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?"

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.

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TCA_Defendants_Court_Exhibit_00011.0002

NIDA Media Guide on "What is drug addiction?"

National Institute on Drug Abuse

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. 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.

Why study drug use and addiction?

Use of and addiction to alcohol, nicotine, and illicit drugs cost the billion a year related to healthcare, crime, and lost productivity. killed over 63,000 people in America, while 88,000 died from exc Tobacco is linked to an estimated 480,000 deaths per year. [5] (He specified, *drugs* refers to all of these substances.)

How are substance use disorders catego

NIDA uses the term *addiction* to describe compulsive drug seeking consequences. However, *addiction* is not a specific diagnosis in the fifth 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).

National Institute on Drug Abuse
Advancing Addiction Science

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

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Literature Cited in Keyes' Rebuttal Does Not Support Causation

Study	Findings
Mars (2013)	• "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 **does not prove a causal link**." (P. 258) • "Younger pill initiates were more likely to report dependence on **diverted** opioid pills prior to heroin initiation[.]" (P. 263)
Jalal (2018)	• "[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) • "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)
McCabe (2021)	• "[T]he vast majority of prescription opioid exposure **does not** lead to heroin use." (P. 1) • "[H]eroin incidence and prevalence rates were significantly greater among those who reported **nonmedical** prescription opioid misuse." (P. 1)

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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

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

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

Keyes and Cerda (2022) p. 4

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Stanford-Lancet Commission (2022)

Finally, the Commission notes that the spate of multi-billion-dollar lawsuits surrounding the opioid crisis in the USA can also create conflicts of interest. We propose that restrictions on regulatory bodies should apply not only to material connections to the pharmaceutical industry, but also to law firms suing some element of the industry and to people hired as expert witnesses by those firms.

Stanford-Lancet (2022) p. 16, P-24908_00016

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