Stimulant Use Disorder - Baumann

Fri, Jul 21, 2023 10:18AM 47:09

SUMMARY KEYWORDS

methamphetamine, mdma, cocaine, drug, dopamine, effects, dopamine transporter, serotonin, stimulant, meth, showing, transporter, serotonin transporter, increases, extracellular, metabolite, amphetamine, type, stimulants, high dose

---

00:01

This presentation is entitled Stimulant Use Disorders: From Neurobiology to Public Health. I will now turn it over to Dr. Michael Baumann to begin our presentation.

00:10

Hello, everyone. Welcome to the lecture on stimulant use disorders. I have no financial disclosures. General outline for this talk, we're going to go over the major categories of illicit stimulants. These include cocaine, methamphetamine, ecstasy, bath salts, or sometimes what are referred to as research chemicals. And then we'll wind up with a summary.

00:44

Topics covered for each substance will be drug trafficking and confiscation, formulations and methods of use, the pharmacokinetics and metabolism, desired and adverse effects, chronic and withdrawal effects, the neurobiology and then finally treatments.

01:04

Our first illicit stimulant is cocaine. Cocaine is a plant-based alkaloid and from a chemical perspective is a phenol tropane. Found in the coca plant. Nearly all cocaine on the planet comes from the Andean region, chiefly from Colombia. And this Andean cocaine is trafficked on a global scale. Its trafficked to the United States, mostly through Mexico by cartels, the Sinaloa Cartel, and Jalisco Cartel. But there are paths of cocaine trafficking to Europe as well. This is just an example of some confiscated cocaine bricks. This is a DEA exhibit- exhibit that shows the cocaine bricks with the scorpion logo. It's like a branding.

02:05

The confiscation of cocaine, though it really remains relatively stable. When we compare it to to heroin, we see there's a large drop from 2008 to 2018, 2019. And it's still the same today, cocaine

has leveled off in terms of encounters. This data here I'm showing you- the y-axis is NFLIS encounters. This is National Forensic Laboratory Information System data. And this is law enforcement confiscation, or encounters of this drug. And we see here that probably around 2014 until the present time, cocaine confiscation has leveled off.

02:47

Formulations and methods of use. There are two basic formulations, the cocaine freebase and the cocaine hydrochloride. The freebase can be ignited, so it can be smoked, and this is what is commonly known as crack. The hydrochloride salt by contrast, cannot be ignited, but it can be freely dissolved in solution. And so the hydrochloride is used for intravenous injection of the solution using needle and syringe and also intra nasal snorting of the powder.

03:19

And this is a good place to introduce a really important concept here with regard to stimulant misuse, and that is the rate hypothesis of drug reward. And so, basically what we have is a situation where pharmacokinetics are going to govern the sort of severity of abuse potential, so that smoked and intravenous routes, they give a faster rate of drug entry into the brain. And this gives enhanced subjective and rewarding effects. And this translates to enhanced abuse potential.

03:55

By contrast, inter nasal and oral routes, you get a slower rate of drug entry into the brain, reduced subjective effects and rewarding effects.

04:05

The desired effects of cocaine include enhanced mood and euphoria, increased attention and alertness, decreased need for sleep, appetite suppression and sexual arousal. Upon high dose administration or repeated binge administration, you start to see adverse effects and these include include psychosis, tachycardia, arrhythmias, heart attack, hypertension, stroke, hyperthermia, Rhabdo, multi-system organ failure. In fact, one of the main causes of death from cocaine is something called excited delirium. And during this situation, you have a patient which is delirious. They're hyperthermic. They're heating up, you start to get muscle tissue breakdown. myoglobin and other proteins leak into the circulation, they clog the kidney tubules and the patient will die ultimately from multi-system organ failure.

