

UC San Diego

UC San Diego Previously Published Works

Title

Addressing the context and consequences of substance use, misuse, and dependence: A global imperative

Permalink

<https://escholarship.org/uc/item/186656qb>

Journal

PLOS Medicine, 16(11)

ISSN

1549-1277

Authors

Tsai, Alexander C
Alegría, Margarita
Strathdee, Steffanie A

Publication Date

2019

DOI

10.1371/journal.pmed.1003000

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

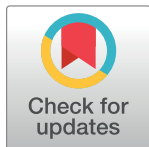
EDITORIAL

Addressing the context and consequences of substance use, misuse, and dependence: A global imperative

Alexander C. Tsai^{1,2,3*}, Margarita Alegría^{2,4}, Steffanie A. Strathdee⁵

1 Center for Global Health, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **2** Harvard Medical School, Boston, Massachusetts, United States of America, **3** Mbarara University of Science and Technology, Mbarara, Uganda, **4** Disparities Research Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **5** Division of Infectious Diseases and Global Public Health, University of California at San Diego School of Medicine, San Diego, California, United States of America

* actsai@partners.org



Substance use, misuse, and dependence contribute immensely to the global burden of disease [1]. Their harms extend far beyond their corrosive effects on health, safety, and wellbeing and additionally include those associated with healthcare expenditures, productivity losses, criminal justice involvement, and other negative effects on social welfare [2]. The incidence and harms of substance use, misuse, and dependence involve multilevel explanatory factors [3,4]. Interventions to reduce their individual- and population-level harms can often be hampered by biological, psychological, and social complexity, especially because substance use is often syndemic with other health and social problems such as HIV infection, hepatitis B and C, mental health disorders, and violence [5,6]. It is in this context that *PLOS Medicine* devotes its November 2019 Special Issue to research on substance use, misuse, and dependence. The contributions to the issue cover a wide range of topics, including social determinants of substance use, health harms resulting from substance use, and interventions to prevent or reduce the harms associated with substance use. There are also a number of gaps in terms of the topics covered, the robustness of the evidence, and its global scope.

OPEN ACCESS

Citation: Tsai AC, Alegría M, Strathdee SA (2019) Addressing the context and consequences of substance use, misuse, and dependence: A global imperative. *PLoS Med* 16(11): e1003000. <https://doi.org/10.1371/journal.pmed.1003000>

Published: November 26, 2019

Copyright: © 2019 Tsai et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The authors received no specific funding for this work.

Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: ACT receives a stipend as a Specialty Consulting Editor for *PLOS Medicine* and serves on the journal's Editorial Board. ACT, MA, and SAS served as Guest Editors on *PLOS Medicine*'s Special Issue on Substance Use, Misuse and Dependence.

Provenance: Commissioned; not externally peer reviewed.

Harms of opioid use

For the first time in several decades—and concomitant with the rise in opioid use, misuse, and dependence—life expectancy has declined in the United States [7], and life expectancy gains have stalled in Canada [8]. Consistent with these global estimates, in an accompanying paper for the Special Issue, Astrid Guttmann and colleagues [9] analyzed 2002–2016 national data from the United Kingdom and Canada to identify women who likely used opioids during pregnancy (proxied by an infant birth hospitalization record coded with neonatal abstinence syndrome) and demonstrated markedly elevated mortality rates over up to 10 years of follow-up. The elevated rates were particularly striking for mortality due to avoidable causes like unintentional and intentional injuries. Using 1998–2014 data from a large sample of primary care practices in the UK, John MacLeod and colleagues [10] show that coprescription with benzodiazepines was highly prevalent among patients receiving opioid agonist and partial agonist treatment and that coprescription was strongly associated with drug-related poisonings. This study adds to the relatively thin evidence base [11] about the potential hazards of benzodiazepine coprescription in the setting of opioid agonist treatment [12]. Although opioid agonist treatment should not be

withheld from patients concurrently taking benzodiazepines or other central nervous system depressants, these studies suggest a need for vigilance by healthcare professionals providing care for such patients to minimize the risk of overdose or death [13]. Coprescription of alprazolam may warrant particularly heightened scrutiny, however, given that it is the short-acting benzodiazepine most frequently involved in drug overdose deaths [14].

