SOMETHING FOR THE PAIN

EPISODE 28: Surveying Substance Use Disorder: Methamphetamine

(30 mins)

(0:00)

[cue guitar music]

[Sam Steffen]

This is *Something for the Pain*, a podcast produced by Project ECHO Idaho, made for Idaho's healthcare professionals working to prevent, treat, and facilitate recovery from opioid and substance use disorders throughout the Gem State. I'm your host, Sam Steffen.

[theme song]

Today we're continuing our theme of 'Surveying Substance Use Disorders' and are going to be talking about Methamphetamine. This episode features a presentation by Cathy Oliphant, PharmD, Co-Chair of Pharmacy Practice and Administrative Sciences, Idaho State University, Pocatello, titled "Pharmacology of Methamphetamine and Other Stimulants." This lecture was recorded on July 14, 2022 as a part of ECHO Idaho's Opioids, Pain and Substance Use Disorders series. Here to introduce today's presenter is former ECHO Idaho Program Manager, Sampson Nde.

[Sampson Nde]

Hi, everyone! Welcome to today's Opioids, Pain and Substance Use Disorders session. My name is Sampson Nde, I am a program manager at ECHO Idaho here. So today we are going to be having a very interesting topic for presentation by Cathy Oliphant. Cathy is a professor and co-chair of the Department of Pharmacy Practice, College of Pharmacy, Idaho State University. The title of the topic is "Methamphetamine and Other Stimulants." So please, at this juncture, I would like Cathy to take it over from here.

[Cathy Oliphant]

So I am Cathy Oliphant, and I am a pharmacist and professor at ISU College of Pharmacy, and like Sampson said, we are going to be talking about stimulants today, so primarily methamphetamine—I've kind of grouped amphetamine and methamphetamine together—and cocaine. I'll mention bath salts a little bit because they are actually derivative of an amphetamine.

So our objectives today will be to kind of look at some just like basic information and then we'll look at basic pharmacology of these agents; we'll describe why these substances are used and how they are used, the different formulations of them. And we'll look at both short- and long-term effects of these stimulants, including some withdrawal symptoms, acute toxicity, but especially the long-term.

Okay, so let's start with amphetamine—methamphetamine. So amphetamines were initially derived from the ephedra plant and they've been used for medicinal purposes for quite a long time. And they were actually synthesized beginning in the late 1800s. And so methamphetamine and then the MDMA

are pretty much substituted amphetamines that are very similar, and those were then derived once we figured out how to synthesize amphetamine. I thought it was interesting that meth was initially used by the German military during WWII as a stimulant to prevent fatigue out on the battlefield, so. But obviously meth has become a big issue.

So meth is illicitly produced, and most of it comes into the US from Mexico, however, there are many smaller, call them 'clandestine' labs in the US, you know kind of like home-grown setup, you know, cooking in the home and such, to manufacture methamphetamine. And meth can be manufactured using pretty cheap OTC products including pseudoephedrine, which is a common product in a lot of cough and cold preparations. And there was a law that went into effect the Combat Meth Epidemic Law of 2005 which requires pharmacies or any retailer of pseudoephedrine, ephedrine or phenylpropanolamine to keep these products in a locked cabinet or at least behind the counter and requires identification and we try to minimize how much one particular individual can buy because they can be using it to produce meth. The process is not that difficult but it can be pretty dangerous between the chemicals in the processes and so meth houses can pose a threat to the environment long after they've been shut down due to the chemicals they're using. Explosions, house fires can occur.

So it is a schedule II medication because it is highly addictive in nature and we do have prescription form of methamphetamine and it's the Desoxyn. Its main treatment is for narcolepsy. And then like I think most of us know we do have amphetamines that are prescribed for ADHD and narcolepsy and the Adderall, Mydayis and Dexedrine are actually a combination of a dextro-amphetamine plus amphetamine and then Ritalin or Concerta, which are used for ADHD, are actually a methylphenidate, which is similar to an amphetamine.