05:07

Now, we have two types of long term effects here when we talk about cocaine. We have tolerance and sensitization. In the first case tolerance refers to blunted effects. And that is when you take the second dose after you've taken the first dose, you will have blunted effects when compared to the first dose. Classic example- this is acute tachyphylaxis or the first dose effect, which cardiovascular effects of subsequent doses is blunted compared to the first dose. Euphoria and sexual arousal can

also be diminished by this acute tolerance. But really, if you have breaks of time between a cocaine binge, you don't have long term tolerance. That is once a binge is over, and there's a period of withdrawal or removal of drug, when you come back to use the drug, you still can achieve those desired effects. And one of the things here is that anorexia does not appear to have any tolerance. That is the anorexic effect the drug is maintained over long periods of time.

06:14

Sensitization, on the other hand is enhanced effects of the drug. And the classic example of this is seizures. So this would be a situation where doses of cocaine that didn't normally produce seizures now after chronic administration, you have seizures. And another example would be psychosis. And we'll talk about this again with methamphetamine. It's even more pronounced with methamphetamine, and that is the emergence of paranoid delusions, visual, auditory and tactile hallucinations. And these psychotic episodes can be virtually indistinguishable from schizophrenia. And so it's really important from a medical perspective that patients be allowed to have some recovery time from acute drug effects before you try to do any kind of diagnoses about mental health issues because the effects of stimulants especially high dose stimulants can manifest as a phren- schizophrenic episode.

07:15

Withdrawal effects. Withdrawal effects include anhedonia and depressed mood, and in fact, anhedonia or the inability to experience pleasure is one of the cardinal features of cocaine withdrawal and stimulant withdrawal in general, and it can be a major driving force for relapse. Severe anhedonia- inability to experience pleasure can often push one towards subsequent relapse and return to drug use. Increased appetite, you have rebound, you have rebound hunger, anergia and fatigue, vivid or unpleasant dreams, insomnia or hypersomnia, either one. Sleep disturbances again are a major issue with with withdrawal from stimulus.

08:04

The molecular sites of action- now we get into neurobiology here. Cocaine acts on the SLC6 monoamine transporters. This is a solute carrier, the dopamine transporter, the norepinephrine transporter, and the serotonin transporter, which I'll abbreviate is DAT, NET and SERT. These these monoamine transporters. These monoamine transporters are expressed on particular nerve cells, that is the dopamine transporter is expressed on dopamine cells. Norepinephrine transporter is expressed on norepinephrine cells and the serotonin transporter is expressed only on serotonin cells. So this is a site-specific marker.

08:54

Other sites of action for cocaine include sodium channels so the most important site for this presentation of action, for this presentation is the dopamine transporter. Under normal circumstances that mediates dopamine uptake. That's our membrane bound proteins responsible for the uptake of released dopamine. And in this simple cartoon, you see that dopamine is taken up by the DAT. You

can think of these dopamine transporters, little mini vacuum cleaners and what they do is they vacuum up the dopamine from the outside world and bring it back into the cells where the dopamine can be recycled for subsequent release.

09:36

Because the dopamine transporter is one of the main players in in metabolizing, or getting rid of dopamine-signaling, drugs to disrupt that function increase synaptic dopamine, and these increases in extracellular dopamine are perceived as rewarding.

09:57

And here we see a cartoon that shows cocaine is a DAT blocker.

10:09

Cocaine is our diamond here in the cartoon. And we see it blocks the permeation pore of the dopamine transporter such that the dopamine transporter is no longer able to take up dopamine. And when this occurs throughout the brain, you get elevations in the extracellular concentrations of dopamine.

10:31

You can actually measure extracellular dopamine in preclinical models, for example, in the rat nucleus accumbens, and nucleus accumbens is an area that's implicated in the positive reinforcing effects of drugs. And here we see some microdialysis data in animals that are freely moving, and we're measuring locomotor activity at the same time. Here on the left hand panel, you'll see dopamine in the y-axis, and this is a percent of baseline so that each time you see- 100 is baseline- 200 is a doubling of the dopamine- 400 is a fourfold increase in dopamine and you see as we give one milligram per kilogram IV, followed by three milligrams per kilogram IV, we have a small increase in dopamine at the low dose, but a much larger increase in extracellular dopamine at the higher dose. It's important to note in the animal models, that these increases in dopamine in the nucleus accumbens are time-locked to increases in locomotor activity. And so this is a cardinal sort of feature of stimulant drugs, they increase extracellular dopamine and reward pathways, and they cause locomotor stimulation.

