

**Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd.,  
Cephalon, Inc., and Actavis Generic Defendants'**

# **Rebuttal Examination of Katherine Keyes, PhD**

**June 27, 2022**

# APA, "What Is Addiction?"



< [Addiction and Substance Use Disorders](#)

[Addiction and Substance Use Disorders](#)

## What Is Addiction?

Addiction is a complex condition, a brain disease that is manifested use despite harmful consequence. People with addiction (severe substance use disorder) have an intense focus on using a certain substance(s), such as alcohol or drugs, to the point that it takes over their life. They keep using alcohol or a drug even when they know it will cause problems. Yet a number of effective treatments are available and people can recover from addiction and lead normal, productive lives.

### People can develop an addiction to:

- Alcohol
- Marijuana
- PCP, LSD and other hallucinogens
- Inhalants, such as, paint thinners and glue
- Opioid pain killers, such as codeine and oxycodone, heroin
- Sedatives, hypnotics and anxiolytics (medicines for anxiety such as tranquilizers)
- Cocaine, methamphetamine and other stimulants
- Tobacco

People with a substance use disorder have distorted thinking, behavior, and emotions. Changes in the brain's wiring are what cause people to have intense cravings for the drug and make it hard to stop using the drug. Brain imaging studies show changes in the areas of the brain



## What Is Addiction?

Addiction is a complex condition, a brain disease that is manifested by compulsive substance use despite harmful consequence. People with addiction (severe substance use disorder) have an intense focus on using a certain substance(s), such as alcohol or drugs, to the point that it takes over their life. They keep using alcohol or a drug even when they know it will cause problems. Yet a number of effective treatments are available and people can recover from addiction and lead normal, productive lives.

APA 2019 website - What Is Addiction

# NIDA Media Guide on “What is drug addiction?”



[Home](#) » [Publications](#) » [Media Guide](#) » [The Science of Drug Use and Addiction](#)

## Media Guide

### The Science of Drug Use and Addiction

#### What is drug addiction?

Addiction is defined as a chronic, relapsing disorder characterized by compulsive drug seeking, continued use despite harmful consequences, and long-lasting changes in the brain. It is considered both a complex brain disorder and a mental illness. It is a severe form of a full spectrum of substance use disorders, and is caused by repeated misuse of a substance or substances.

#### Why study drug use and addiction?

Use of and addiction to alcohol, nicotine, and illicit drugs cost the United States over \$1 trillion a year related to healthcare, crime, and lost productivity. In 2014, over 63,000 people in America, while 88,000 died from overdoses. Tobacco is linked to an estimated 480,000 deaths per year. (Here, *drugs* refers to all of these substances.)

#### How are substance use disorders categorized?

NIDA uses the term *addiction* to describe compulsive drug seeking and use despite harmful consequences. However, *addiction* is not a specific diagnosis in the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*—a diagnostic manual for clinicians that contains descriptions and symptoms of all mental disorders classified by the American Psychiatric Association (APA).



## What is drug addiction?

Addiction is defined as a chronic, relapsing disorder characterized by compulsive drug seeking, continued use despite harmful consequences, and long-lasting changes in the brain. It is considered both a complex brain disorder and a mental illness. **Addiction is the most severe form of a full spectrum of substance use disorders**, and is a medical illness caused by repeated misuse of a substance or substances.

NIDA 2019 website - Media Guide on Science of Drug Use and Addiction

# Literature Cited in Keyes' Rebuttal Does Not Support Causation

Study	Findings
<b>Mars (2013)</b>	<ul style="list-style-type: none"><li>• "The large literature on the 'gateway hypothesis' cites tobacco, alcohol and cannabis as the first drugs typically used prior to progression to harder drugs, either singly or sequentially, but <u>does not prove a causal link</u>." (P. 258)</li><li>• "Younger pill initiates were more likely to report dependence on <u>diverted</u> opioid pills prior to heroin initiation[.]" (P. 263)</li></ul>
<b>Jalal (2018)</b>	<ul style="list-style-type: none"><li>• "[t]he increase in drug poisoning mortality in 2016 is due to increased mortality from multiple drug-specific subepidemics: synthetic opioids (most likely fentanyl) among males, whites, and those in urban counties; heroin among young adults; prescription opioids among the middle-aged and blacks; and cocaine and methamphetamine among a wider age range, males, and whites." (P. 4)</li><li>• "The epidemic of drug overdoses in the U.S. has been inexorably tracking along an exponential growth curve since at least 1979, well before the surge in opioid prescribing in the mid 1990s." (P. 7)</li></ul>
<b>McCabe (2021)</b>	<ul style="list-style-type: none"><li>• "[T]he vast majority of prescription opioid exposure <u>does not</u> lead to heroin use." (P. 1)</li><li>• "[H]eroin incidence and prevalence rates were significantly greater among those who reported <u>nonmedical</u> prescription opioid misuse." (P. 1)</li></ul>

