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

Rebuttal Examination of Katherine Keyes, PhD

June 27, 2022

1

TCA_Defendants_Court_Exhibit_00011.0001

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 su an intense focus on using a certain substance(s), such as alcohol or takes over their life. They keep using alcohol or a drug even when th problems. Yet a number of effective treatments are available and pe 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 trar
- Cocaine, methamphetamine and other stimulants
- Tobacco

People with a substance use disorder have distorted thinking, behav

Changes in the brain's wiring are what cause people to have intense Gravings for the area 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

TCA_Defendants_Court_Exhibit_00011.0002

NIDA Media Guide on "What is drug addiction?"



National Institute on Drug Abuse Advancing Addiction Science

Home » Publications » Media Guide » The Science of Drug Use and Addiction

Media Guide



National Institute on Drug Abuse Advancing Addiction Science

The Science of Drug Use and Addicti

What is drug addiction?

Addiction is defined as a chronic, relapsing disorder characterize seeking, continued use despite harmful consequences, and long-It is considered both a complex brain disorder and a mental illne severe form of a full spectrum of substance use disorders, and is 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. J killed over 63,000 people in America, while 88,000 died from ex Tobacco is linked to an estimated 480,000 deaths per year. $\stackrel{5}{\sim}$ (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 more encoded of the encoded

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
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 <u>does not prove a causal link</u>." (P. 258) "Younger pill initiates were more likely to report dependence on <u>diverted</u> 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 <u>does not</u> lead to heroin use." (P. 1) "[H]eroin incidence and prevalence rates were significantly greater among those who reported <u>nonmedical</u> prescription opioid misuse." (P. 1)

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

onal Journal of Drug Policy 104 (2022) 10367-Contents lists available at ScienceDirect International Journal of Drug Policy

journal homenage: www.elsevier.com/locate/drugo

Response

Reply commentary by Jalal and Burke

Donald S. Burke^{a,*}, Hawre Jalal^b

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We thank the commentors for their excellent commentaries. Rather than respond point by point, in the interest of readability we have orga-nized our reply to addresses all four expert commentaries collectively. Our publications have been admirably summarized in the commentaries. The key points are:

- Annual rates of accidental drug overdoses in the USA from all drugs have been increasing exponentially for four decades
 Paradoxically this overall smooth epidemic trajectory is the sum of multiple sub-epidemics of shifting drugs, geographics, and sex, race,
- and urbanicity There is a strong age cohort effect, with every birth year cohort after World War II showing a faster increase in OD death rates than the
- preceding birth year cohort Deviations from the long-term trajectory are temporary, with return to the exponential growth pattern.
 Novel data management and visualizations have facilitated these dis-
- coveries

In this reply we pose and then answer seven questions drawn from the expert commentaries

- 1. Is the exponential growth trajectory real or coincidence, and does the
- fitted curve have future as well as retrospective predictive power? 2. Is the exponential growth pattern of accidental overdose deaths in
- the USA unusual? 3. Is the curve truly exponential?

- as is the curve truly exponential?
 Is the exponential growth inevitable?
 What is causing the exponential growth trajectory?
 How did we make these discoveries? 7. What do we need to do to understand the exponential growth pat-
- tern?

Is the exponential growth trajectory real or coincidence, and does the fitted curve have future as well as retrospective predictive power?

We first discovered the exponential trajectory of USA accidental drug overdose deaths five years ago using then available death record data through 2015, and promptly reported this observation in a short note to bioRxiv entitled "Exponential growth of the USA Overdose Epidemic" (Buchanich et al., 2017).