So lots of street-names out there, right? and you may have heard of some of these. Here's a list from the DEA website, and I just pulled out a couple that I kept seeing that were being referred to as crystal-meth, but crank, crystal, ice, glass and Tina. And we'll talk about the differences in our formulations of meth.

So I'm a pharmacist and this is you know kind of the pharmacology talk so here's structure: so this basic structure of amphetamine is what we call a phen-ethyl-amine and so it has this side-chain, this methyl group that's attached to this carbon molecule, and methamphetamine is very similar, it just has a different substitution. And so based on this, you will expect, right, that these have a very similar mechanism of action and associated effects—which they do, although we'll see that meth is going to be much more potent than amphetamine, for the most part.

So we all know that the addiction potential of meth and amphetamines is very high. And so I looked at the 2020 national survey on drug use and 2.6 million individuals reported using meth in the last 12 months—remember this is from 2020—and 1.5 million individuals would fall into the meth use disorder. And if we look at overdose deaths, it's pretty significant. If we look from about 2015, overdose deaths involving meth have about tripled. And meth use has obviously become more frequent but what's also leading to this increase in deaths is that it's being combined with a lot of products; methamphetamine is also being mixed with fentanyl, so that's driving some of it. And we'll talk about many individuals who use methamphetamines use it with other illicit substances as well. In 2021 over 32,000 individuals died from an overdose involving a stimulant and they particularly state that this is primarily meth.

And so polysubstance abuse is actually very common across the board in individuals who use these substances illicitly. And a big one that people who use meth—heroin is one of those agents that they like to use in combination. And I did some research more into it, I mean some of it makes sense, right? I mean they get addicted to both of those substances then they're more likely to use to counteract the effects of each other, right? And so stimulant versus heroin which is not. But their use-potential is high, right? Between the two, using them. Their overdose potential is very high. And they kind of note that heroin is quick-on, quick-off, meth kind of lasts longer, and so they may keep using heroin to try to feel those effects, and so these individuals are certainly at a higher risk of overdose and death.

Okay, so let's talk about some of the different formulations of meth. Essentially, we've got crystal meth, we've got meth powder and then kind of this meth base. And what I was seeing is that crystal meth has a much higher purity than other forms of meth. And a lot of stuff that I was seeing was 80% or more of pure meth. Meth powder because it's often mixed and cut in with many other substances is about 10% pure. And then meth base which I saw described as this 'damp, oily formulation' is about 20% pure. And then I actually saw some reference to this P2P meth—I don't know if anybody is familiar with that—but it's pretty potent because it contains more of the D-isomer of the amphetamine/methamphetamine. And it's produced without ephedrine, so it has a lot more chemicals that go into it, it's impure even though it's more potent, and the likelihood of experiencing pretty significant adverse effects post-use including severe mental health issues and other pretty significant health problems…and it, though, tends to be laced with fentanyl like many of our other preparations of meth.

So some of the ways that meth can be used: you know, if we look at just meth, not crystal meth, yet, but so it's available in this powder pill, this oily-substance, it can be in a rock-form. The base tends to be swallowed, intranasal, so snorted or injected. Crystal meth, it's kind of interesting that it is typically smoked, however it could be injected or swallowed. And you may find it interesting that there's this 'blue crystal meth' and a lot of people say that was what was seen on *Breaking Bad* and that it really wasn't a thing, but now there is some of it, but typically crystal meth looks kind of like glass shards—you know kind of like glass-like shards.

So how do these agents work? So they're going to work very similarly, right? Because meth is going to be metabolized into amphetamine. And so these agents are indirect agonists at the dopamine, nor-epinephrine and serotonin receptors, so they increase the release of these catecholamine neurotransmitters leading to much higher concentrations of these neurotransmitters in the synapse, and actually these agents have some other kind of secondary actions as well that can be prohibitive of the breakdown of these neurotransmitters within the synapse as well as preventing the re-uptake of these catecholamine neurotransmitters.

