A Chronic Condition Disguised as an Acute Event: the Case for Re-thinking Stimulant Overdose Death

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Recent reports indicate that stimulant-related deaths are increasing dramatically. People who die from acute stimulant toxicity have high rates of pre-existing cardiovascular disease (CVD), much of which is undiagnosed. Moreover, people who use stimulants with CVD often remain asymptomatic until presenting to an emergency department with an acute event. Prior research shows that symptoms of stimulant toxicity may occur on a regular basis, and that people who die from stimulant toxicity are older than those who die of opioid toxicity. Taken collectively, the existing evidence suggests that death from acute stimulant toxicity is often an outcome of long-term, cumulative exposure leading to cardiovascular dysfunction rather than acute intoxication. Strategies tailored to the distinct etiology of stimulant overdose are needed. We propose a three-part approach including (1) implementing stimulant use interventions that promote not only abstinence, but also use reduction, (2) treating ongoing stimulant use as a chronic cardiovascular condition, and (3) making stimulant toxicity interventions relevant to the populations most affected, which includes people outside of the traditional health-care system. In short, to reduce stimulant-related fatality, we need to transform our approach in ways that are tailored to address its natural history.

J Gen Intern Med
DOI: 10.1007/s11606-022-07692-1

OVERDOSE IN THE UNITED STATES AND THE ROLE OF STIMULANT TOXICITY

There were more than 93,000 reported overdose deaths in 2020—a 30% increase from 2019 and more than any previous year in U.S. history.[1] In 2021, we surpassed this tragic milestone. While fentanyl is a leading factor in recent trends, stimulant-related deaths have also increased dramatically. Research shows that stimulant-related deaths are often attributed to severe cardiovascular and cerebrovascular dysfunction,[2–4] including sudden cardiac death,[5] myocardial infarction, and cerebrovascular infarction.[6]

Received February 16, 2022
Accepted May 31, 2022

Published online: 17 June 2022

While acute toxicity contributes to stimulant-related deaths, decades of research suggest a more complex dynamic. Chronic conditions such as hypertension, atherosclerosis, structural heart disease (e.g., cardiomyopathy), and electrical conduction disorders are often driven by stimulant use, and contribute to cardiovascular and cerebrovascular events.[7] People who die from acute stimulant toxicity have higher rates of pre-existing cardiovascular disease (CVD) compared to those who die from opioid overdose or injuries.[6] Moreover, CVD is often undiagnosed in this population. In fact, silent CVD progression is frequently pronounced in people who use cocaine regularly, many of whom remain asymptomatic until presenting to an emergency department with an acute event.[8] In addition, the consequences of silent progression may be exacerbated in low-income individuals for whom CVD is more prevalent and health-care is less consistent.[9–12] A recent study among unsheltered and unstably housed women found that those who co-used cocaine and alcohol had higher levels of cardiac injury, even after adjusting for CVD risk factors.[13] Those who used cocaine were also seven times as likely to have white matter hyperintensities compared to those who did not.[14]

On average, people who use stimulants self-report more than one acute toxicity event per year (defined as taking enough of a stimulant to feel so sick or scared that one's life may be in danger).[15] Many consider symptoms of stimulant toxicity, such as chest tightness, a "normal" part of the experience,[16] implying that cardiovascular symptoms in the setting of drug use often occur over long periods of time and may be difficult to separate from stimulant-related toxicity. Almost two-thirds of acute stimulant toxicity deaths in 2019 were among people over age 40, while most opioid overdose deaths occurred in younger individuals between 25 and 34.[17]

In contrast to death from acute opioid toxicity, which can readily occur even with first-time use, we hypothesize based on the existing evidence that death from acute stimulant toxicity is often an outcome of long-term, cumulative exposure.

MISSED OPPORTUNITIES TO REDUCE STIMULANT-RELATED MORBIDITY AND MORTALITY

The U.S. health-care system misses many opportunities for effective interventions by addressing stimulant use from two

extremes: drug treatment mainly promotes abstinence, while emergency medical services provide life-saving measures to patients with acute toxicity. While abstinence is a laudable goal, research shows that quitting drug use is often a lengthy endeavor in which relapse is not only common, but also expected. The silver lining is that we may have a longer timeframe to identify those at elevated risk and promote interventions which interrupt the trajectory toward stimulant-related deaths.