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

Check for spitales

Cases in year Y = 10^{(3.2871 + .0372+(Y-1978))}

with a log linear $R^2 = .99$. At that time, we proposed that this s but predictable pattern was likely to continue into the foreseeab ture. We forecast an exact number of expected OD deaths in the for the next five years by simply extrapolating the 1979-2015 for the next new years by simply extrapolating the 1979-2013 curve for five more years, from 2016 through 2020. Fig. 1 show the year-by-year forecasts we made five years ago are closely all with the subsequently recorded actual data. As we had hypother, annual OD death counts continued to increase exponentially. The ob served to expected ratios for each year 2016-2020 were respectively 1.09 (54,793/50,199); 1.12 (61,311/54,689); 0.99 (58,908/59,579); 0.96 (62,172/64,908); and 1.18 (83,558/70,713). The total number of accidental OD deaths that we forecasted for the five-year interval 2016-2020 was 300,089, close to the actual recorded total of 320,742 (observed to expected ratio = 1.07). While it is always possible that these accurate forecasts made five years ago were coincidental, this seems unlikely. For this current commentary, we have extrapolated the initial exponential growth curve for yet another five years, from 2021 to2025, as shown in Fig. 1. While we fervently hope that curve will be deflected, if it is not, the forecasted five-year total will be close to an additional half million (460,523) accidental overdose deaths

Is the exponential growth pattern of accidental overdose deaths in the USA unusual?

Our papers have focused on the growth of accidental drug overdos deaths in the USA, and we have not systematically examined the trajectories of other causes of death. To facilitate these kinds of compa ative analyses we have developed a new visualization method for age, period, and birth cohort (APC) data that we call "hexamaps" (Jalal 8 Burke, 2020).

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:

Our Science paper was published 18 months after this initial obser-

vation and used data through 2016 (Jalal et al., 2018). For the bioRxiv

Jalal (2022) p. 1

Compton (2022) – "Astonishingly Smooth Exponential Curve"

International Journal of Drug Policy 104 (2022) 103676



International Journal of Drug Policy

Commentary

Exponential increases in drug overdose: Implications for epidemiology and research

iournal homepage: wy

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Introduction

Starting with a high impact paper in Science in 2018, the team at the University of Pittsburgh lead by Hawre Jalal has documented intriguing observations about the factors undergirding the trajectory of the drug overdose epidemic in the United States (Jalal et al., 2018). Their work monstrates that the epidemic of unintentional drug overdose deaths types as the primary drivers of the epidemic over the decades since 1979. Of note, in July 2021, the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC) released provi-sional mortality data indicating an approximately 30 percent increase in the number of overdoses in the U.S. during the 12-months ending De cember 2020 compared to the same time period for 2019 (H et al., 2020; Ahmad et al., 2021). While the 2020 data include deaths determined as from any cause (i.e. unintentional, intentional and unde-termined), these overall increases suggest that the exponential growth in overdose deaths identified by Jalal and colleagues continues (see Fig. 1). Additionally, analyses by Jalal and colleagues demonstrate shifting pat-terns of overdose death by birth cohort and provide insight into the deviation from this curve seen in 2018 when overdose deaths dropped slightly (Jalal & Burke, 2021; Jalal et al., 2020a). Their work includes both intriguing overall observations about the epidemic as well as contributions to analytic methods and data visualization techniques that have implications for epidemiology and public health practice (Jalal & Burke, 2020b). While other commentaries may focus on the methods used by Jalal and the strengths of the evidence supporting the work, in this commentary, we review the major implications of their findings. In particular, we describe some of the potential next steps in public health research and practice that could be informed by this important line of research.

Summary of Jalal and colleagues papers

Jalal and colleagues' 2018 study published in Science zoomed out from the opioid-centric view of the overdose epidemic dominant at the