11:47

Rats will ready, readily learn to self administer cocaine. Again, this is sort of the litmus test for what drugs are rewarding and reinforcing. That is they'll be self-administered. In this graphic, you'll see on the left hand side is lever presses per session. On the x-axis here, this is the day of acquisition: A-1 through A-10. These are the acquisition days, and what you see is the active lever presses. Pretty soon, there's, by the third day, a large separation between active lever presses, presses which give a drug infusion versus inactive lever presses that have no programmed response. And so animals will learn very, very quickly to self-administer cocaine they maintain, maintain stable cocaine self

administration, and extinction. Here we- E-1, this is where we remove drug. And you'll notice even when there is no drug, the animals will keep pressing. And this is called an extinction burst. But at some point, they realized that they're no longer going to get the reinforcer and then in the lever presses go down.

12:56

So this is again a classic example preclinical model showing the rewarding slash reinforcing effects of drugs and the animals will learn very quickly to self-administer these substances such as cocaine and other stimulants.

13:12

Treatment for cocaine dependence. Unfortunately, there's still no FDA-approved medication for cocaine dependence. So treatments are psychologically-based. Cognitive behavioral therapy. CBT is a very effective treatment modality for some patients. However, if you have patients who have compromised executive function, then cognitive behavioral therapy might not be the best approach. Contingency management. Contingency management has been shown very effective for treating cocaine, cocaine dependence problems, the problem is with contingency management, it's not widely available. And finally, group and community therapies can also be very effective for example, 12 Step programs.

14:04

Now, even though there is no FDA-approved medication so far for cocaine, there has been some success when stimulant medications and in particular mixed amphetamine salts or slow release amphetamine preparations. Now, this is a very busy slide. This was a metaanalysis done by Tardeilli et al. in 2020. And what they show is that even though we don't have an FDA-approved medication for cocaine use, some success has been realized with stimulant medications. And the take home message from this slide is that the medications that are shifted to the right of this line, this is a signal showing that the medication is more efficacious than placebo. And so there have been some some successes and hopefully this will be something that, next time I give this talk, we can show even even greater efficacy for some of these stimulant medicines.

15:10

Okay, so the next stimulant drug we're going to talk about is methamphetamine. Methamphetamine is a synthetic amphetamine analog. Here you see phenethylamine, which is amphetamine, the phenol, the ethyl on the amine, here we have an n methyl and an alpha methyl. And this is methamphetamine.

15:36

In contrast to what I showed you with cocaine, methamphetamine confiscation is increasing dramatically in recent years. And again, I have heroin in there for for comparison. But you'll notice in the last- last data that I'm showing here is 2019. It's continued to increase beyond that in the last

the last- last data that I'm showing here is 2019. It's continued to increase beyond that in the last couple of years. The bottom line here is we had in 2019, over 400,000, NFLIS encounters, right. So this is 400,000 methamphetamine exhibits were confiscated by local state and federal law enforcement. So we have a serious meth- methamphetamine problem in our country right now. And this is basically because we have massive amounts of cheap, highly potent methamphetamine. It's being trafficked into the United States through the southern border, chiefly by the Sinaloa and Jalisco cartels in Mexico.

16:37

Now, as I've already mentioned, most meth is now trafficked by Mexican cartels. This picture here shows a relatively small basement laboratory where methamphetamine is being synthesized. This is an older DEA picture. Most of the methamphetamine now that's coming into the United States is actually made in these super labs where they're- where they're making kilogram quantities scale up quantities, not from this type of smaller lab.

17:09

Formulations and methods of use. Methamphetamine, similar to what we saw with cocaine, there's a freebase, there's a hydrochloride salt. Methamphetamine freebase ice or crystals- smoked using pipes. Methamphetamine hydrochloride is dissolved in aqueous solution and is injected using a needle and syringe and also we see snorting of crystals, sometimes known as crank.