Determinants of opioid use–related harms

The elevated mortality risks facing people with opioid use disorders are attributable to a complex web of interrelated structural and psychological causes [15–18]. The concept of the “risk environment” [19] may be useful to reference here, given its focus on the interplay between various structural factors that increase vulnerability to morbidity and mortality. The study by Zehang Li and colleagues [20] provides an example of the use of spatiotemporal data to characterize one aspect of the risk environment. Applying a Bayesian space–time model to emergency medical services dispatch data on suspected heroin-related overdose incidents from Cincinnati in 2015–2019, the investigators identified significant spatial heterogeneity in the distribution of these calls, with strong associations with features of the built environment and temporal spikes corresponding to local media reporting.

Analyzing 2005–2016 claims data, Yu-Jung Wei and colleagues [21] identified more than 200,000 adults with new claims related to opioid use disorder or overdose. They found that, by the end of the study period, nearly one-half had filled no opioid prescriptions in the 12 months prior to an incident opioid use disorder diagnosis or overdose. Among those who had filled opioid prescriptions, nearly three-quarters were prescribed a mean daily dose lower than the threshold needed to trigger most risk stratification algorithms. Also noteworthy is the analysis of 2015–2016 data from the US National Survey on Drug Use and Health (NSDUH) by Joel Hudgins and colleagues [22]. These authors found that approximately 1 in 20 adolescents and young adults reported either past-year opioid use disorder or past-year nonmedical use of prescription opioids and that three-quarters of those reporting nonmedical use of prescription opioids had obtained them from outside the healthcare system. These estimates are generally consistent with trends identified in similar, previously published analyses of NSDUH data [23–26]. Thus, although opioid prescribing patterns undoubtedly played a significant role in how opioid use disorders came to be so highly prevalent [27–29] and asymmetrically distributed in the US [30–32], a public health response that focuses solely on prescribing behavior is likely to be ineffective in reducing the number of fatal and nonfatal opioid overdoses.

Interventions to reduce the harms associated with opioid use

For people with existing opioid use disorders, opioid agonist treatment is known to reduce mortality [33,34]. Monica Malta and colleagues [35] add to this evidence base with a systematic review showing a wide range of health and prosocial benefits of opioid agonist treatment for people with opioid use disorders who are incarcerated or have recently been released. Opioid agonist treatment may have important collateral health effects as well. Analyzing data from a 3-country (i.e., Canada, the US, and Mexico) cohort of people who inject drugs [36–38], Charles Marks and colleagues [39] found that people who inject drugs and who receive opioid agonist treatment are approximately half as likely to assist others in initiating injection drug use. They then developed a deterministic, dynamic transmission model of initiation into injection drug use, ongoing drug use, and cessation of drug use. Currently about 1 in 5 people with opioid use disorders receive any kind of treatment [40]; if treatment coverage were doubled to 40%, Marks and colleagues’ model suggests that the number of initiations into injection drug

use could fall significantly. This is an underappreciated benefit of opioid agonist treatment and underscores its potential public health impact, extending beyond its benefit to the individual.

To assist with prevention and treatment efforts, Jesse Yedinak and colleagues [41] aggregated data from 2015–2016 state and national data sources to estimate the proportions of Rhode Island residents in various states: at risk of, in treatment for, and in recovery from opioid use disorders. The authors' cross-sectional approach requires assumptions about exchangeability in the transition probabilities of individuals at each stage and the absence of biases due to selective mortality, but their addition of the "recovery" stage is a novel modification to the existing framework. This body of work echoes the familiar "voltage drops" analogy pioneered by John Eisenberg and Elaine Power [42], who used this model to illustrate how the potential for high-quality care is lost at various stages of access, enrollment, and treatment. So-called treatment cascade models have been used to identify gaps in the access and treatment continuum for a wide range of health conditions, including HIV treatment [43], prevention of mother-to-child transmission of HIV [44], depression [45], and, most recently, opioid use disorders [46].