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time, analyzing the records of nearly 600,000 unintentional deaths in the United States over the period of 1979-2016 (Jal 2018). This extended period of analysis covered drug epidemis than the opioid crisis of the past 20 years, including the cocain cocaine epidemic of the late 1980s and early 1990s. Due to the sh ICD-9 to ICD-10 coding, most other published work has begun w from 1999, cropping trends to the beginning of the opioid cr capturing the shift from deaths predominantly involving pres opioids to heroin, and finally to a curve driven by overdoses in illicitly manufactured fentanyl and other synthetic opioids (Con Jones, 2019; Hedegaard, Miniño, & Warner, 2020). By adding ditional two decades of data, the work by Jalal and colleagues r, 2020). By adding i an astonishingly smooth exponential curve of increasing drug of deaths over the entire 38-year period examined. While the di approaches shifted during this long time frame, Jalal and coll work is a reminder that broad trends may still be examined in ting of data inconsistency. The resulting curve revealed that th and receding roles of various opioids in the overdose epidemic the most recent iteration of the shifting sub-epidemics of overdo different substances, involving multiple substances in the early with cocaine predominant in the 1990s followed by opioids si late 1990s. These patterns, along with shifting involvement o graphic groups and geographic areas, have converged in a stead of drug overdose mortality nationally in the United States. What plain these results, particularly the ways that multiple subcom merge into a single growth curve, is a key question. While the speculate that both vector factors - demand and supply - may portant in shifting drug markets as well as sociopsychological increasing demand for drugs due to negative internal and neight conditions, many important research questions to understand the nomena remain. A goal is to determine how these components elucidated in further research and then translated into effective tion, harm reduction, treatment, and recovery support approact will shift these longstanding trends.

Next, in their 2020 Nature Medicine study, Jalal and colles plored the contributions of birth cohort factors to the shifting of

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"



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nal Journal of Drug Policy 104 (2022) 10367

Should drug use trends be studied holistically, or piece by piece?

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Jalal et al.'s challenge

Contemporary academic literature that strives to understand patterns of drug use tends to focus on distinctions, contextual explanations, and special populations. There are exceptions, Historians David Musto (1999) and David Courright (2020) write about broad trends and fundamental forces, and Golub, Johnson, and Dunlap (2005) propose a cultural theory that spans drugs and is set in explicit contrast to a "postmodern outlook that holds a more fractionated and tenuous view for the influence of various cultural elements" (pp.218-219). However, scanning the tables of contents of leading journals reveals a proclivity to "complexify" – diving into particular outcomes for a particular subpopulation in a particular country or region, often with a particular drug or class of drugs. It is a literature that embraces every tree, but less frequently steps back to contemplate the forest.

trequently steps back to contemplate the torest. Against that backdrop, the analysis of Jalal et al. (2018), Jalal et al. (2020), and Jalal & Burke (2021) is like a satellite photo-graph 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 birthcohort specific trends in total deaths. Jalal et al.'s core empirical observation is easy to state formally. If

- Y. = # of overdose deaths in the U.S. in year
- $X_{i_1} = #$ of overdose deaths in the U.S. in year t of drug i.

 $x_{it} = w$ of orelates teams in the 0.5 m year of or any i. then by definition Y_t is the sum over i of the X_{it} . Jalal et al. observe that Y_t shows steady exponential growth over nearly 40 years (1979–2016) even though the individual X_{ia} 's do not. There are two possible explanations for this empirical regularity: (1) It is sheer coincidence or (2) Some force or tendency "coordinates" the

substance-specific X_{it}'s to make their sum grow steadily. Forty years seems too long to shrug off as coincidence. However, if this stability is not just coincidence, then we are left with an embarassing admission. Despite billions of dollars in funding and decades of research conducted by tens of thousands of bright scholars, few of us has even thought about the possibility that some mechanism may be "coordinating" different drug-specific time trends in death rates, let alone identified what that mechanism might be. And the trend in total

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overdose deaths, Yr, is not just some obscure detail. It is arg single most important outcome in our field. In this commentary, I will first think about some possible co ing mechanisms, but find none satisfying. I'll then make a pitc might just be a coincidence, but close with agnosticism about t sternation about the way our field has not yet fully with the Jalal et al. challenge.

Mechanisms that might coordinate different drug-specific o

Overdose deaths are a sequelae of drug consumption, w market-related phenomenon, so it is natural to divide the hunt dinating mechanisms into factors related to drug demand, drug and broader social and cultural trends.