We talk a lot about dopamine, it's having its big effect. We know that dopamine is part of the pleasure center, and we'll talk about that in a second. The big thing is, with these agents is that they pretty much re-wire the brain. And if an individual is using meth or even the amphetamines pretty much not how they're supposed to be, that meth results in about 3.5 more pleasure than what's felt from cocaine and about 6 times what our brain can feel naturally on its own. And so this drives individuals wanting more and more and then they develop sort of torrents, I guess, and so they use more, higher and higher doses, and we'll kind of talk about that they often use multiple times a day for many days and it can lead to some pretty significant mental health adverse effects and such.

Okay, so let's talk about the reward system, so the mezzo-limbic dopamine system. And kind of what we want to focus on is the VTA, which is the ventral tegmental area which extends into the nucleus acumens. And this, like I said, is all part of this reward sort of pathway. And these are dopamine-mediated, quite a bit, and so it's reward-motivation-pleasure-euphoria and we talk about the effects of these stimulants, the pleasure and the euphoria are the big, at least, initial, feelings that individuals get.

So a little bit—I'm not going to get a lot—into the pharmacokinetics, just a little bit here so meth as well as amphetamines are metabolized in the liver through 2D6 pathway of the cytochrome P450, so that kind of means that there's potential for other drug interactions. We've already mentioned that meth is metabolized to amphetamine and 2D6, there is polymorphism so you can get some inter-individual variability in metabolism of meth.

We'll look at half-lives, but we'll also look at like the onset of action and how long some of these effects last, there's a lot of discordant effects. The plasma half-life of meth is about 10 hours. How long it's detected and such will be dependent on how much was taken and how it was taken. But about 70% is excreted in the urine within 24 hours and about 30-50% of this is as meth and 10% as amphetamine, because remember meth gets metabolized.

So a little bit more: if we kind of look at bio-availability, and that is how much of the drug is available for an effect. We get the peak plasma level and the time to peak effect and we're going to see that there's a lot of discordant things happening, right? And we'll kind of tell you that the effects from meth can go anywhere from 8-24 hours but really drops off pretty substantially after about 4 hours. And how long it lasts will depend on how much is taken, how it was administered, how the individual's liver and kidney function is, and even though some of the clinical subjective effects that the person using the meth can feel, the cardiovascular risks maintain high levels. And there are a lot of cardiovascular complications with these agents—in particular, meth. And so, if an individual is smoking—and remember, this may be crystal meth, which is more potent than other forms of meth as well—its peak effect is in about 18 minutes, but the peak level occurs way after that. So they hit a very quick, rapid onset, and they can have a pretty quick significant high, their rush, they call it a "flash" of euphoria, it can drop off fairly rapidly. If you give it IV, it's kind of the same way, I mean it's a little bit different that you're peak effect because you're giving it inter-vascularly is fast, but your peak-effect is also less than 15 minutes. If an individual is snorting it, so using it inter-nasally, their peak-effect is also within that 15 minute time period, but peak levels don't happen for about 3 hours, so you still have it around but their big high, their rush, is no longer there even though they still have significant levels. And then, if they were to take it orally, it's much longer for both your peak effect as well as your peak levels. And so they kind of call that the dissociation between peak plasma concentrations and those subjective or clinical effects, and this can really lead to an increased risk of overdoses and like I said, the cardiovascular effects still remain high because we still have levels that are around even though the individual isn't feeling the significant effects.

Okay so let's talk about detection times and the different ways that individuals can be using it. It kind of depends on how long then you can detect it. If you wanted to do drug screens, you can detect meth and its metabolites for about 3-5 days in the urine, about 24 hours in blood, saliva maybe up to 4 days, but in hair up to 90 days.

