , you get large release of serotonin , but you also get accumulation of the drug molecules into the nerve terminals themselves which can cause damage. MDMA chronically impairs neurons, depletion of the stores of serotonin, inhibition of the synthesis, and loss of serotonin uptake sites in the brain. This has been shown for animals and in some cases in people as well. Happy ecstasy users have a loss of serotonin transporter site . When viewed as a serotonin lesion. Whether this is true toxicity, in my mind it is available but it really doesn't matter. You definitely have long-lasting deficits in serotonin systems with heavy ecstasy use. The nets drug up for discussion is methamphetamine. Methamphetamine is a synthetic amphetamine analog. It is made in a laboratory. You can see some methamphetamine rock, here you see the structure. The only difference between methamphetamine and if that amine itself, here you have this . So, methamphetamine --in contrast to what we saw with the other drugs we saw so far, methamphetamine confiscation is increasing dramatically at an annoying rate. Since 2008 where we had 100,000 , we have country pull that in the last decade and the continues to rise. This is a disturbing observation. As I mentioned, methamphetamine is made in laboratories. This is a mom-and-pop lab where somebody's making this in a trailer or a basement. Today, the vast majority is being trafficked from Mexico. It is a being made in these little mom-and-pop labs. It is being made and large industrial labs where they're making kilogram quantities and making these available. Formulations, this is smoke that leaves and pipes. Soluble in water, you can use the needle and syringe. There is some intranasal snoring. As I've mentioned, smoke drug reaches the brain within seconds. The metabolism , metabolism of methamphetamine , this is removal of all of that group and this forms the amphetamine itself. We have a drug that is biotransformed. There is some hydroxylation but the major route is the amphetamine itself. The desired effects, very similar to what we saw in cocaine, enhanced euphoria, increased alertness , increased need for sleep. Adverse effects , psychosis , arrhythmia, palpitations, heart attack, hypertension, stroke hypothermia multisystem organ failure. Very similar to what we sow for cocaine. You get a syndrome , this is characterized by hypothermia, the breakdown for Marshall tissue. This can be fatal. This is a public service announcement from years back , faces of meth. You see a wonderful young person , and after year of methamphetamine, you see the signs of overall health deterioration. This is absolutely true , chronic methamphetamine use causes a myriad of health problems. Deterioration of general health. One of the classic symptoms is meth mouth. This is due to changes in the saliva, decay of the gum tissue and actual toxicity to the tooth itself. The molecular sites of action, similar to other stimulant drugs and abuse. Methamphetamine, interacts with monoamine transporters and it has a very high affinity for the dopamine transporter and the norepinephrine

transporter. These are probably related to different properties. Here you see a cartoon of how math works in the brain. Here is our dopamine transporter, here is our methamphetamine. Like ecstasy, , methamphetamine is a substrate transporter. That is it goes through the transporter permeation port , it goes inside of the dopamine terminal , it disrupts vesicles, and then dopamine is released into the extracellular space. Methamphetamine is a powerful dopamine releaser. It's mechanism of action is particularly problematic because it can release tremendous amounts of dopamine. Here, we see some microdialysis data. Looking at the actual release of dopamine and serotonin in the rat brain, we have seen the layout before. Here is dopamine, here is serotonin. Here is the amount that we are measuring in the extracellular compartment. They had a large increase, 600%. This is a sixfold increase in baseline. We probably saw cocaine effects. This is a massive increase in extracellular dopamine . This IV dose is greater than 15 fold increase in extracellular dopamine. The drug also increases extracellular serotonin. This is predominantly a dopamine release. Increasing extracellular dopamine to a much greater extent when compared to the drug which blocks the transporter like cocaine. When we are comparing cocaine versus methamphetamine, cocaine inhibits doping mediated uptake. Mass. also inhibits uptake. This transporter mediation, we have this aftereffect which is really giving large extracellular dopamine. Another important thing when we are comparing cocaine versus methamphetamine is how long it acts. This effect lasts one or two hours. Meth is very slowly metabolized and it is metabolized in bioactive methamphetamine. It can last 10-20 hours and the withdrawal is more severe and can last many days. In terms of severity, in some ways, methamphetamine is much worse than cocaine. Additionally it is now shown not only in animal models but even in people that cocaine doesn't really cause toxicity whereas methamphetamine does. It decreases dopamine transporter sites in the brain. Here we see an upper panel , the normal control subject, imaging of the dopamine transporter. We see highly enriched whereas someone who has used methamphetamine. Even a month after abstinence. This has been viewed as toxic. One of the problems with methamphetamine, used in subculture. This allows people to stay up for sometimes days at a time and they have increased inhibition to judgment. Increase sensation seeking and sexual arousal coupled with unsafe sexual practices which leads to HIV transmission and other blood-borne diseases as well. Meth, sex and the Internet is a perfect storm. Sex both virtual and real, both safe and unsafe is only a click away. Here you see examples of Internet websites that foster risky behavior , on the left-hand side you see intravenous drug use, on the right-hand side you see websites that allow people to basically hook up just for sex. So you have this convergence of drug use and risky sexual behavior. , There is no approved pharmacotherapy and this is similar to what we saw for cocaine efficacy where there is no FDA approved medication. Treatment is psychologically-based, cognitive behavioral therapy, grouping therapies, twelve-step programs. , Nevertheless, even though there is medication, there are new medication strategies that seem to work . What you see is the use of bupropion which can be thought of as an agonist medication because it is a stimulant. They actually reduce Matthews quite effectively when compared to placebo. The blue line shows the percent of meth negative urine over the treatment, the first treatment arm and second treatment arm. Both treatment arms, you had the medications performing much better than placebo in terms of negative . There are some

