**The Federal Response to the Drug Overdose Epidemic**

**NIDA**

**Questions for the Record from Senator Charles E. Grassley**

**U.S. Senate Caucus on International Narcotics Control**

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**Submitted on July 27, 2021**

1. Polydrug use and trafficking also need to be central in the National Drug Control Strategy. Nowadays, an overdose isn’t due to only one drug. Rather, users are often addicted to multiple drugs, and traffickers adapt and sell any drug to earn a profit. This problem is exacerbated by the influx and constant threat of fentanyl analogues.
	* What treatment options are available to treat polydrug users?
	* What has been effective and where is there room to improve?

**Answer:**

The National Institute on Drug Abuse (NIDA) recognizes the urgent need to address polysubstance use and polysubstance use disorders. Although deaths from opioids continue to command the public’s attention, an alarming increase in deaths involving the psychostimulant drugs methamphetamine and cocaine are a stark illustration that the nation no longer faces just an opioid crisis, but a complex and evolving addiction and overdose crisis. This crisis is characterized by changes in use and availability of different substances and use of multiple drugs (and drug classes) together. In fact, drug overdose deaths have increased exponentially since at least 1980, with different substances driving this upward trend at different times.[[1]](#footnote-1)

Polysubstance use is complex; taking two or more substances at the same time can produce additive or synergistic euphoric effects, while taking substances concurrently may be a strategy to balance the effects of different drugs. People may also use one drug when another is unavailable. Analyses of Veterans Health Administration data suggest that, compared with a single substance use disorder, multiple substance use disorders are associated with more severe medical and psychiatric presentations.[[2]](#footnote-2)

Currently, individuals with polysubstance use disorder are typically treated for their primary substance use disorder. Although effective medications exist for the treatment of individual substance use disorders, including opioid and alcohol use disorder, there are no U.S. Food and Drug Administration (FDA)-approved medications for the treatment of polysubstance use disorder. Likewise, although several behavioral therapies, including cognitive behavioral therapy, motivational enhancement therapy, and contingency management, are effective for treating more than one substance use disorder, there is relatively little data on their effectiveness for polysubstance use disorder.

Research to develop effective approaches for treating polysubstance use disorder, therefore, is sorely needed. To that end, NIDA is supporting studies to elucidate biological mechanisms and potential medication targets common across substances, which are essential for advancing the development of new treatments. For example, NIDA investigators are using a combination of preclinical and clinical laboratory models to identify mechanisms that contribute to the co-use of opioids and cocaine.[[3]](#footnote-3)

NIDA recently expanded its Clinical Trials Network (CTN) by adding experts with practical experience in addressing multiple substance use disorders. Leveraging this expertise, the CTN is conducting trials to identify and address treatment barriers among rural and other underserved populations, and to test medications and behavioral interventions for co-use of opioids and other substances such as methamphetamine and alcohol.[[4]](#footnote-4),[[5]](#footnote-5),[[6]](#footnote-6),[[7]](#footnote-7) This is essential as clinical trials have not typically included individuals with polysubstance use disorders or other co-occurring conditions, limiting the real-world applicability of these studies.

Research is also needed to understand patterns of and motivations for polysubstance use, which can guide the implementation of targeted interventions. NIDA supports the National Drug Early Warning System (NDEWS), which collects community-level indicators of emerging drug trends and includes identifying patterns of polysubstance use.[[8]](#footnote-8) NIDA-supported investigators are also conducting an in-depth examination of polysubstance use among people who use illicit opioids, which could inform overdose prevention strategies.[[9]](#footnote-9) In addition, through the Collaborative Research on Addiction at NIH (CRAN), a trans-NIH partnership composed of NIDA, the National Institute on Alcohol Abuse and Alcoholism, and the National Cancer Institute, NIH is currently soliciting targeted research on polysubstance use, including basic science research, human-based laboratory research, and epidemiological, treatment development, and services research studies.[[10]](#footnote-10)

To better understand needs and inform research priorities for addressing opioid use in the context of polysubstance use, the NIH HEAL Initiative convened a meeting in April 2021 that brought together key federal, academic, and advocacy stakeholders.[[11]](#footnote-11) Participants emphasized the importance of collecting timely population-level data on polysubstance use—a challenge NIDA is working with its sister agencies to address. The need to develop new medications, behavioral treatments, supportive digital therapeutics, culturally responsive treatment programs, and harm-reduction strategies were also identified, as was the importance of patient education, shared decision-making, and stigma reduction. Addressing these challenges through research is a key priority for NIDA and will be highlighted in our 2021-2025 Strategic Plan.

