



Polysubstance use is “when two or more [drugs] are taken together or within a short time period, either intentionally or unintentionally.” This definition includes legal, illegal, and prescription substances.

EXPLAINER

Drug Use 101: Polysubstance Use

December 2024

Background

Drug overdose deaths in the United States have risen for the [past three decades](#), driven by increases in opioid use and a widespread transition to an increasingly potent and mercurial illicit supply. The current “fourth wave” of the opioid overdose crisis is characterized by an increase in [polysubstance-related deaths](#).

Defining Polysubstance Use

[Polysubstance use](#) is “when two or more [drugs] are taken together or within a short time period, either intentionally or unintentionally.” This definition includes legal, illegal, and prescription substances.

Why People Use Multiple Substances

Polysubstance use may be [voluntary or involuntary](#). Individuals who involuntarily use multiple drugs typically do so because they are unaware of what they have taken. This is most often due to the [volatility](#) and [opacity](#) of the illicit drug market. For example, [recent data from Maryland](#) estimates that 80 percent of fentanyl in the state is contaminated with xylazine—a substance that 85.8 percent of surveyed syringe services program participants reported having used unknowingly.

[Reasons are more varied](#) when it comes to voluntary polysubstance use. Individuals may use substances to relieve physical and emotional pain, induce euphoria, adapt to social situations, work longer hours, and more. Similarly, people report a [variety of motivations](#) for mixing drugs, depending on the specific substance(s), their unique combination, and personal needs or preferences.

Common Motivations for Mixing Drugs

To adapt to changing availability and cost of other drugs

To amplify or extend euphoria

To delay the onset of [withdrawal symptoms](#)

To balance or counteract undesired effects of other drugs, such as excessive sedation due to fentanyl

To try to prevent overdose

How Polysubstance Use Affects Risk

[Roughly two-thirds](#) of people who use substances use only one drug at a time, making polysubstance use [atypical but not rare](#). Nonetheless, polysubstance use can [affect risk](#) in a variety of ways. In particular, people who engage in polysubstance use are more likely to struggle with complex, hard-to-treat health issues.

Substance Use Disorder and Mental Health

Although a minority of people who use substances report polysubstance use, the [majority](#) of those with a [substance use disorder](#) (SUD) do. In fact, individuals with an SUD [report using](#) an average of 3.5 substances, and an estimated 11.3 percent



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Depressants like alcohol and xylazine increase overdose risk because they cause sedation and respiratory depression, which compound the effects of opioids.

Contact us

For more information, please contact:

Stacey McKenna
Senior Research Fellow
Harm Reduction
smckenna@rstreet.org

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of people diagnosed with an SUD simultaneously struggle with addiction to alcohol or other drugs. These [multi-substance use disorders](#) tend to be multifaceted, poorly understood, and difficult to treat. Not only must providers help patients grapple with issues like drug interactions and increased intoxication, but they may also find that best practices for treating one SUD (such as medications for opioid use disorder) do little to help overcome addiction to other substance(s).

Additionally, people with polysubstance use disorder are more likely to suffer from [mental health](#) issues like schizophrenia, depression, and bipolar and personality disorders than their single-substance using counterparts. Patients with [co-occurring mental health issues and SUDs](#) can have difficulty accessing treatment for either one.

Overdose and Physical Health Risks

Because polysubstance use can either [amplify or mask](#) the effects of other individual drugs consumed, it may also compound a range of health risks, from heart attack to organ failure. Among people who inject drugs, polysubstance use can [increase injection frequency and the associated risk](#) of infectious diseases or injection-related complications like endocarditis. Additionally, certain substances—such as xylazine—increase the likelihood and severity of [injection-site injuries](#).

Perhaps the most immediately consequential health risk for people who use multiple substances is overdose. Still largely driven by potent synthetic opioids, the [current wave of the overdose crisis](#) increasingly involves other drugs as well. In 2017, alcohol was present in [about one in seven](#) U.S. overdose deaths involving opioids, and in 2018, [approximately two-thirds](#) of opioid-involved overdose deaths in the country also involved cocaine, methamphetamine, or benzodiazepines. More recently, we have seen another class of sedatives—[potent veterinary tranquilizers](#) like xylazine—showing up in the illicit supply and alongside opioids in overdoses.

Depressants like alcohol and xylazine [increase overdose risk](#) because they cause sedation and respiratory depression, which compound the effects of opioids. Meanwhile, many people who mix [stimulants like cocaine and methamphetamine](#) with opioids do so unintentionally, or only on occasion. Because these individuals are unlikely to have opioid tolerance, their overdose risk is elevated. However, even those who use opioids regularly risk [more complicated, less predictable overdoses](#) when they use opioids and stimulants at the same time. And because the overdose reversal medication naloxone [only targets opioids](#), polysubstance overdoses are more likely to require follow-up medical care.

Implications for Policymakers

The rising frequency of polysubstance-related deaths highlights a growing need for policy that allows public health organizations to tailor prevention, treatment, and harm reduction programs to local needs and adapt quickly to changing drug supplies and drug use patterns.