# Jalal (2022) – Observed 7.4% Growth for Case Rates Along Exponential Curve



Our Science paper was published 18 months after this initial observation and used data through 2016 (Jalal et al., 2018). For the bioRxiv note, we observed that in the 37 years from 1979 through 2015, accidental OD case counts increased by an average of 9% per year (9% growth for case counts, 7.4% growth for case rates per unit population) along a simple yet remarkably predictable exponential curve where cases are purely a function of the year:

Jalal (2022) p. 1

# Compton (2022) – “Astonishingly Smooth Exponential Curve”



Jones, 2019; Hedegaard, Miniño, & Warner, 2020). By adding in an additional two decades of data, the work by Jalal and colleagues revealed an astonishingly smooth exponential curve of increasing drug overdose deaths over the entire 38-year period examined. While the diagnostic approaches shifted during this long time frame, Jalal and colleagues' work is a reminder that broad trends may still be examined in the setting of data inconsistency. The resulting curve revealed that the rising and receding roles of various opioids in the overdose epidemic are just the most recent iteration of the shifting sub-epidemics of overdose from different substances, involving multiple substances in the early years, with cocaine predominant in the 1990s followed by opioids since the late 1990s. These patterns, along with shifting involvement of demographic groups and geographic areas, have converged in a steady surge of drug overdose mortality nationally in the United States. What can explain these results, particularly the ways that multiple subcomponents merge into a single growth curve, is a key question. While the authors

Compton (2022) p. 1

# Caulkins (2022) – “Great Stability In Drug-Related Death Trends”



Against that backdrop, the analysis of Jalal et al. (2018), Jalal et al. (2020), and Jalal & Burke (2021) is like a satellite photograph showing remarkable order that had been overlooked by the armies of specimen-collecting scientists on the ground. They show that for 40 years, trends in total drug-related deaths manifest great stability. To be specific, total deaths grew exponentially at a startlingly regular annual rate, whereas trends for individual drugs followed traditional epidemic curves, rising to a peak and then receding (albeit not yet for opioids). Furthermore, Jalal et al. (2020) show interpretable regularity in birth-cohort specific trends in total deaths.

Caulkin (2022) p.1

# Keyes and Cerda (2022) – Response to Jalal (2018)

## Commentary

Dynamics of drug overdose in the 20th and 21st centuries: The exponential curve was not inevitable, and continued increases are preventable

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Drug poisoning deaths in the United States continue to be a public health crisis. Over 840,000 Americans have died from drug poisoning due to overdose since the late 1990s (The Drug Overdose Epidemic: Behind the Numbers, 2021); opioids have been the predominant class of drugs contributing to the increase. The nature and the dynamics of this overdose crisis are complex, heterogeneous by geographic location, type of drug and co-occurring drugs, and they affect different generations of Americans in different ways. In this commentary, we discuss a series of studies that have examined the dynamics of drug overdose in the last forty years in the US, beginning with Jalal et al. (2018). We focus on contextualizing public health, policy, and prevention implications of the trends in overdose, understanding that the increases in drug poisoning deaths in the US have had both common and distinct causes at each stage and by each specific drug that thereby require policy responses that are both general across substances and unique to some. Moreover, our view is that the variation across period, place, and cohorts illustrates that each stage of the unfolding opioid and other drug overdose epidemic was, and continues to be, preventable.

Exponential increases in overdose: multiple intersecting epidemics that were preventable

In a series of studies, Jalal and colleagues analyzed the functional form of the rise in drug poisoning deaths in the United States since 1979 (Jalal & Burke, 2021; Jalal et al., 2018; Jalal, Buchanich, Sindal, Roberts, & Burke, 2020). They found that while specific drugs contributing to drug poisoning increases have varied over the course of forty years, the overall mathematical function has been routinely exponential, beginning in at least the late 1970s. The rise in drug poisoning has exhibited variation by age, period, and cohort (Fuang, Keyes, & Li, 2018; Jalal, Buchanich, Sindal, Roberts, & Burke, 2020), and the overall risk has been devastating for public health. Because the shape of the overall curve has been exponential that began more than forty years ago, Jalal et al. conclude that the drug epidemic in the US has been a

'fundamental long-term process' and that the epidemic is longer.