1. In response to questions asked by Senator Cornyn about marijuana at the hearing, you stated, “I think it’s one-hundred percent necessary that we actually have an understanding of the consequences of legalizing marijuana . . . on children and adolescent brains.” You also mentioned that “marijuana is not a benign drug and some are more vulnerable to its adverse effects than others.”
	* Would an increase of research into the marijuana plant be helpful to answer these questions as to consequences of use?
	* If so, why is that important information to ascertain prior to efforts to decriminalize or legalize the marijuana plant?

**Answer**:

With a rapidly shifting state legal landscape and shifting perceptions of the harms and potential benefits of marijuana, rigorous research to better understand the health effects of marijuana is critical. This is especially important given that analyses show that the delta-9-tetrahydrocannabinol (THC) potency in marijuana seized by the Drug Enforcement Administration has more than tripled since 1995,[[12]](#footnote-12) and there has been a proliferation of concentrated marijuana products that can deliver even higher levels of THC. Understanding the health effects of exposure to these high potency products, particularly during vulnerable periods of development and among groups that may be at especially high risk from marijuana exposure, is critical.

The first few years of life are a period of exponential brain growth and development, and the effects of early exposure to marijuana on infant and child development are not well understood. Marijuana use during pregnancy can perturb the fetal endocannaboid system, which is present from early embryonic stages and active in the control of neurodevelopment. Prenatal marijuana exposure has been associated with lower birth weight,[[13]](#footnote-13) preterm birth, reduced size given gestational age,[[14]](#footnote-14) and impaired neurodevelopment, academic underachievement, and increased rates of adolescent marijuana and cigarette use.[[15]](#footnote-15) In addition, recent findings show dose-dependent increases in clinically significant psychopathology at ages 9-10 among children with early prenatal exposure to marijuana, alcohol, and tobacco. [[16]](#footnote-16) However, in human studies it has been difficult to disentangle the effects of prenatal marijuana exposure from those of other environmental factors, including exposure to other drugs. Large-scale, prospective research is needed to allow researchers to clarify the multiple factors that influence infant and child health and well-being. To this end, the HEALthy Brain Child Development (HBCD) Study, a longitudinal research study supported through the NIH HEAL Initiative, will follow approximately 7,500 pregnant women and their children from the prenatal period until ages 9-10 to determine the influence of multiple factors, including marijuana exposure, on child brain development and other outcomes.

Marijuana use is widespread among young people,[[17]](#footnote-17) and the number of young people who believe regular marijuana use is risky is decreasing.[[18]](#footnote-18) Adolescents, whose brains are undergoing major developmental changes, are particularly vulnerable to the drug’s negative effects. Preclinical studies have found that THC exposure during adolescence increases subsequent sensitivity to the rewarding effects of other drugs[[19]](#footnote-19), which could be one rea son why those who use marijuana at a young age are more vulnerable to marijuana and other drug use disorders later in life.[[20]](#footnote-20) Frequent marijuana use during adolescence is associated with changes in areas of the brain involved in attention, memory, emotions, and motivation.[[21]](#footnote-21) Additional research is needed to determine if these changes account for the adverse cognitive and behavioral effects associated with youth marijuana use.

Studies on the effects of adolescent marijuana exposure on IQ have yielded inconsistent results. One study showed that people who started smoking marijuana heavily in their teens, and had an ongoing cannabis use disorder, lost an average of eight IQ points between ages 13 and 38. The loss did not fully recover in those who quit marijuana as adults.[[22]](#footnote-22) However, another study on twins found that those who used marijuana showed a significant decline in general knowledge and verbal ability (equivalent to four IQ points) between the preteen years and early adulthood, but no predictable difference was found between twins who used marijuana and those who did not. These data suggest that the IQ decline in people who used marijuana may have been caused by other factors, such as shared genetics or family environment.[[23]](#footnote-23)

As with prenatal marijuana exposure, it has been difficult to disentangle the effects of adolescent marijuana use from other factors, making this an important area for additional research. Prospective studies like the Adolescent Brain Cognitive Development (ABCD) study, which is following children – including twins and triplets – and their families from ages 9-10 through young adulthood, will expand our knowledge on the short- and long-term effects of marijuana and other environmental exposures on brain and cognitive development and other child health outcomes.

