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BEFORE THE
UNITED STATES SENTENCING COMMISSION

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HEARING ON
METHAMPHETAMINE

- - -

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WASHINGTON, D.C.

Introduction

I would like to thank the Sentencing Commission for giving me the opportunity to discuss the pharmacological effects of racemic methamphetamine (some combination of both *d*-methamphetamine and *l*-methamphetamine and hereinafter referred to as “methamphetamine”), *d*-methamphetamine, and *l*-methamphetamine. It is my goal to assist the Commissioners as they seek to better understand these issues as part of the multiyear study of methamphetamine sentences. In particular, the Commission seeks information regarding the potency of various forms of methamphetamine, the pharmacological effects and toxicity of methamphetamine compared to other drugs of abuse, abuse potential or “addictiveness,” and the long-term pharmacological effects of methamphetamine use.

The purpose of this statement is to address the pharmacological properties of methamphetamine from the perspective of a pharmacologist in the Drug Enforcement Administration. Further, this statement utilizes the term “methamphetamine” to denote racemic methamphetamine, that is, some combination of both *d*-methamphetamine and *l*-methamphetamine. Where this statement seeks to differentiate between the isomeric forms, the form is identified by name.

Background

Methamphetamine is a highly addictive drug known for its potent central nervous system stimulant properties. Methamphetamine abuse has been documented in the United States since the mid-1900s. Methamphetamine can be smoked, snorted, injected, or taken orally, often with other substances, resulting in an intense euphoric high. The desired effects of methamphetamine—including euphoria, elevated mood, and increased energy—are often associated with serious adverse effects such as mental impairment, seizures, and cardiotoxicity, which may lead to death. Public health reports have repeatedly demonstrated that methamphetamine use results in violent behavior, mood swings, and psychosis such as paranoia, delirium, and auditory and visual hallucination when used chronically.

Clinical Application

Methamphetamine exists in two isomeric forms, *l*-methamphetamine and *d*-methamphetamine. Presently, only one pharmaceutical drug product featuring *d*-methamphetamine, Desoxyn®, remains on the market. Desoxyn®, formulated as *d*-methamphetamine and dispensed as a 5mg tablet, can be prescribed for the treatment of attention deficit hyperactivity disorder or the short-term treatment of obesity. *L*-Methamphetamine is currently formulated as nasal decongestant inhaler products due to its vasoconstrictive properties and is available as an over-the-counter (OTC) drug product.

Mechanism of Action

Methamphetamine produces its stimulant effects by increasing the levels of the monoamine neurotransmitters, primarily dopamine and norepinephrine, within the neuronal synapses of the brain. This is the typical mechanism of action for stimulant drugs including cocaine and amphetamine.

Methamphetamine, similar to cocaine, inhibits the reuptake of dopamine into the synaptic vesicles.^{1,2,3} In addition, methamphetamine reverses the dopamine reuptake pump, resulting in a higher accumulation of dopamine in the synapse as compared to the amount following the use of cocaine. While both isomers of methamphetamine increase neurotransmitters in the brain, their effects on the neurotransmitters differ. Primarily, *d*-methamphetamine acts as a potent releaser of both dopamine and norepinephrine in the brain. In contrast, *l*-methamphetamine primarily acts as a selective norepinephrine releasing agent, with significantly fewer effects on dopamine release, contributing to its clinical use.

Potency

A measure of drug activity that is important in pharmacology is potency. Potency is the concentration or amount of a drug that is required to produce a given or desired effect. Regarding methamphetamine, *d*-methamphetamine is more potent than *l*-methamphetamine. That means that substances that have a higher proportion of *d*-methamphetamine compared to *l*-methamphetamine are considered to be more potent than substances that have a higher proportion of *l*-methamphetamine. This was demonstrated in a clinical study⁴ that compared the effects of racemic methamphetamine (consists of equal amounts of both *d* and *l* isomers), *d*-methamphetamine, and *l*-methamphetamine. The study concluded that it takes more *l*-methamphetamine to produce the same pharmacological effects as *d*-methamphetamine or racemic methamphetamine.

Purity

Purity is the amount of desired drug (i.e., methamphetamine) compared to adulterants or other substances in a sample. Purity is related to potency such that substances that have 100% purity only have methamphetamine (*d*-, *l*-, or both isomers). Seized drug samples, however, can consist of multiple or poly-substances. Some of these substances, such as cocaine, heroin, and fentanyl, also have central nervous system effects. Thus, it would be difficult to determine the overall effects of any of the isomers of methamphetamine based on purity alone because the overall effects of a drug sample will depend on all the substances that are present in that sample. In other words, a pharmacologist cannot infer with a reasonable level of certainty the pharmacological effects of the *d*- or *l*-isomers of methamphetamine based solely on purity. The pharmacological effects would also be based on the adulterants present in the drug sample that may also have pharmacological effects on the body and therefore also play a role in the behavior of a hypothetical individual who ingested this sample.

¹ Partilla JS, Dempsey AG, Nagpal AS, Blough BE, Baumann MH, Rothman RB (2006) Interaction of amphetamines and related compounds at the vesicular monoamine transporter. *The Journal of pharmacology and experimental therapeutics* 319: 237–46.