17:36

Pharmacokinetics and metabolism. Smoked drug reaches the brain within seconds, intravenous drug reaches the brain within seconds, whereas intra nasal drug reaches the brain within minutes. Now, it's important to mention here that the metabolism of methamphetamine if you recall, the structure I showed you, the first metabolite and major metabolite of methamphetamine is N-demethylation. And this forms amphetamine, which is also bioactive. And so because of this, the effects of methamphetamine can be very prolonged when compared to a drug like cocaine, for example, because the drug is biotransformed to an active metabolite. But there are- so there are also inactive metabolites that are hydroxylated versions, where you get ring hydroxylation, particularly at the Para position on the phenyl ring and this ina- inactivates the molecule.

18:39

The desired effects are very similar to cocaine's. But I will say- many times they're more intense and they're longer lasting. And I'll show you why in a few minutes, when we look at molecular mechanism. You have enhanced mood and euphoria, increased attention and alertness, a decreased need for sleep, appetite suppression and sexual arousal.

19:01

Similar to what we saw with cocaine. The chief adverse effects of methamphetamine are under the neurological and cardiovascular domains. Under the neurological we have psychosis, psychotic

episodes. Under the cardiovascular we have arrhythmias, palpitations, heart attacks, hypertension, stroke, and again, with methamphetamine, we can get that excited delirium situation where you have hyperthermia and the breakdown of muscle tissue and clogging of kidney tubules with multi-system organ failure.

19:40

Now, this was an ad campaign that was around in the mid 2000s, called Faces of Meth and what this shows an individual on the left prior to using meth, and then after using meth to the right. And so what this really shows and I think this is an important thing for folks to realize is that there is a general deterioration of overall health. When folks become addicted to methamphetamine and use in a compulsive way, there becomes a complete misallocation of behavior so that people aren't doing the normal things that they normally would do in terms of self care, for example, they become vulnerable to infection. And really, the only thing that matters to folks when they're in this situation is is getting more drug. And so this is a terrible, terrible affliction.

20:35

This example of meth mouth, you see the deterioration of teeth in the gums. And this is due to drying mouth, dry mouth, right, the salivary glands don't function properly. The drug itself has adverse effects on enamel. And that's just an example of the overall deterioration you see with longterm methamphetamine misuse.

21:00

Now, I'm not going to talk about methamphetamine tolerance, because there's not much evidence for that, however, sensitization to particular effects of methamphetamine are well established and in particular- psychosis. And here again, we see a situation where a person is using methamphetamine and they're not really seeing any kind of serious psychotic episodes. But after high dose use or repeated binge dose use you see the emergence of psychotic symptoms such as paranoid delusions, visual, auditory and tactile hallucinations, like feeling like there's bugs on the skin, hearing voices, paranoid delusions where, for example, feel like the they're being watched. Again, these can be virtually indistinguishable from schizophrenia.

21:53

And finally, stereotypical behaviors we see with methamphetamine, also people that are chronically searching for something that they can't find. Perseverating around cleaning, cleaning the house and things like this.

22:11

Withdrawal effects: Anhedonia and depressed mood and again, anhedonia or the ability to experience pleasure is a cardinal feature in methamphetamine withdrawal, which often drives patients back to drug use. Increased appetite, anergia and fatigue, vivid or unpleasant dreams, insomnia or

hypersomnia.

22:35

The molecular site of action for these drugs for methamphetamine is similar to cocaine. It's the same sites of action, in fact, mostly dopamine transporters and norepinephrine transporters. There are other sites of action, the circular monoamine transporter, which we'll look at in a second, and also something called the trace amine-associated receptor.