There is some evidence for an association between marijuana use and negative mental health consequences, but whether and to what extent marijuana actually causes these conditions is not always easy to determine. A recent study of young adults ages 18-35 showed that marijuana use was associated with increased risks of suicide thoughts, suicide plan, and suicide attempt, especially in women and even after taking depression into account.[[24]](#footnote-24) There is also some research suggesting that marijuana may trigger or exacerbate psychosis, particularly in those with a pre-existing genetic or other vulnerability.[[25]](#footnote-25),[[26]](#footnote-26) Multiple studies have associated adolescent marijuana use (especially use of high potency products) with an increased overall risk for, and early onset of, chronic psychosis such as schizophrenia,[[27]](#footnote-27),[[28]](#footnote-28) particularly in those with other risk factors.[[29]](#footnote-29) High doses of THC can trigger acute psychotic episodes, which is one of the main causes for emergency department visits associated with marijuana use.[[30]](#footnote-30) While evidence for a relationship between marijuana use and mood and anxiety disorders is mixed, an analysis of national longitudinal data that accounted for various confounding factors revealed no such association.[[31]](#footnote-31) These associations warrant further research, especially given the great burden of mental illness and suicide on young people.

Our understanding of the health effects of marijuana is still evolving, and more research is needed, particularly in light of the proliferation of high potency products and new modes of administration. NIDA is currently supporting more than 250 studies on cannabinoids, including marijuana and its constituents, that will improve our understanding of the short-term and long-term consequences of marijuana use, the development of cannabis use disorder, as well as the impact of legalization on factors such as perceptions of safety among youth and pregnant women.

**Questions for the Record from Senator James Risch**

**U.S. Senate Caucus on International Narcotics Control**

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1. In Idaho, we’ve seen a rise in overdose deaths in many parts of the state. In May alone, Kootenai County experienced five fentanyl-related overdose deaths, including a 15-year-old boy who bought a fentanyl-laced pill marketed to him as Oxycodone.
	* Can you elaborate on the steps your agency is taking to address the rise in counterfeit prescription drugs and resulting overdoses?

**Answer**:

# NIDA is deeply concerned about the alarming increase in overdose deaths involving fentanyl. Provisional data from the CDC indicate that out of 93,300 overdose deaths in 2020, more than 57,500 involved fentanyl.[[32]](#footnote-32) The rapidly evolving drug supply is often adulterated with fentanyl, which is highly potent and especially dangerous if used unknowingly. [[33]](#footnote-33) Further, the high potency of fentanyl makes it desirable to some people in its own right. People who use fentanyl may be more likely to have severe opioid use disorder, but the current treatment strategy is the same as for other opioid use disorders.

# While the high potency and increased distribution of fentanyl together contribute to its lethality, there are also other characteristics that affect risk. Fentanyl is different from other opioids in important ways that may affect how an individual responds to medications for opioid use disorder, including life-saving naloxone to reverse overdose. NIDA supports approximately 200 studies on or related to fentanyl, including fentanyl countermeasures. For example, to alert scientists and the public about trends in hotspots in near real time, NIDA’s National Drug Early Warning System (NDEWS) conducts on-the-ground epidemiology and gathers poison control center data to examine trends in exposures related fentanyl and its analogs, as well as other substances.[[34]](#footnote-34) To help support strategies that allow people to detect fentanyl in drugs so they can take steps to prevent overdose, NIDA is currently supporting studies on fentanyl test strips (FTS) including research to: validate FTS;[[35]](#footnote-35) longitudinally assess whether use of FTS results in decreased drug use and overdose, and increased treatment initiation;[[36]](#footnote-36) and test whether adding FTS education and distribution to overdose counseling programs decreases opioid overdoses in rural and urban communities.[[37]](#footnote-37) In addition, NIDA is supporting research to develop vaccines against fentanyl that can be used to treat opioid use disorder and prevent overdose by preventing fentanyl from entering the brain and other organs.[[38]](#footnote-38),[[39]](#footnote-39),[[40]](#footnote-40),[[41]](#footnote-41) NIDA also supports numerous other projects on opioid overdose prevention, including the HEALing Communities Study which has the goal of reducing opioid overdoses by forty percent in participating communities and includes overdose education and naloxone distribution.[[42]](#footnote-42)

# Additional research is needed to better understand the nature, extent, and clinical manifestations of fentanyl use, and to develop better treatments for fentanyl addiction and overdose. In March 2021, NIDA issued a notice of special interest highlighting the urgent need for research on fentanyl and its derivatives.[[43]](#footnote-43) Priorities include, but are not limited to epidemiology, risk factors for and clinical characteristics of fentanyl use, medications for treating fentanyl addiction and to reverse overdose, pharmacological and non-pharmacological interventions for pregnant women who use fentanyl and their infants, relapse prevention, and understanding and mitigating the impact of fentanyl addiction and overdose on society.