bright spots on the horizon for medication development. To our next group of drugs and this would be the bath salts. These are drugs that appear in the 2000 and are still around. These are tracked over the Internet. These are drugs that are made in Asian laboratories and they are trafficked over the Internet. They're all placed on cathinone which is a plant-based alkaloid. Here you see someone who is harvesting. This is the raw material where it is the main constituent. One thing, they use it for TV , it is true. Once it dries out, , it has to be moist. Once it dries out, it breaks down. So, the freshness is really important. So in the Arabian Peninsula, this is used like we would have a place to go drink tea, the men especially will gather together and chew caught for its mild stimulant properties. This is the plant that is bundled up. Here is the active ingredient, naturally occurring cathinone molecules is a beta keto amphetamine. The only difference, here you see what we see with methamphetamine. The only difference is the beta keto group. And all of the analogs, this synthetic analog is referred to as beta keto . Bath salts products were originally sold to people , they was sold as as bath salts as a guys. This is to subvert legal scrutiny. These are not really bath salts. They are used for their psychoactive properties. They are just called bath salts as a means of selling them legally. The products contain synthetic cathinone's and they also will say on the front of the labels, not for human consumption, wink wink, that these are taken by folks. They know what they are. Many of these original bath salt and some of the one still available today contain a substance that is called MD PV. Deconstruct this molecule, you can see that it has a methylene dioxin . It has the phenyl ring and the methyl amine of amphetamine and then has this bulky group on the nitrogen. It turns out this is a very potent dopamine uptake inhibitor. It binds to the site just like cocaine but it is at least 10 times more potent. Here we see a cartoon of the presynaptic dopamine terminal. There is the transporter, here is our MDPV. Just like cocaine, it binds to the transporter. It is a dopamine uptake inhibitor. Importantly, is at least 10 times more potent than cocaine which makes this quite dangerous. Another drug that was found in bath salts is methyl loan. This is essentially beta keto and MDMA. It is the same structure as MDMA except the addition of this beta keto on. Because it is similar to MDMA structure , it is predictable that it is a substrate for serotonin releaser similar to MDMA we see our cartoon , this is our serotonin cell. There is the drug. Disrupts vesicles and causes release of serotonin into the extracellular space. This is an older slide , what happened with these cathinone's, their speculation that the number of crime reports in the early 2000's , you see what happens with ecstasy. You have this dramatic decrease in exit see confiscation and the reason is , here in 2010, the raw materials for making ecstasy were confiscated by DEA and other law enforcement agencies so you had no ecstasy. There was no ecstasy available in the clandestine drug market so these cathinone's came in to replace that ecstasy. Even though ecstasy is now back and there's plenty of ecstasy on the trees , the cathinone's remain the problematic source of slowing the growth. In summary, cocaine is prototypical dopaminergic stimulant. And you may ask is a mild stimulant and the listeners due to it serotonin mediated , serotonin release. It's affect on SERTs to elevate serotonin in the brain are the reason white has is the reason why. Meth is a powerful stimulant due to its DAT mediated dopamine release. MDPV is a cocaine like drug. Clinical challenges, there is substantial clinical challenges to treating

the stimulant abuse. There is no approved medication for stimulant dependence so treatment is largely psychological based. There is no specific antidotes for stimulant intoxication's and treatment is supportive. Stimulant induced steps are increase easy due to Fentanyl coadministration . What is happening on the clandestine drug market , you were seen a lot of death cases that are positive for a stimulant, whether it is cocaine or methamphetamine. Whether this is intentional, people are using Fentanyl and stimulants on purpose or whether this is accidental, which would be adulteration of stimulants with Fentanyl by the cocaine cartels for example. It is hard to know from epidemiological data what is going on. I would actually guess that much of this is accidental. Cartels are putting fentanyl into the stimulants and then there being sold. A lot of people are being exposed inadvertently or accidentally to fentanyl without her knowledge. Thanks for your attention and the questions are forthcoming. [Event Concluded]