23:00

Now, even though cocaine and methamphetamine interact at the same molecular sites of action in the brain, there's a subtle difference in their mechanism of action, that's of note. So I told you previously that cocaine was an uptake inhibitor or an uptake blocker, which would get on the dopamine transporter and sort of sit on the extracellular face blocking the pore. Well, here with methamphetamine, we have a more insidious mechanism of action because the drug here as a diamond, in the cartoon, it actually goes through the transporter permeation pore and into the cell itself. So methamphetamine enters the cell through the dopamine transporter. And what I'm showing here is, it's affecting the vesicular monoamine transporter, and in doing so, it disrupts vesicles. So, methamphetamine increases extracellular dopamine by a two-prong mechanism. The first is it disrupts vesicles, so that the contents of these vesicles the dopamine is released into the intracellular space here, into the cytoplasm. And then methamphetamine reverses the normal direction of flux for DAT. So the dopamine is leaking out. So you can get tremendous increases in extracellular dopamine with methamphetamine that you can't get with cocaine.

24:30

So to illustrate this, we can look at our micro-dialysis in rats, again, like we saw with cocaine. And you'll notice here, the scale that I'm showing you, dopamine percent increases and serotonin percent increases is much larger than what I showed you with cocaine. You'll recall that we saw about fourfold increases in extracellular dopamine with cocaine here with .3 and one that is much lower doses than what we saw with cocaine. We're having a 500 fold or a five fold increase 500% Or five fold increase in dopamine. Here we're seeing nearly 18 fold increase in extracellular dopamine. So these are tremendous, super physiological amounts of dopamine that are in the extracellular space. And again, this is because methamphetamine acts as a dopamine releaser. Rather than uptake blocker, it actually facilitates reversal of the transporter and allows tremendous increases in extracellular dopamine.

25:35

And just for comparison to the right here we see the effects on serotonin. So methamphetamine also affects serotonin, but these effects are much smaller in terms of sheer magnitude when compared to the effects on the dopamine system.

25:50

So what about the comparison between cocaine versus methamphetamine? Just to recap, cocaine inhibits dopamine-mediated reuptake. Whereas meth, it also inhibits dopamine uptake because it binds to the transporter, but its major mechanism is it evokes that mediated release of dopamine, which allows for much larger increases in extracellular dopamine from methamphetamine when compared to cocaine.

26:14

Also, another thing that's important to note, differences between cocaine and methamphetamine is cocaine is rapidly metabolized. The ester linkage in the phenoltropane molecule was broken very readily. So the effects last an hour or two. Withdrawal lasts one or two days. Whereas methamphetamine, as I've already mentioned, it's slowly metabolized, and even when it is metabolized one of its principal metabolites is bioactive is the amphetamine itself. So its effects lasts 10 to 20 hours. And withdrawal can last many, many days. And it could be more severe with methamphetamine than with cocaine.

26:57

One of the more interesting topics about methamphetamine and we don't see this with cocaine is that methamphetamine actually causes toxicity in the brains of users. And what we see here in this brain imaging, we see a normal control brain and this is the caudate putamen, we see it's very highly labeled. This is a a DAT marker, you know, this is a PET scan, looking at the DAT marker, if you look at the methamphetamine abuser, much less. And this is a reflection of the loss of dopamine transporter sites in the in the brain. And there is some evidence that this is that this is a neurotoxic effect that takes a really long time to recover. If there's recovery at all. In some cases, there isn't much recovery. So this is another reason why methamphetamine in some ways is a much more insidious drug than cocaine because it gets inside nerve terminals, it does damage and we've seen loss of dopamine transporter sites in the brain.

28:08

Now another real problem is the role of methamphetamine in the gay subculture, chem sex for example. And this has to do with a sort of synergism of effects. And that is the meth intoxication decreases inhibition and judgment, increased sensation seeking and sexual arousal and unsafe sexual practices, which lead to HIV and other types of infections being transmitted.

28:40

Meth, sex and the internet again, I said, this is the perfect storm, sex both virtual and real, both safe and unsafe is only a click away. It's this type of variable intermittent reinforcement that can be really problematic for certain individuals.

28:56

Here's just an example of an internet website where you can see okay, on the left hand side, people

are talking about their drug use on internet chat sites. And on the other hand, there's places where you can sort of solicit you know, companionship, for sexual experiences. And all this is freely available on the internet. I mean, it is available on the deep web, but you don't necessarily even need to go to deep web. Surface websites are sharing this type of information as well.

