National Institutes of Health
HEAL Initiative

Opioid Use in the Context of Polysubstance Use: Research Opportunities for Prevention, Treatment, and Sustained Recovery

April 14, 2021
Noon – 6:00 pm ET
Executive Summary

The National Institutes of Health (NIH) Helping to End Addiction Long-term℠, or NIH HEAL Initiative℠, convened a workshop on Opioid Use in the Context of Polysubstance Use on April 14, 2021. The workshop's primary goals were to review current trends, research opportunities, and strategies for treatment for opioid use combined with other substance use (particularly stimulants, such as cocaine or methamphetamines). More than 200 participants attended the conference.

The HEAL Initiative is a ~$500 million per year sustained research investment supporting more than 25 research programs led by 12 NIH Institutes and Centers (ICs) representing collaborations among 20 ICs to address the opioid crisis. The Initiative uses a trans-NIH governance structure to promote a broad research platform ranging from prevention and implementation science, basic and translational research, and clinical research. The HEAL Initiative has established partnerships across federal, state, and local government; within communities and the private sector to take an "all hands-on deck" approach to address the opioid crisis.

The opioid overdose crisis has changed due to the increasing prevalence of highly potent synthetic opioids, such as fentanyl and fentanyl analogs, often used with other substances such as stimulants (cocaine, methamphetamine), alcohol, and benzodiazepines. Polysubstance use is a term for using multiple substances at once, often in the context of substance use disorder. Polysubstance use is more common than single substance use, and individuals who use numerous substances are less likely to seek or receive treatment.

In 2019, more than 70,000 people died from overdose in the United States. More than seventy percent of those overdose fatalities involved opioids and, of those, nearly two-thirds involved fentanyl category opioids.[1] In the same year, nearly 16,000 (22%) of overdose deaths involved cocaine and more than 16,000 (23%) involved methamphetamine, frequently in combination with opioids.[2] The COVID-19 pandemic appears to be worsening the overdose crisis; in the 12-months ending in October 2020, provisional data indicate that more than 90,000 overdose deaths occurred, again driven primarily by synthetic opioids. Overdose deaths involving cocaine increased by28% and other psychostimulants

[1] CDC, National Center for Injury Prevention and Control, March 3, 2021

[2] CDC WONDER, Multiple Causes of Death, 2019

(mainly methamphetamine) increased by 46%.[3] This evolving overdose crisis shines a light on the issue of polysubstance use, illuminating a vital frontier for research.

Current Trends

Presenters detailed the rise in polysubstance use and drug overdoses, including during the Coronavirus Disease 2019 (COVID-19) pandemic. The substance combinations differ depending on the geographic location of use. Cocaine is more prevalent as a part of a polysubstance combination in the eastern United States and methamphetamines in the western United States. The rise of polysubstance use is correlated with pharmaceutical industry marketing patterns during the 2000s and 2010s. From 2013-2015, the marketing of opioid products was widespread among physicians. Nearly 1 in 5 family doctors received opioid marketing during this period.[4] A study of this period showed that after adjusting for claims, physicians receiving marketing had more than 9 percent more opioid claims than those who did not receive marketing.[5] Similar patterns occurred with more recent stimulant marketing, including amphetamines prescribed for attention deficit hyperactivity disorder (ADHD).[6] Studies found that 1 in 5 pediatricians received marketing in these substances from 2014 to 2018.[7]

Participants reported that the combination of methamphetamines with opioid use was a particular concern, noting that methamphetamine counteracts the drowsy side effects of opioids, which makes the combination more attractive. Panel participants discussed how having "safe spaces" to recover from methamphetamine use and using prescription medications to counter the side effects of opioid use and withdrawal are potentially ways to decrease the risk of overdose.

One consistent theme throughout the presentations was the lack of data on polysubstance use. There are no population-level surveys or standardized treatment data to enable researchers to assess the true breadth of the crisis. While some localities (e.g., Seattle, WA) have good local data, the national picture is still murky.