Finally, for people with opioid use disorders who either cannot or do not choose to achieve sustained remission, alternative approaches might be considered to reduce the harms associated with ongoing use. Stephanie Lake and colleagues [47] analyzed 2014–2017 data from Vancouver, Canada, on people who use drugs and who experience chronic persisting pain and found that daily cannabis use was associated with significant reductions in high-frequency nonmedical opioid use. This finding echoes previously published studies showing that expansions in access to marijuana in the US have been associated with reductions in opioid overdose mortality [48,49]. Among those for whom opioids remain the drugs of choice, use of supervised consumption facilities can reduce the risk of overdose mortality, and the potential for either individual-level adverse health effects or neighborhood-level adverse social effects appears to be minimal [50,51]. Mary Clare Kennedy and colleagues [52] contribute to this literature by showing that, among clients of the first supervised consumption facility in North America (in Vancouver), frequent utilization was associated with a reduction in all-cause mortality over 2006–2017. Although "deaths of despair" [53] ranked highly among the causes of death observed in this study, other nonaccidental causes of death (e.g., cancer, cardiovascular disease) were also prominent. In the US, only 1 supervised injection facility currently exists, although 13 cities have sought approval to support their implementation.

Ongoing misalignment between state and federal laws governing use of recreational marijuana and availability of supervised injection facilities seriously undermines harm-reduction efforts in the US. These and other interventions across multiple sectors involving healthcare, economic, and social welfare systems need to be scaled up, dramatically and immediately, in order to substantively reduce the number of opioid overdose deaths [54,55]. However, as discussed by Alexander Tsai and colleagues [56], the single most all-consuming force that restrains an effective policy and programmatic response to the opioid overdose crisis—through multi-level pathways that have nimbly adapted to the contours of the crisis over time—is the stigma attached to opioid use. Women whose children are affected by neonatal abstinence syndrome (studied by Guttman and colleagues [9]) carry a stigma for the rest of their lives. Current media attention devoted to the "mommy drinking" myth (debunked in the Special Issue study by Sarah McKetta and Katherine Keyes [57]) is driven by the stigma resulting from the intersecting levels of scrutiny targeted toward women who parent and toward those who consume alcohol. Moreover, the disparate geospatial burden of opioid-related incidents, such as those studied by Zehang Li and colleagues [20], generates a stigma that attaches to entire neighborhoods [58]. Indeed, as a class, harm-reduction interventions have been tainted by stigma, leading to their chronic underfunding and underutilization. These and other forms of stigma must be eliminated before the overdose crisis can be successfully overcome. Tsai and colleagues [56] provide suggestions for anti-stigma interventions at multiple levels to achieve this goal.

Gaps in the literature and the way forward

This issue of *PLOS Medicine* is notable for several gaps. First, the majority of contributions to the Special Issue concern the North American opioid overdose crisis, but the global burden of disease attributable to alcohol use disorders greatly exceeds that attributable to opioid use disorders [1]. Touching on harms owing to alcohol use, McKetta and Keyes [57] used data from the 2006–2018 US National Health Interview Survey to examine national trends in binge drinking and heavy drinking. Consistent with concurrently published findings from the NSDUH [59], they found that heavy drinking has declined or stabilized for most age/sex subgroups but that binge drinking has increased, particularly among women and older men.

A second evidence gap has to do with the global reach of the evidence. Although *PLOS Medicine* publishes research findings of general interest to the medical and public health communities, we received manuscript submissions describing research conducted in only a limited number of countries. In this Special Issue, the sole paper representing research conducted outside the US, Canada, and the UK is the report by Samantha Harris and colleagues [60], who analyzed Swedish register data from 1984–2016 to show that both refugee and nonrefugee migrants had lower rates of substance use disorders compared with Swedish-born individuals but that over time, the rates among migrants converged to that of Swedish-born individuals. The issue regrettably features no articles from Africa, Asia, or South America, and no articles focused on indigenous populations or on racial, ethnic, or sexual minority groups.

A third evidence gap has to do with the portfolio of methods underlying the evidence base. Causal methods have an important role to play in characterizing the relationships between exposures and outcomes when experimental data are difficult to come by (as one might expect in research on substance use disorders). Among the articles included in this Special Issue, only Kennedy and colleagues [52] used the “E-value” [61] to estimate the minimum strength of association on the risk ratio scale that an unobserved variable would need to have with both the exposure (frequent utilization of a supervised consumption facility) and outcome (all-cause mortality) to fully explain away their observed association. More studies using causal mediation analysis [62], instrumental variables [63], marginal structural models [64], natural experiments [49], regression discontinuity designs [65], and synthetic control methods [66] are needed. This Special Issue also lacks articles based on qualitative data. Qualitative methods can be used to study complex phenomena like substance use disorders in greater depth [67], probe for mechanistic pathways linking the phenomena of interest [68], and generate new insights that can be tested in future studies [69].