29:31

Treatment for meth dependence. Similar to what I mentioned for cocaine, there is no FDA-approved medication for meth dependence. So we're left with psychologically based therapies, the same ones I mentioned previously, cognitive behavioral therapy, group and community therapies and 12 Step programs.

29:50

There is no FDA approved medication. However, emerging evidence suggests that certain agonist approaches for example, the bupropion plus naltrexone reduce methamphetamine use in certain patient populations. This is a figure from a very high profile paper by Trivedi et al in 2021. And what it shows, the blue lines show the percent of negative urine drug screens, the blue is for the bupropion plus naltrexone medication group versus the red for the placebo. And you see there's a really large difference. And this was a two stage experiment, two stage clinical study and it appears like at least for certain patients, this the negative drug urines, that is abstinence from drug use was maintained over long periods of time, even during the second arm of the study. So hopefully, these types of studies will will be repeated. And we will have at some point, pharmacological interventions that will help with methamphetamine abuse.

31:13

Next ecstasy, that's our next drug, ecstasy or MDMA. It's a synthetic club drug. Now one of the things that you want to point out here with ecstasy, it looks just like methamphetamine. The only difference is the presence of this methylenedeoxy moiety right here. And what we'll see is the presence of this methylenedeoxy at the three, four position on the phenol ring, markedly changes the pharmacology of methamphetamine giving it much more serotonergic activity rather than dopaminergic activity. These are just over here to the left are some examples of some ecstasy tablets. And this is often associated with rave parties or dance parties in the summertime.

32:02

So MDMA, as I mentioned, it's a ring-substituted amphetamine analogue, we see meth on the left, we see MDMA on the right, the only difference between these two molecules is the presence of that three, four methylenedeoxy. And again, this is going to dramatically affect the mechanism of this drug in the brain.

32:21

Confiscation of MDMA remains very, very low compared to other drugs. And recall what we saw with

methamphetamine, over 400,000 encounters in 2019. And here, MDMA is barely a blip on the radar screen. So in terms of its problems, for public health, it's very low. And in fact, most people already know about this, that MDMA is being explored for its therapeutic attributes, and the treatment of PTSD and other indications like depression.

32:57

Formulations and methods of use: powders, capsules and tablets. Oral ingestion of tablets is the most common. There is some intranasal and intravenous use. Bumping- this refers to repeated intermittent dosing. Stacking refers to taking multiple doses at once. And then these drugs are often used with binge and crash cycling. That is, you go on a binge where you take a lot of the drug, and then you just crash for three or four days afterwards. And this is, you know, sort of the weekend party scenario

33:27

Pharmacokinetics and metabolism. The pharmacokinetics of MDMA reaches maximum at about two hours after oral ingestion. The problem with MDMA and one of the dangers of using it illicitly is that there's nonlinear drug accumulation at doses above three mgs per kgs, and I'll explain this in the next slide. MDMA is chiefly metabolized by N-demethylation to form MDA and O-demethylenenation to form hydroxylated metabolites.

33:56

So we want to look at MDMA metabolism in a little bit more detail because it is very problematic. And we see MDMA molecule up here in the upper left hand corner and the principal mechanism of inactivation of MDMA is the breaking open of this methylenedeoxy ring to generate this dihydroxy metabolite, which is subsequently o-methylated to a dropsie methoxy. And this is conjugated and goes out in the urine. The problem is, these dihydroxy metabolite here, it irreversibly inhibits cytochrome 2D6, so that the cytochrome is no longer active. Once you've stopped this sort of mechanism here, then you're pushing MDMA into the formation of MDA, which is bioactive and you get nonlinear accumulation of the drug. That is you get more than would be predicted by the dose administered because you're no longer able to metabolize the drug through this mechanism. So it's a suicide inhibitor of cytochrome 2D6. One of the spin offs of that is if any of the therapeutic medications that one is taking is metabolized by cytochrome 2D6, you're going to have a drug-drug interaction, you're going to have problem disposing of any substance that's metabolized by that particular enzyme.