So if we talk about some of the effects, right? So I've kind of broken it out into the intended and then the acute toxicity or overdose. And so why do people use meth? What happens, I guess, when they're

using it? So, remember it very rapidly enters the brain, creating that big burst of our neurotransmitters, particularly dopamine which is linked to the pleasure-center. And you get euphoria, they become very energetic, aroused, they have a very positive mood, a lot of them feel improved cognitive domains, although we'll see that some report the opposite. And so they may have improved attention, reasoning ability, pattern of recognition, improved motor coordination. It doesn't last super long, but that can be how they can feel. Very sociable, improved confidence, can decrease their appetite—so they're just raring to go, right? Negative effects, though, is they get these behavioral inhibitions, right? And they've talked a lot about, especially depending on ways that you're using it, but with lowering of inhibitions and it can actually increase their sex-drive and so they can take part in very risky behaviors which can increase their risk of hepatitis, HIV, and so there are a lot of potential infectious complications as well. They can start feeling anxiety and then they get physiological effects of pupil dilation, elevated heart rate and blood pressure. So these effects can go away fairly quickly and this will lead the individual to likely use again and multiple times a day for days and days in a row.

So acute toxicity or overdose situations we get some additional things. We'll see that psychosis is a big thing. They can get very violent. Individuals who are found either potentially harming themselves or becoming violent or at risk for others, meth is certainly something to look for. Paranoia, agitation. They can get pretty significant bumps in their blood pressure, heart rate, hyperthermia. Significant chest pain, shortness of breath. They can get rhabdomyolysis which is break down of skeletal muscle, as well as heart, liver and kidney failure. And it's even been known for pulmonary edema, ventricular fibrillation and cerebral vascular hemorrhage, so strokes are associated. And we'll look at long-term effects as well.

Meth, we kind of talked about some of the acute effects. It also has some severe effects on physical appearance. It can lead to significant weight-loss, it can affect their skin, they can get sores and they itch a lot, scabs, and they just don't really heal well. They also get this sallow complexion, and it has to do with the use of meth and the destruction of blood-vessels and of muscle tissues in the user's body and it really tends to be visible on the face. And then they also get something called 'meth-bugs,' it's a sensation that there are bugs crawling on them, and so they pick, and they can worsen the acne that they can get plus they can develop sores and by constant picking they can worsen that. Probably a lot of you have seen or heard of 'meth-mouth' which, it's probably the most visible sign of chronic meth use. Severe tooth decay, gum-disease, and extensive tooth decay is contributed not only to the poor nutrition, right, because we know that meth reduces appetite, but also they get dry mouth and due to the other effects of meth they're less likely to have good oral hygiene and so there's pretty significant damage to the teeth. They can also develop bruxism, so grinding of the teeth, and their teeth can actually fall out.

So long term effects, we've talked about some of it—so psychosis, it's pretty much like a paranoid, hallucinatory state, and it's similar to acute paranoid schizophrenia, and this can be long-term as well as during acute use. Neurotoxicity over time resulting in significant memory deficits, psychotic symptoms, impaired coordination, pretty significant cognitive deficits, impulse control, they have learning deficits, inability to maintain attention, and I mean along with other neuro-effects, Parkinson's has been associated with meth use as well as cocaine, when we talk about that next. Increased risk of developing it later in life with prolonged use of meth.

And we've talked about a little bit of heightened sexual behaviors, right, and high-risk behaviors. It can also cause erectile dysfunction, so some individuals also use Viagra quite a bit. And then there's a lot of

cardiovascular complications, stroke, myocardial infarctions, sudden cardiac death, enlargement of the heart, hypertension, arrythmias, aortic dissection—so it's pretty significant effects, long term. I work in a hospital and we see a lot of these things from long-term use.