² Rothman RB, Baumann MH (2003) Monoamine transporters and psychostimulant drugs. *European journal of pharmacology* 479: 23–40.

³ Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS. (2001) Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 39: 32–41.

⁴ Mendelson J, Uemura N, Harris D, Nath RP, Fernandez E, Jacob P 3rd, Everhart ET, Jones RT (2006) Human pharmacology of the methamphetamine stereoisomers. *Clinical pharmacology and therapeutics* 80: 403–20.

Pharmacological and Potency Variation

Clinical reports have demonstrated that both similarities and differences exist between the two isomeric forms of methamphetamine. As mentioned previously, *d*-methamphetamine is the more potent and widely abused isomer responsible for the drug's stimulant and euphoric effects. Data shows that *l*-methamphetamine has minimal psychostimulant effects at therapeutic doses found in OTC products. In a clinical study using *l*-methamphetamine at low oral doses, *l*-methamphetamine had less subjective drug responses (i.e. drug liking), and minimal effects on heart rate, blood pressure and body temperature compared to equivalent doses of *d*-methamphetamine. However, higher doses of *l*-methamphetamine can increase heart rate, blood pressure, and produce some subjective effects like intoxication and drug liking, though these are generally less intense and shorter-lived when compared to *d*-methamphetamine. This difference in activity explains the lower potential for abuse of *l*-methamphetamine as compared to *d*-methamphetamine. This data suggest that methamphetamine (*d* and *l* isomers) and the *d*-methamphetamine will have similar abuse potential.

Pattern of Abuse

Regarding methamphetamine mixture versus that of methamphetamine (actual), the potential for abuse rests, in part, on the amount of pharmacologically active ingredients in each formulation. However, these two terms (methamphetamine actual and methamphetamine mixture) are not pharmacologically pertinent and therefore their potencies cannot be readily defined. Additionally, the pharmacological effects associated with a drug are also partly determined by the speed at which the drug takes effect. This is determined by the method in which the drug is introduced into the body and hence its bioavailability. Bioavailability is defined by how much of the drug is released into the bloodstream to exert its effects. Smoked methamphetamine has nearly immediate effects on the body followed by injected methamphetamine, followed by snorted methamphetamine, then oral methamphetamine. Drugs taken orally for instance must pass through the intestinal walls and travel to the liver before being transported in the bloodstream to its target site. Both the intestinal walls and the liver metabolize many drugs, decreasing the amount of drug reaching the bloodstream. This reduces the amount of drug that reaches the target site which can potentially reduce the intensity of the high.

Risk to Public Health

According to the Centers for Disease Control and Prevention (CDC), psychostimulants, the class of drugs that includes methamphetamine, were involved in 31% of overall deaths occurring in 2023. Additionally, according to the 2023 data from the National Survey on Drug Use and Health, 2.6 million Americans aged 12 or older reported using methamphetamine. Methamphetamine use can cause an overdose, often called "overamping," and is characterized by hyperthermia, cardiovascular collapse, and seizure. In recent years, there has been a steady increase in methamphetamine-involved overdoses in the United States across many demographic groups. Most deaths involving psychostimulants with abuse potential involved methamphetamine. The Center for Disease Control and Prevention (CDC) overdose death data from 2022

showed that about 34,000 drug overdose deaths involved psychostimulants with abuse potential, a nearly 5% increase from the previous year.⁵

Chronic or long-term methamphetamine abuse has been associated with serious negative health effects. Adverse effects associated with the long-term use of methamphetamine include insomnia, memory loss, development of substance use disorder, other health related issues like “meth mouth, and death.”^{6,7}

Physiological and Psychological Dependence

Methamphetamine can cause physical and psychological dependence and increase the development of tolerance. Due to increased tolerance, methamphetamine users frequently need to escalate the dose to achieve the desired “high,” which can be very dangerous. Excessive use of methamphetamine can increase the risk of an overdose and potentially death.

Comparison to Other Commonly Trafficked Drugs

Methamphetamine, similar to other commonly trafficked drugs such as cocaine, heroin, and fentanyl, is psychologically addictive. These drugs have largely contributed to illicit drug use throughout the United States. While all these commonly trafficked drugs have contributed to the current public health crisis due to high addiction potential and severe health consequences, their danger profiles are distinct. For example, while methamphetamine does not cause respiratory depression resulting in death as observed with fentanyl, its use can be fatal due to cardiotoxicity (see figure 1). Figure 1. depicts national trends in provisional drug overdose death counts by selected drug type over time. Between 2019 and 2024, the number of overdose deaths associated with fentanyl was greatest, followed by methamphetamine, and then closely by cocaine, followed by heroin. Between January 2019 and June 2024, there were 3,886,370 deaths involving fentanyl, 1,716,727 deaths involving methamphetamine, and 658,916 deaths involving heroin.^{8,9}

⁵ <https://www.cdc.gov/overdose-prevention/about/stimulant-overdose.html> (Accessed July 18, 2025).