Community-based Treatment

A growing area for research in OUD and polysubstance use is treating opioid and methamphetamine co-use in community settings. Recent years have seen increased incidence of methamphetamine use among people who inject heroin in western cities such as Denver[8] and Seattle.[9] In examining this phenomenon, clinics in the Seattle area collected data on past month use at baseline and 6 months later from individuals with OUD. They found that individuals who reported methamphetamine use were two times more likely to drop out of treatment.[10] An issue around low retention may be feelings of "shame" for using multiple substances even when part of a treatment program. The researchers found that methamphetamine use was typically due to the need to wake someone up from the sluggishness of

[3] NCHS Provisional Drug Overdose Death Counts – predicted values: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

[4] Hadland SE et al. Am J Public Health, 2017;107(9):1493-5

[5] Hadland SE et al. JAMA Intern Med, 2018;178(6):861-863

[6] Piper B, et al. PLoS One, 2018;13(11):e0206100

[7] Hadland SE, et al. JAMA Pediatr, 2020;174(4):385-387

[8] Al-Tayyib A, et al. Subst Use Misuse. 2017

[9] Glick SN, et al. Am J Addict. 2021

[10] Tsui JI, et al. Journal of Substance Abuse Treatment (2020)

opioid use and that individuals may stop using the methamphetamine on their own.[11] The self-induced reduction in methamphetamine use points to the need for low-barrier programs aimed at harm reduction, which do not require abstinence from stimulants in order to treat OUD and may reduce stigma associated with medications for OUD.[12] Keeping a patient engaged creates opportunities for further treatment.[13]

Balancing of effect is one reason people report stimulant and opioid co-use. For example, people report using methamphetamine to offset sleepiness associated with opioid use, prevent pain associated with opioid withdrawal, and to prevent opioid overdose because they believe that it is not possible to overdose on methamphetamine. Presenters also noted the importance of educating patients about overdose, using shared decision-making to develop treatment strategies, and treating the whole person by addressing social determinants of health such as housing. As there are no FDA approved medications to treat methamphetamine use disorder, researchers are assessing the effectiveness of medications approved for other purposes. A recent study showed that every 3 weeks naltrexone (an opioid antagonist) plus daily oral buproprion (a norepinephrine-dopamine reuptake inhibitor) reduced methamphetamine use and cravings.[14]

The necessity of low-barrier treatment is becoming clear, particularly after an overdose. With overdoses rising during the COVID-19 pandemic, changes to emergency department (ED) protocols are necessary to reduce stigma and increase treatment uptake. To date, there are no broadly implemented ED-based detection, intervention, and referral protocols for patients with opioid and stimulant co-use. The upcoming publication from the Substance Abuse and Mental Health Services Administration, *Use of Medication-Assisted Treatment in Emergency Departments* (2021), will provide guidelines for ED physicians to use when presented with patients OUD.

Medical Treatment Options

Presenters discussed various potential treatment options for polysubstance use. An important theme to emerge from the sessions was to "meet people where they were," whether it was culturally, in a specific physical location, or more generally to try and anticipate their basic needs as they recover from the use of one or more substances.

Culturally responsive treatment, such as that provided by the Northwest Portland Indian Health Board (the Board), has positively affected individuals, their families, and the community. The Board identified opioid use/misuse as a danger to tribal members and asked for community participation in designing a treatment program. The result was a program that prevented new cases through a harm reduction model, provided culturally responsive treatment covered by insurance, and encouraged community participation in healing through engagement and educational events.

A treatment model in Oregon included needle exchanges, safe spaces for use and withdrawal, and peer recovery efforts. These features appear in other modalities as well. Recovery Community Centers (RCCs) and Recovery Community Organizations (RCOs) are two other culturally responsive modalities for treatment. These organizations use a peer recovery model and are staffed by people in recovery who

[11] Tsui, et.al.

[12] Hood JA, et al. Subst Ab. 2020

[13] Poorman E, et al. J Sub Ab Treat. 2021

[14] Trivedi et al. N EnglJ Med. 2021;384(2):140-153.

can identify with individuals in the program. Through a coaching model combined with extensive data collection and analysis, RCCs and RCOs can create a shared responsibility for sobriety.