1. Since 2003, there has been an alarming increase in methamphetamine abuse in Idaho, especially in the more rural parts of the state. It’s estimated that in 2016, approximately one Idahoan died each week from methamphetamine and about 7,000 Idahoans 12 and older used meth that same year with 120,000 having used meth in their lifetimes.
	* What types of treatment options are available for individuals with methamphetamine addiction, particularly for youths with this type of addiction?
	* Are there any types of new treatments in the pipeline?

**Answer**:

Several psychosocial interventions are recommended as first-line treatments for people with methamphetamine use disorder, including contingency management, motivational interviewing, the community reinforcement approach, and cognitive behavioral therapy. Contingency management stands out as the most effective treatment. In contingency management, evidence of behavioral change (such as negative urine drug screens) is monitored and rewarded with tangible incentives, such as vouchers for food or other goods, or the chance to win a prize. Despite its effectiveness for treating both methamphetamine and cocaine use disorders, contingency management is not widely used due in part to policy barriers that have prevented its widespread adoption.

There are currently no FDA-approved medications for methamphetamine or other stimulant use disorders; hence this is a high-priority research area for NIDA. We are encouraged by recent findings from a study conducted through the NIDA Clinical Trials Network showing that a combination of bupropion and naltrexone, two drugs approved by the FDA for other uses, —reduced methamphetamine craving and use in patients with moderate and severe methamphetamine use disorder. NIDA is also supporting numerous other studies aimed at developing new and improved treatments for methamphetamine use disorder and overdose. These include: three phase I trials, one examining the efficacy of a combination duloxetine and methylphenidate, which are FDA-approved for other uses, another examining the new molecular entity pomaglumetad methionil, and the third examining long-acting buprenorphine, which is FDA-approved for other uses, for treating methamphetamine addiction among people who also use opioids. Following results from a proof-of-concept study indicating that mirtazapine, which is FDA-approved to treat major depressive disorder, shows promise for treating methamphetamine use disorder, NIDA-funded researchers are conducting a drug-drug interaction study to examine the safety of the compound in combination with methamphetamine and opioids. These studies are required by the FDA before investigators can launch a Phase III trial of mirtazapine.

Immunotherapies are another promising treatment approach, and NIDA is supporting Phase II studies to evaluate IXT-m200, a monoclonal antibody designed to bind methamphetamine in blood and prevent it from entering the brain, as a treatment for both methamphetamine use disorder and overdose. NIDA is also supporting preclinical research on a sequestrant—a small, synthetic molecule that can bind and remove foreign substances from the blood stream—to treat methamphetamine overdose. This work is expected to lead to a phase I clinical trial to establish safety and appropriate dosing in humans. These and other methamphetamine studies are complemented by over a dozen studies to develop new medications for treating addiction to cocaine, another stimulant that has been involved in a growing number of overdose deaths.

NIDA’s Clinical Trials Network stimulant use treatment task force is developing proposals for several additional combination drug trials, which include drugs FDA approved for other uses and that may hold promise over single drug studies as stimulant use disorder treatments. These include studies of the dopamine agonist lisdexamfetamine and an alpha-2-adrenergic agonist to decrease hypertension and stress-induced methamphetamine craving, a combination of ketamine and kappa opioid receptor agonists to treat extended withdrawal symptoms and prevent relapse in people with cocaine use disorder, and topiramate used in combination with bupropion or another agent that enhances the activity of dopamine for treating methamphetamine use disorder. The taskforce is also developing adaptive clinical trials designed to test a series of different medications and behavioral interventions for mitigating specific symptoms in patients with stimulant use disorder, such as craving, sleep disturbances, depression, cognitive impairment, impulsivity, and low motivation. Such trials will aid the development of personalized treatments that together can reach a broader range of patients.

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