Okay, so withdrawal: I mean, a lot of these symptoms we've already talked about. The big thing is because they have such a drive, right, because nothing gives them the same pleasure as meth does, right, because we know of that remodeling in the brain, so individuals who are using keep using because of these symptoms they develop as well as trying to derive some sort of pleasure.

So bath salts are very similar to meths or our amphetamines, it's a similar version of it. And they block the re-uptake of these neurotransmitters as well as stimulate the release of dopamine, so very similar effects that we've already talked about.

So cocaine: cocaine is a tropane-ester alkaloid found in the leaves of the Erythroxylon coca plant found pretty much in South America. Mexico, though, is the primary route through which cocaine enters the US, and cocaine is pretty much specific to this area in South America. It, too, is a schedule-2 medication and it's because cocaine comes as different percent solutions for use as topical or local anesthetic primarily for ear, nose, and throat surgeries. Cocaine is a fine, white crystalline powder. And so it also is very potent behaviorally reinforcing medication with very powerful neuro-psychological reinforcing properties, so very much like meth. Probably not as potent. A lot of individuals start recreationally but about 10% go on to more chronic, heavy use. So again, based on that that 2020 survey about 5.2 million individuals report using cocaine in the last 12 months and 1.3 million individuals had a cocaine use disorder. If we look from data of 2021, close to 25,000 individuals died from overdoses involving cocaine, and this has also increased much like meth over the past several years. Cocaine is also increasingly laced with fentanyl and also kind of polysubstance abuse as well. So with heroin, we call that a speedball. But I thought the alcohol and cocaine was interesting, and so taken together, you get cocaine being metabolized to this different metabolite, this coca ethylene, which is a toxic, long-acting and potentially deadly metabolite, and so using these two together pretty much increases your cocaine level by up to about 30% and it has a much longer half-life so it sticks around for about 5 times longer than regular cocaine, and it has about up to a 25-fold higher risk of immediate death than cocaine alone. So pretty significant, and we'll see that a lot of individuals are using both cocaine and alcohol together.

How is cocaine used? Two forms—so we'll talk about cocaine-hydrochloride which is typically found as the powder and based on the salt form and it really doesn't get smoked very well because it has a very high melting point, like we wouldn't be able to do it safely, and it also breaks down really before it gets to that vaporization phase. And so it's mostly injected or snorted, it's highly water-soluble so it's easy to dissolve and make an injection formulation. Now the cocaine freebase which is also known as 'crack', or some know it as 'rock', it's a crystalline form of it, which is primarily smoked and it's because it has the right kind of pharmacokinetics with its melting point being much lower and it's very addictive. So it also increases the neurotransmitters dopamine, nor-epi and serotonin within the synapses, but how it does it, it doesn't fully stimulate the release of it, it blocks their uptake, right? So we have these receptors and other substances that kind of re-uptake these neurotransmitters and cocaine blocks that. And so we get those high concentrations of these neurotransmitters within the synapse. It can also cause vasoconstriction which is part of its use for topical—you know, the ear, nose and throat surgeries. Also associated with platelet activation and thrombus formation. That will play a role in its cardiovascular adverse effects.

So a little bit different pharmaco-kinetics than meth. It's a very fast onset and a very intense but short-lived euphoric high, shorter than meth. Its half-life is about 1 hour. If an individual is either smoking or injecting it, they get very intense, rapid effects. Snorting is a less effect but a longer effect. So it kind of depends on how long their effects last based on how they're administering it. It also gets metabolized to active metabolites and it is renally eliminated. And again, same with meth, they develop tolerance and they need more and more to produce that same level of euphoria, so they often chase that feeling which is very hard to come upon again.

So if we wanted to see if someone has recently used cocaine, the urine can show cocaine or metabolites for three days up to two weeks; the two-week is potentially somebody who has been using for a long time, pretty routinely. Blood, it can be found for two days, and saliva, for up to two days. And hair, it can be months to years if they've used cocaine. Hair is typically used in criminal cases and such.