The observation that drug overdose deaths, when together, fit a long-term exponential curve underscores that there are, and remain, root drivers that contribute to hard drug types. Factors that drive increases in overdose of the type of drug involved include stigmatization and of people who use drugs (Davis, Green, Lesh, & Belong, 2019). Policies that maintain poverty and unsafe conditions (Friedman et al., 2020; Tsai et al., 2019). The shape of the long left tail indicates high statistical precision in predicting drug overdose death across the nation across the last 40 years, suggesting that public health and policy interventions require of the social determinants of health of people who use drugs and overlay the many subepidemics involved in the overdose death. Reducing drug overdose deaths will require improving housing, health care access, and reducing system involvement.

Yet Jalal et al. also note that that overall exponential trend of distinct sub-epidemics that have affected different in different geographic locations, each of which have different prevention and intervention implications. Thus, the return power of the exponential curve should not be misinterpreted as indicating that these deaths were, or continue to be, inevitable. An accurate reading of the exponential curve of drug use in the US is as an interplay between fundamental social processes that continue to place individuals at risk for drug use, and specific drug access and supply factors that place at risk and accelerate specific types of drug deaths. As et al., prescription opioids, heroin, synthetic opioids are contributing to a rise in drug poisoning at different ages, and different locations. Taken together, we agree with Jalal et al. that overdose deaths increase involve fundamental social processes that continue to place individuals at risk for drug use, and specific drug access and supply factors that place at risk and accelerate specific types of drug deaths. As et al., prescription opioids, heroin, synthetic opioids are contributing to a rise in drug poisoning at different ages, and different locations. Taken together, we agree with Jalal et al. in concluding that the epidemic will not be a time longer; we have the public health and public policy

K.M. Keyes and M. Cerda

ity in different cohorts of young people who then have higher rates of use through the lifecycle (Kandel, Griesler, Lee, Davies, & Schaffman, 2007; Kerr, Greenfield, Ye, Boud, & Rehm, 2013; Keyes, Li, & Hsiao, 2011). Current examples of other strong associations with birth cohorts in substance use in the United States include cannabis and alcohol use. Cannabis use increased among youth in the 1970s, and among these cohorts who were adolescents and young adults at that time, cannabis use remained elevated throughout the lifecycle compared with other cohorts (Kandel et al., 2001). Alcohol

consumption among 'early millennials', the 1980s (Kerr et al., 2013), while it is lower than young adults (Keyes & Hsiao, 2011), it is still higher than older adults (Dietz, Johnson, & O'Neil, 2019). These reflect social factors, an interplay with drug availability and acceptance, and conflict between social norms of age.

Further, the way in which social conditions in social processes is not understood, strong associations with birth cohorts of health outcomes described in cases with known infectious origins and Hepatitis C (B. D. Smith et al., 2018), comes such as obesity (Robinson, & smoking-related disease (Jin, 2018). These associations are so strong that they are consistent across countries and time (Kernack, McKendrick, & McKinley, 2001). They reflect what Glen Elder terms our 'interconnected lives' as members of a birth cohort; we share geopolitical exposure and awareness, competition for labor market and educational resources, social norms, and life-altering constraints and opportunities as we move through the lifecycle (Elder, 2018).

Thus it is not surprising, but in many ways illuminating, that the overdose epidemic has exhibited strong birth cohort patterns. It reflects that drug use and its consequences are not inevitable outcomes of high levels of exposure and distribution of drugs that can cause overdose, but an interaction between individual and society, patterned by age and generation in which exposure occurs. Cohort associations also reflect that prevention efforts that attend to generational differences have a better chance of success. Understanding the drug use pattern, and desires and needs of each generation undergoing drug use, will allow for a suite of programming approaches that aim to address each generational need as potentially distinct.

## Conclusion

In 2019, 70,630 individuals in the US are estimated to have died from drug poisoning (Greenland, Michaud, & Warner, 2022), and provisional data from 2020 indicate that overdose increased during the SARS-CoV-2 pandemic. Drug poisoning deaths undercount the total harm to the public from other addictive substances: alcohol and tobacco-related deaths continue to claim thousands of lives every year, and while policy and public health responses over decades have been tirelessly formed and refined to protect health, deaths from alcohol are again on the rise (White, Castle, Higgins, & Powell, 2020). The series of papers by Jalal et al., and others, are critically important in framing the issues that urgently require a multi-pronged public health investment: Public health efforts to reduce overdose, expand treatment accessibility and reduce barriers to access continue to be urgently needed. Rethinking how we as a public health community support efforts to reduce harm associated with substance use in the US will continue to save lives and reduce stigma. Rather than considering the epidemic curve of drug poisoning deaths as an inevitable consequence of underlying dynamical processes, we view

the epidemic curve of drug poisoning deaths as a rebuke on the systems of regulation and care that have failed and resulted in these preventable deaths.

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## Declarations of Interest

KMK has been compensated for expert witness work in litigation.

Keyes and Cerda (2022) p. 4

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