"Contagious spread" is a familiar demand-side driver of ext growth because initiation into the activity is driven by the curr or amount of that activity; in the language of differential eq when the derivative of X is proportional to X, then X(t) will be e tial. Such "epidemic models" explain exponential growth of d infectious diseases like COVID-19, rumors, and new product a But those are drug-specific stories that explain exponent X_{it}, not exponential growth in the aggregate across drugs. ential g

One can imagine stories that would apply across drugs. Fo ple, if most drug dependence is caused by growing up in ch and parents' drug dependence creates chaotic home situations kids, then that feedback loop could create exponential growt number of people with substance use disorder (SUD). However grew much faster than did SUD. General population surveys a while some for studying growth in drug dependence (Reuter, Camerus, & Midgette, 2021), but it is telling that over the 17 years from 2002 to

2019, the U.S. household survey's estimates of per capita rates of de pendence on an illicit drug other than marijuana grew by only 17 per cent. That's an annual growth rate of 0.9 percent vs. the average annual growth of 7.4 percent that Jalal et al. estimate for deaths. Somehow the sequence of drugs-of-choice and/or the way those

drugs were used combined to produce steady growth in deaths per per son with SUD. That's a real puzzle for demand side explanations because there is no underlying demand for overdose deaths per se. There may be demand for euphoria, intoxication, and self-medication, but not death Turning to supply side theories, it is easy to interpret trends in fatal overdoses from specific drugs as being influenced by supply side factors;

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 birthcohort specific trends in total deaths.

Caulkin (2022) p.1

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

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Commentary

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

Katherine M. Keves ".", Magdalena Cerdá Department of Ipidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA Department of Population Health, New York University School of Medicine, New York, NY, USA

Drug poissning denits in the United States centime to be a gab-lic health crisis. Over 840,000 Americans have idea from drug poi-soring due to overdose since hiel are 1996 (The Drug Overdee Fipi-demic: Behind the Numbers, 2013; opioids have been the predomi-nant class of drugs contributing to the increase. The nature and the dynamics of this overdose erists are complex, heterogeneous by goo-difference generations of Americanis in different ayout find in commen-tary. And the second second second second second second intervent of the overdose erists are complex, heterogeneous by goo-difference generations of Americanis in different ayout find in commen-tary, we discuss a series of studies that have examined the dynam-ics of drug overdose in the last forty years in the US, beginning with Jaki et al. (2016). We focus on constrainable poise heads, policy, and prevention implications of the traction is overdose, underscoring that the increases in drug poisoning detabs in the US have had both that the etdy require policy engouses that are both general across sub-stances and unique to some. Moreover, our view it that the variation across period, agenet, and cohost illutratices that es obt general across sub-tances and unique to some. Moreover, our view it that the variation errors period, agenet, and cohost illutratices that es obt general exists of the unifi-ing opioid and other drug overdose epidemic was, and continues to be, preventible.

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, Buchanich, Sin-clair, Roberts, & Burke, 2020). They found that while specific drugs contributing to drug poisoning increases have varied over the course of

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remained elevated throughout the j hors (kinade el a., 2003). Alcohol trated among 'early millenniak', th 1980s (Kerr et al., 2013), while its's lecents and young adults (Kerse, i y system is exponentially increase older adults (Mitch, Johnnet, O' These reflect scale factors, an incre-with drug availability and accepts collice between social norms of a utilizer in no cella processes is no tu edeed, arrong associations with birth eyed health outcomes described for ease with known infections critice 'the description of the second sec ndamental long-term process' and that the epidem ety of health outcomes described fe eases with known infectious origin and Hepatitis C (B. D. Smith et al. comes such as obesity (Robinson, and smoking-related disease (Jen associations are so strong that th ity across many countries and time Kermack, McKendrick, & McKinlay,

KM Keess and M Conk

ise through the lifecourse (K

01). They reflect what Glen Elder terms our 'interconnected lives' as members of a birth cohort; w share geopolitical exposure and awareness, competition for labor mar-ket and educational resources, social norms, and life-altering constraints and opportunities as we move through the lifecourse (Elder, 2018).