35:26

The desired effects are somewhat different than what we've seen before. There's combined effects of a stimulant and hallucinogen in particular: enhanced mood and energy, heightened and altered sensory perception. Colors look a little brighter; music sounds a little nicer. But really the most important and noteworthy effects are these empathogen effects or entactogen effects, which are feelings of empathy and closeness to others, a feeling of oneness with others, a tendency to communicate with others. And there's also cardiovascular stimulation and appetite suppression, which are shared with other stimulants.

36:09

Adverse effects- again, we can see psychosis at significant dose levels. Also sympathetic stimulation, palpitations, heart attacks. And finally, the worst scenario here is something called serotonin syndrome. This is hyperthermia, dehydration. And the best way to treat this is with hydration cooling, sometimes sedation in some cases, and it's noteworthy that beta blockers should be avoided. In this case, even even if heart rate is elevated, because these could exacerbate hypertensive effects of the drug.

36:46

Withdrawal: anhedonia again, we see this with all stimulant type medications and even with entactogens, lethargy and fatigue for several days, sleep disturbances. One thing that's different about MDMA, though there doesn't seem to be a significant enough withdrawal that will require treatment of any type.

37:07

Molecular sites of action: same sites of action that we saw for the other drugs for cocaine, and methamphetamine. But the important difference is with MDMA, you dial in serotonergic activity. So the effects of this drug are going to be predominantly on the serotonin transporter, and not DAT and NET. Other sites are the vesicular monoamine transporter and 5-HT2A receptors.

37:36

And so here's cartoon showing us a serotonin transporter, very similar and now it goes to what we saw with DAT. You see our serotonin molecule, it's going in through the serotonin transporter. That serotonin is going to be put back into vesicles and recycled for subsequent release. So SERTs are like little mini vacuum cleaners on serotonin nerve terminals that vacuum up the extracellular serotonin and bring it back into the cell. Drugs that disrupt this SERT function will increase synaptic dopamine and increases 5-HT. It's important to note they're not rewarding. And in fact, in some cases, they're therapeutic because we know blocking SERT is a principle mechanism for SSRIs, the serotonin selective reuptake inhibitors.

38:28

So the mechanism, the molecular mechanism, we look at the neurobiology of MDMA. It's analogous to what we see with methamphetamine. The principal differences though, again, the major site of action here is we've dialed in effects. It's SERT, which we did not see with the other stimulants we've mentioned previously. So MDMA is a SERT substrate. That is, it's a 5-HT releaser. It's similar and analogous to the mechanism for MDMA. The only difference is it's principally happening in serotonin nerve terminals. And so here's our diamond drug, it goes in, it disrupts vesicles, to release serotonin from vesicles into the cytoplasm, reversal of the normal direction of the serotonin transporter, and the serotonin is released out into the extracellular space.

39:25

We can look at micro dialysis in rat brain, as we've seen before. And here we see the effects of MDMA at point three and one milligram per kilogram doses. We see very small effects on dopamine and at our highest dose, MDMA causes about a doubling of dopamine. Remember, to put this in perspective as to what we saw with cocaine and especially with methamphetamine, these are very small increases in dopamine with MDMA. By contrast, look at the effects on serotonin. You get about a 400% increase or a four-fold increase at the lowest dose, and about an eight-fold increase at the highest dose. So these are tremendous super physiological elevations in extracellular serotonin. And a lot of evidence both human and animals suggests that these rapid and marked elevations in extracellular serotonin are the underpinnings of the unique subjective effects of MDMA.