⁶ De-Carolis C, Boyd GA, Mancinelli L, Pagano S, Eramo S. (2015) Methamphetamine abuse and "meth mouth" in Europe. *Med Oral Patol Oral Cir Bucal*. 20:e205-10.

⁷ Meth mouth is characterized by severe tooth decay and tooth loss.

⁸ <https://www.cdc.gov/nchs/nvss/vsrr/prov-drug-involved-mortality.html> (Accessed July 18, 2025).

⁹ Technical notes from CDC source data: Specific drugs are identified as being involved in a drug overdose death when the drug or substance is mentioned in the literal text of the death certificate. The drugs or substances mentioned in literal text fields are assumed to be involved in the death unless contextual information indicates otherwise.

Figure 1. 12-month ending provisional drug overdose death counts by selected drugs

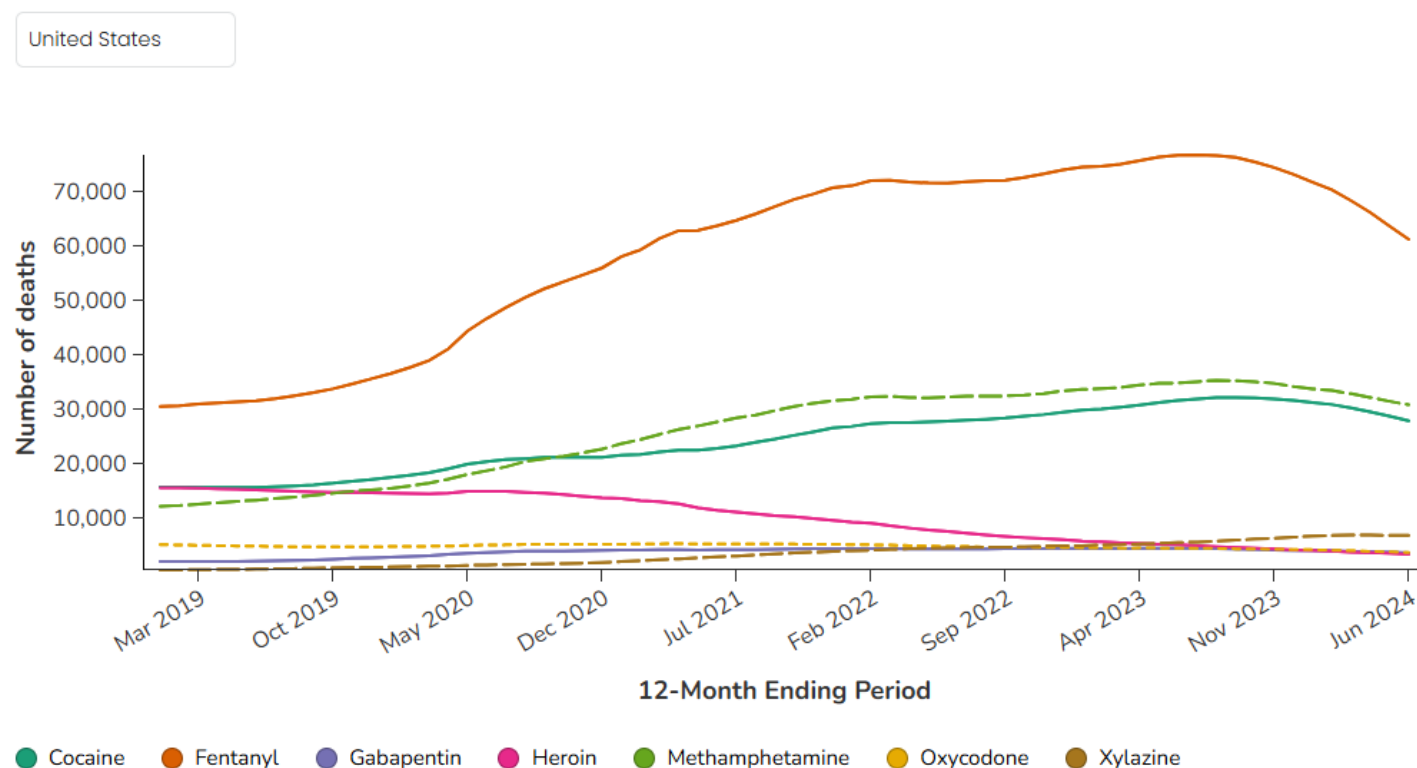


Figure1. Table taken from CDC National Center for Health Statistics: Provisional Drug Overdose Death Counts for Specific Drugs. The figure represents trends in provisional drug overdose death counts by selected drug type over time nationally. Methamphetamine is represented by the dashed green line.

Conclusion

Methamphetamine is a dangerous drug of abuse, and its illicit trafficking has negative effects on public health and safety. The abuse potential of methamphetamine is similar to that of other schedule II stimulants such as cocaine, amphetamine, and methylphenidate. Racemic methamphetamine and *d*-methamphetamine have similar effects and would be expected to have comparable abuse liabilities. *d*-methamphetamine exerts more potent physiological and pharmacological effects than *l*-methamphetamine does, and the stimulating effects exerted by *l*-methamphetamine on the central nervous system are less potent than those of *d*-methamphetamine.