and apportunities are move through the lifecourse (10.66, 2011). Thus it is not surprising, but in many ways limitiating that the that is the second second second second second second second theory of the second second second second second second an interaction between individual and society, patterned by age and growth of second secon

Conclusio

In 2019, 70,630 individuals in the US are estimated to have idea from durp poioning (individuals). Whereas, 2020, and powi-sional data from 3220 indicate that weedsdoe increased during the Sar-Oreo 74 andremic. The positoring databat undercoautt the tetal harn to the public from other addictive substances; alcohol- and tokacce-situated datas continue to data increasing of large every year, and while publy and priority. The priority data that the second strategies of the public hard neuron barries data from individual strategies of the public data and the second strategies of the second every strategies and the second strategies of the second every strategies and the second strategies of the second every strategies and the second strategies of the second every require a multiproposed public house (large linking how we as a public health community support efforts to relace item as associated state relate considering the second strategies of educy points and and an environ large strategies the second strategies of educy points and state relate considering the second strategies of educy points data strategies and an invisible consequence of underlying dynamical processes, we view In 2019, 70,630 individuals in the US are estimated to have died

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Andrey M., Pincikk, M., Snith, N., Birera-Agaire, A., Davis, G. S., Marhall, B. D. L., et al. (2020). Measuring relationships between pseuritie reporting state-level gen-eryticino drug monitoring programs and coursy-level faal preception option dynamic dynamics. *J. Markal. J. Markal. J. M. J. M. J. M. Markal. J. M. J. M. Markal. J. M. D. M. Pincika, J. M. Statella, J. M. D. Pincika, J. M. Statella, J. M. J. M. Markal, J. M. J. M. M. Markal, J. S. C. 2015. Nonmedi-ela prescription option dynamical hubit and and early addresses predicts transitions to break and in your galdhabod. <i>A national study, Journal of Padiris, 16733*, OSC 1995.

3.1016/j.jpeds.2015.04.071. eler Martin, K., Bruzelius, E., Ponicki, W., Gruenewald, P., Mauro, C., et a atiotemporal analysis of the association between pain management clim piold prescribing and overdose deaths. American Journal of Rpidemiolog

mpton, W. K. J., Jones, v. m. preception copies and use and heroin use. New Engineeries 168, 10166, negrana 2008/09, 1600, 1000, State approaches to addressing the weak C., Green, T., Lakik, L. & Bittone needs. The Journal of Law, Molicine & Ethics, seesalose epidemicine and an engineeries and the second s

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st, W. H. (1939). The age selection of mortality from tuberculosis in successive de American Journal of Epidemiology, 30(3), 91–96–30 SectionA. 10.1093/oxfor

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ity in different cohorts of young people who then have higher rates of the epidemic curve of drug poisoning deaths as a rebuke on the system of regulation and care that have failed and resulted in these preventable

Griesler, Lee, Davies, & Schaffsan, 2001; Kerr, Greenfield, Ye, Bond, & Rehm, 2013; Keyes, Li, & Hasin, deaths. 2011). Current examples of other strong associations with birth cohorts in substance use in the United States include cannabis and alcohol use. Funding Cannabis use increased among youth in the 1970s, and among these co-horts who were adolescents and young adults at that time, cannabis use remained elevated throughout the lifecourse comnared with other co-

Declarations of Interest

KMK has been compensated for expert witness work in litigation.

Keyes and Cerda (2022) p. 4

Stanford-Lancet Commission (2022)

et based on scientific evidence and int

7 to material connections to the industry, but also to law firms suin f the industry and to people hired a by those firms.

billion-dollar lawsuits surrounding the the USA can also create conflicts propose that restrictions on regulate apply not only to material con pharmaceutical industry, but also to some element of the industry and the

in lobbying on behalf of an

encod).⁻⁻⁻⁻ Positive incentives should also be -eg, civil servants working in regulatory uld be paid higher salaries, with added centives for senior officials with particularly dge of regulatory processes.



Finally, the Commission notes that the spate of multibillion-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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