So cocaine effects—pretty much, the intended effects as well as negative effects—are going to be very much similar to the ones we talked about with meth. Acute intoxication, kind of pretty significant facial constriction, tachycardia, hypertension, so a lot of the same issues. We can see seizures and strokes as well and pretty significant cardiovascular effects with arrythmias and myocardial infarctions. And chest pain is actually very common with cocaine and actually brings a lot of individuals who've used cocaine into the ED because they think they're having a heart-attack. And then you can also see track marks if they're injecting.

So long-term effects, if they are using it inter-nasally, so snorting it, you see loss of smell, nosebleeds, chronic runny nose. You can see septal damage, lung damage if they're inhaling it. They're often malnourished, anorexic because if they use a lot they're not hungry. They can develop strokes and seizures, we've already mentioned a lot of different cardiovascular, and then we have a lot of the CNS effects, so mood disturbances, paranoia, hallucinations, psychoses and then again much like meth the increased risk of Parkinson's if they have chronic long-term use.

Cognitive impairment deficit's a big issue with long-term use, as well. Both of these agents really effect the brain, remodeling, sort of, of the brain, which over time leads to a lot of these CNS effects.

So my key points, just to kind of re-emphasize some of these: we know that these agents have effects on the neurotransmitters, either blocking the re-uptake or causing increased release, and have a lot of effects on dopamine. They're associated with very euphoric effects that are hard to obtain that kind of initial first couple use, right, and so they keep chasing that and often use pretty frequently to try to obtain those euphoric effects. They are very highly addictive and they are associated with significant acute and long term adverse effects.

Music

[Sam Steffen]

That again was Cathy Oliphant, PharmD, Co-Chair of Pharmacy Practice and Administrative Sciences, Idaho State University, Pocatello presenting "Pharmacology of Methamphetamine and Other Stimulants." That lecture was recorded live on July 14, 2022 as a part of ECHO Idaho's Opioids, Pain and Substance Use Disorders series.

If you'd like to watch the Zoom recording of that presentation, that video is currently available on the ECHO Idaho YouTube channel, which you can access through our website. The PowerPoint slide deck as well as information about how to contact some of the organizations and services mentioned in that talk, are available in our podcast show notes, on our podcast webpage: www.uidaho.edu/echo-podcast

Banjo music

If you're interested in joining our free, live ECHO sessions to receive Continuing Education credit, learn best practices, ask a question or grow your community—please visit our website at www.uidaho.edu/ECHO where you can register to attend, sign-up to receive announcements, donate, and find out more information about our programs.

[Fade out banjo music]

Season three of Something for the Pain is brought to you by ECHO Idaho, supported by the WWAMI Medical Education Program and the University of Idaho, and is made possible with funding provided by BJA, the Bureau of Justice Assistance.

[cue guitar strum and guitar theme w/ lyrics in background]

We here at ECHO also want to hear your feedback. We welcome your questions, comments and suggestions and invite you to email us at echoidaho@uidaho.edu. And don't forget to subscribe to Something for the Pain using your podcast app. And if you have a moment, write us a review!

[bring up theme song lyrics and chorus until first "echo Idaho", then drop volume and continue playing]

Something for the Pain was supported by Grant No. 15 PBJA-21-GG-04557-COAP awarded by the Bureau of Justice Assistance. The Bureau of Justice Assistance is a component of the Department of Justice's Office of Justice Programs, which also includes the Bureau of Justice Statistics, the National Institute of Justice, the Office of Juvenile Justice and Delinquency Prevention, the Office for Victims of Crime, and the SMART Office. Points of view or opinions in this document are those of the author and do not necessarily represent the official position or policies of the U.S. Department of Justice

The contributing voices on today's episode were those of: [Cathy Oliphant and Sampson Nde].

We'd also like to thank all of our listeners, without whom none of this would be possible. Without you, we'd just be talking to ourselves.

[Continue to theme chorus, fade]