Preliminary data from research conducted in community-based treatment programs in Ohio, Kentucky, Massachusetts, and New York indicate that a high number of overdose deaths are due to confounding risks from synthetic opioids and other substances. Also, data related to overdose fatalities is often delayed. These delays severely limit proactive adaptations of community-based services around prevention and treatment to address changing trends in substance use patterns. To better predict trends and inform intervention strategies, alternative sources of data (outside of overdose death data) are needed and can include data related to drug markets, urine testing from substance abuse treatment or employer programs, etc. Timely data that identifies geographic patterns and changes in drug availability and drug combinations is key.

Presenters also discussed opportunities for repurposing existing medications, either singularly or in combination, for the treatment of polysubstance use. Other promising approaches included the possibility of a vaccine to treat opioid misuse currently in the initial phase of testing. However, due to potentially lengthy regulatory approval processes, even if effective, this would not be an option for the near future.

Presenters also discussed behavioral treatment options, specifically two possibilities that use similar approaches. Both use the contingency management approach, in which participants are rewarded with material items for achieving particular goals in their path to recovery. The contingency management approach (CM) is evidence-based though not as common, in practice, as peer recovery approaches. Contingency management is particularly effective when combined with community reinforcement in inducing sobriety and keeping individuals sober.

Contingency management is also the basis for digital therapeutic approaches reSET™ and reset-O™ (specifically for opioid use) which are authorized by the U.S. Food and Drug Administration and can be prescribed by physicians as needed. These digital therapeutic approaches increase treatment retention,[15] improve polydrug abstinence,[16] and specifically increase opioid abstinence when used as an adjunct to medications for opioid use disorder,[17] making it an increasingly viable option for polysubstance use.

New Directions

In closing remarks, Nora Volkow, M.D., Director of the National Institute on Drug Abuse, commented that the evidence discussed in the meeting made clear the need for at least three new directions in research on polysubstance use. First is the need to include polysubstance use and co-occurring use disorders in clinical research trials. Excluding polysubstance use limits the applicability of current trials and adds to the internal stigma participants may feel about having multiple addictions. The second need is for more prompt data collection, so that communities can get ahead of potential crises with new substance combinations and implement changes to community-based treatment programs tailored to current needs. The third need is for treatment to be both adequately resourced and adequately reimbursable for participants with insurance. There is a dearth of culturally responsive care and trauma-informed care that receives reimbursement. Changing this dynamic would lead to greater adoption of

[15] Campbell ANC, Nunes EV, et al. (2014). *American Journal of Psychiatry.*
[16] Campbell ANC, Nunes EV, et al. (2014). *American Journal of Psychiatry*.
[17] Guarino, Acosta, Marsch 2016

these programs because the costs would be covered. The final new direction is to end the stigma of addiction and greater awareness of the impacts of social determinants of health on addiction and treatment options.

Research Gaps

To address gaps in the current research, presenters stated a need to:

- improve timely data collection at the local, state, and national levels.
- understand further the impact of stimulants including methamphetamines and cocaine on OUD.
- improve ability to add new fentanyl and other drug analogs as they develop to laboratory testing.
- increase the understanding around transitions from prescription stimulant misuse to illicit stimulant misuse.
- conduct clinical trials on new combinations of medicines and new long-acting injectable formulations.
- increase adoption of machine learning that can serve to stimulate drug development and testing.
- test behavioral change models of treatment including CM, online technologies, and modalities linked to specific cultures for short-term and long-term impacts.

Policy Needs/Gaps

To address the epidemic of polysubstance use in the United States, presenters suggested the following:

- Increased coverage for treatment including provider reimbursement for SUD services, culturally appropriate care, and emerging models of treatment that focus on whole person care.
- Increased adoption of low-barrier treatment for opioid and other substance use in clinical settings as well as clinical trials to increase access to much needed services.
- Faster regulatory processes around new treatment drugs, methodologies, and testing mechanisms.