To leverage this opportunity, we need to adapt our thinking, health-care delivery, and research to reflect that stimulant use, alongside associated morbidities, is a chronic condition requiring long-term preventive interventions. For example, implantable cardioverter defibrillator devices are the standard of care for certain individuals with heart failure, but current substance use is still considered a contraindication to device implantation by many institutions. A national strategy that recognizes the importance of chronic conditions resulting from ongoing stimulant use, in areas such as risk assessment and health-care delivery, may help reduce cardiovascular and cerebrovascular events.

Understanding that many stimulant toxicity events are likely the result of chronic exposure, as opposed to acute intoxication, radically shifts the objective and approach for interventions. Naloxone is life saving for opioid overdose, but even if we developed an analogous reversal agent for stimulants, it is unlikely to have the same impact on a fatal event that is actually the end result of chronic insults. Instead, we recommend three strategies tailored to the distinct etiology of stimulant overdose.

A THREE-PART APPROACH FOR ADDRESSING STIMULANT TOXICITY AS A CHRONIC CONDITION THAT LEADS TO CARDIOVASCULAR AND CEREBROVASCULAR EVENTS

1. Beyond Abstinence: Promote Additional Strategies to Reduce Drug Consumption

Because reduced stimulant exposure over time likely prevents or at least delays onset of medical sequelae, stimulant use interventions should promote not only abstinence but also use reduction. No medications are yet approved for stimulant use disorder, but several are under study. Evaluation of these medications relies on qualitative urine drug screening, which is insensitive to use reductions falling short of abstinence. Moreover, the U.S. Food and Drug Administration (FDA) has historically required abstinence as the benchmark for approving medications to treat substance use disorders. This policy has begun to shift for alcohol. In recent years, the FDA approved biomarkers that indicate not only whether alcohol has been consumed, but an estimate of how much. This sea change recognizes that any reduction in alcohol use has health benefits. We urgently need to follow in these footsteps by advancing research, pharmacotherapies, and the FDA approval process to effectively address stimulant use at all levels.

2. Treat Ongoing Stimulant Use as a Chronic Cardiovascular Condition

Although using stimulants such as cocaine and methamphetamine is a risk factor for cardiovascular and cerebrovascular dysfunction, it is generally absent from risk assessments and treatment plans. The current overdose epidemic is a clarion call to incorporate routine assessment of stimulant use as a major risk factor for cardiovascular and cerebrovascular events during health-care encounters, and to prescribe preventive therapy when appropriate. Some changes can be made immediately. For example, multiple studies have confirmed that patients with heart failure and reduced ejection fraction (HFrEF) who use cocaine can safely use life-saving nonselective β-blockers.[18] Evaluation of therapies like statins, which are known to reduce CV mortality in the general population, should receive more attention in people who use stimulants.

3. Make Stimulant Toxicity Interventions Relevant to the Populations Most Affected

To effectively address the sharp rise in stimulant-related deaths, we must tailor research, risk evaluation, and health-care delivery to real-world populations of people who use stimulants. Most of our current policies and services addressing stimulant use are based on studies of the general population, or people who use opioids or alcohol, then extrapolated to people who use stimulants. To create an accurate evidence base, we need a major investment in research focusing on stimulant use. We also need studies with diverse recruitment strategies that include a representative sample of people most at risk, many of whom are not engaged in traditional health-care systems. Finally, we need sufficient enrollment of women. Female sex is a risk factor for stimulant-related toxicity and death,[19–21] yet addiction research is often conducted in populations predominantly composed of men, with results extrapolated to women.[22]

CONCLUSIONS

A sizable portion of deaths attributed to acute stimulant toxicity is related to long-term, likely cumulative, exposure to stimulants. Recognizing this provides multiple opportunities to mitigate the effects, and to avoid or delay death from stimulant toxicity. Instead of focusing on a reversal agent for this category of severe drug toxicity, which would likely be far less effective than naloxone is for opioid overdose, our current predicament requires a major shift. We need to reimagine how we design research, weigh the benefits of various interventions, deliver health care, and create policies to support each. To reduce stimulant-related fatality, we need to transform our approach in ways that are tailored to address its natural history.

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Declarations:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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