Collectively, the articles published in this issue highlight the scope of discovery and implementation needed to reduce the global burden of disease attributable to substance use, misuse, and dependence. Challenges—some related to science, others related to politics—are apparent. Multiple lines of evidence have already charted a road map that can be followed with respect to immediate policy making and program deployment. But there is a yawning chasm between what we know works to reduce the burden of disease from substance use disorders and what, at a societal level, is actually done about this burden. Eliminating this gap is not beyond our reach, given the available scientific evidence and substantial burden of ill health and suffering calling for prompt action, making it a public health imperative.

References

1. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry*. 2018; 5(12):987–1012. [https://doi.org/10.1016/S2215-0366\(18\)30337-7](https://doi.org/10.1016/S2215-0366(18)30337-7) PMID: 30392731

2. Harwood H, Fountain D, Livermore G. The economic costs of alcohol and drug abuse in the United States, 1992. Rockville: US National Institute on Drug Abuse; 1992.
3. Kendler KS. Levels of explanation in psychiatric and substance use disorders: implications for the development of an etiologically based nosology. *Mol Psychiatry*. 2012; 17(1):11–21. <https://doi.org/10.1038/mp.2011.70> PMID: 21670729
4. Tarter RE, Vanyukov MM. Introduction: theoretical and operational framework for research into the etiology of substance use disorders. *J Child Adolesc Subst Abuse*. 2001; 10(4):1–12.
5. Tsai AC, Mendenhall E, Trostle JA, Kawachi I. Co-occurring epidemics, syndemics, and population health. *Lancet*. 2017; 389(10072):978–28. [https://doi.org/10.1016/S0140-6736\(17\)30403-8](https://doi.org/10.1016/S0140-6736(17)30403-8) PMID: 28271848
6. Singer M. A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. *Free Inq Creative Sociol*. 1996; 24(2):99–110.
7. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. NCHS Data Brief No. 328. Hyattsville: US National Center for Health Statistics, 2018.
8. Orpana HM, Lang JJ, George D, Halverson J. At-a-glance—The impact of poisoning-related mortality on life expectancy at birth in Canada, 2000 to 2016. *Health Promot Chronic Dis Prev Can*. 2019; 39(2):56–60. <https://doi.org/10.24095/hpcdp.39.2.03> PMID: 30767855
9. Guttman A, Blackburn R, Amartey A, Zhou L, Wijlaars L, Saunders N, et al. Long-term mortality in mothers of infants with neonatal abstinence syndrome: A population-based parallel-cohort study in England and Ontario, Canada. *PLoS Med*. 2019; 16(11):e1002974. <https://doi.org/10.1371/journal.pmed.1002974>
10. MacLeod J, Steer C, Tilling K, Cornish R, Marsden J, Millar T, et al. Prescription of benzodiazepines, z-drugs, and gabapentinoids and mortality risk in people receiving opioid agonist treatment: Observational study based on the UK Clinical Practice Research Datalink and Office for National Statistics death records. *PLoS Med*. 2019; 16(11):e1002965. <https://doi.org/10.1371/journal.pmed.1002965>
11. Ding KY, Mosdol A, Hov L, Staumann GH, Vist GE. The effects of concurrent prescription of benzodiazepines for people undergoing opioid maintenance treatment: systematic review. Report from the Norwegian Institute of Public Health No. 2016–27. Oslo: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health; 2016.
12. Abrahamsson T, Berge J, Ojehagen A, Hakansson A. Benzodiazepine, z-drug and pregabalin prescriptions and mortality among patients in opioid maintenance treatment—A nation-wide register-based open cohort study. *Drug Alcohol Depend*. 2017; 174:58–64. <https://doi.org/10.1016/j.drugalcdep.2017.01.013> PMID: 28315808
13. US Food and Drug Administration. FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. Rockville: US Food and Drug Administration; 2017.
14. Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2017. NCHS Data Brief No. 329. Hyattsville: US National Center for Health Statistics; 2018.
15. Dasgupta N, Beletsky L, Ciccarone D. Opioid crisis: no easy fix to its social and economic determinants. *Am J Public Health*. 2018; 108(2):182–6. <https://doi.org/10.2105/AJPH.2017.304187> PMID: 29267060
16. Ruhm CJ. Drivers of the fatal drug epidemic. *J Health Econ*. 2019; 64:25–42. <https://doi.org/10.1016/j.jhealeco.2019.01.001> PMID: 30784811
17. King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: a systematic review. *Am J Public Health*. 2014; 104:e32–e42. <https://doi.org/10.2105/AJPH.2014.301966> PMID: 24922138
18. Venkataramani AS, Bair EF, O'Brien RL, Tsai AC. A difference-in-differences analysis of the association between automotive assembly plant closures and opioid overdose mortality in the United States. *JAMA Intern Med*. 2020; 180(2):1–9. <https://doi.org/10.1001/jamainternmed.2019.5686>
19. Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. *Soc Sci Med*. 2005; 61(5):1026–44. <https://doi.org/10.1016/j.socscimed.2004.12.024> PMID: 15955404
20. Li ZR, Xie E, Crawford FW, Warren JL, McConnell K, Copple JT, et al. Suspected heroin-related overdose incidents in Cincinnati, Ohio: A spatiotemporal analysis. *PLoS Med*. 2019; 16(11):e1002956. <https://doi.org/10.1371/journal.pmed.1002956>
21. Wei Y-JJ, Chen C, Fillingim R, Schmidt SO, Winterstein AG. Trends in prescription opioid use and dose trajectories before opioid use disorder or overdose in US adults from 2006–2016: A cross-sectional study. *PLoS Med*. 2019; 16(11):e1002941. <https://doi.org/10.1371/journal.pmed.1002941>