40:29

MDMA acutely increases synaptic 5-HT. The SERT-mediated 5-HT release or reverse transport. One of the problems with MDMA is if you take high doses of it, as I showed you, it actually goes through the serotonin transporter through the permeation pore and deposits into cells. And if this happens to a high degree, that is you have a lot of MDMA onboard, it gets trapped inside of serotonin neurons, and this will cause a putative neurotoxicity. Depletion of serotonin. This is because disruption of the vesicles. Inhibition of 5-HT synthesis. This is because tryptophan hydroxylase is actually poisoned. And you can often see loss of the serotonin transporter sites in the brain analogous to what you saw with dopamine transporter sites in methamphetamine abusers. And they're still up for debate whether this is true toxicity but nevertheless, high doses of MDMA are quite dangerous in terms of serotonin deficits. And this is shown in both animal models and in humans.

41:45

The final group we're going to talk about are the probably the most newly emerging of the stimulants and these are bath salts. All these bath salts compounds are research chemicals. So sometimes sold on the internet as research chemicals. They're all chemically related to a natural product called cathinone. Cathinone is a plant-based alkaloid. If we look at the structure of it, it comes from the khat plant, Catha edulis.

42:14

But if we look at the structure of it, you'll notice we have amphetamine then ethyl amine, alpha methyl phenethylamine. The only difference here is the introduction of a beta keto group. So we have the alpha methyl group of amphetamine, but we also have added this beta keto moiety. So cathinone is simply the beta keto amphetamine, the beta keto invert, sometimes called BK amphetamine.

42:45

Bath salts products contain a variety of synthetic cathinones. MDPV is an analogue of pyrovalerone. You see, in this molecule, sort of a hybrid between ecstasy, right, we have the three, four methylene deoxy here. We have this purity ring, this long chain, so it's a much more complicated molecule than

the others we looked at, but still has the beta ketone. It turns out MDPV was a constituent of the first wave of bath salts that was responsible for a tremendous number of overdose intoxications and even deaths.

43:22

And in our laboratory, we published findings to show that this drug, there's our triangle, it's an extremely potent uptake inhibitor at DAT, so it targets the DAT as an uptake blocker. It's about 10 times more potent than cocaine, so this could be a very dangerous drug.

43:44

Now methylome- This is another common common drug that was in the initial bath salts wave that came in during 2010 2011 and 2012. And if you'll look at this drug, this is the beta keto version of MDMA of ecstasy. This is often referred to as BK ecstasy. Here's a three four methylene deoxy group, phenol ring, alpha methyl, n-methyl and here is the beta keto.

44:14

So as predicted methylone is very similar in its mechanism of action to MDMA. It is a SERT substrate. Here we see the diamond going into the pore, hitting the vesicles which would disrupt the ves- vesticular compartmentalization of serotonin and you'll get subsequent serotonin release. Very similar again to what we've seen with MDMA.

44:41

So since the initial emergence of the bath salts compounds, a number of methylone analogs have appeared on the clandestine market, mostly as counterfeit MDMA. And there's a lot of chemical structures here. Here's the amphetamine. Here's the MDMA. Here's methylome. Remember, that's the BK analog of MDMA. And so what the clandestine chemists have done is simply add carbons here to the alpha carbon moiety or added carbons here to the amine group, and we have eutylone, dibutylone and penylone, which are some of the more prominent bath salt compounds that are out there now.

45:25

So, that's the end of the talk, we get to the summary here. Cocaine is a prototypical dopaminergic stimulant. Meth is a powerful stimulant due to its DAT-mediated dopamine release. MDMA acts as a mild stimulant and hallucinogen due to its SERT-mediated 5-HT release. MDPV is cocaine like, whereas methylone is MDMA like.

45:54

Finally, the clinical challenges for treating stimulant dependence or stimulant use disorders. There's

no FDA approved medications for stimulant dependece, so treatment is psychologically based or psychosocially based. There's no specific antidotes for stimulant intoxication. So treatment is largely supportive. And it's important to mention that stimulant-induced deaths are increasing at a really high rate at present. And this is due to fentanyl administration. In some cases, folks are knowingly taking stimulants and fentanyl together. In other cases, fentanyl was being added to the stimulant products. And so you're going to have accidental or inadvertent fentanyl overdose.

46:50

Thanks for your your time. And you can always get in touch if you have comments for improvement or questions or any other types of interactions you want to have related to this presentation. Thank you so much.