22. Hudgins JD, Porter JJ, Monuteaux MC, Bourgeois FT. Prescription opioid use and misuse among adolescents and young adults in the United States: A national survey study. *PLoS Med.* 2019; 16(11): e1002922. <https://doi.org/10.1371/journal.pmed.1002922>
23. Martins SS, Segura LE, Santaella-Tenorio J, Perlmutter A, Fenton MC, Cerdá M, et al. Prescription opioid use disorder and heroin use among 12–34 year-olds in the United States from 2002 to 2014. *Addict Behav.* 2017; 65:236–41. <https://doi.org/10.1016/j.addbeh.2016.08.033> PMID: 27614657
24. Monnat SM, Rigg KK. Examining rural/urban differences in prescription opioid misuse among US adolescents. *J Rural Health.* 2016; 32(2):204–18. <https://doi.org/10.1111/jrh.12141> PMID: 26344571
25. Edlund MJ, Forman-Hoffman VL, Winder CR, Heller DC, Kroutil LA, Lipari RN, et al. Opioid abuse and depression in adolescents: Results from the National Survey on Drug Use and Health. *Drug Alcohol Depend.* 2015; 152:131–8. <https://doi.org/10.1016/j.drugalcdep.2015.04.010> PMID: 25981310
26. Schepis TS, Krishnan-Sarin S. Characterizing adolescent prescription misusers: a population-based study. *J Am Acad Child Adolesc Psychiatry.* 2008; 47(7):745–54. <https://doi.org/10.1097/CHI.0b013e318172ef0d> PMID: 18520963
27. Ballantyne JC, Sullivan MD. Intensity of chronic pain—the wrong metric? *N Engl J Med.* 2015; 373(22):2098–9. <https://doi.org/10.1056/NEJMp1507136> PMID: 26605926
28. Baker DW. History of The Joint Commission’s pain standards: lessons for today’s prescription opioid epidemic. *JAMA.* 2017; 317(11):1117–8. <https://doi.org/10.1001/jama.2017.0935> PMID: 28241189
29. Sharfstein JM, Olsen Y. Making amends for the opioid epidemic. *JAMA.* 2019; 321(15):1446–7. <https://doi.org/10.1001/jama.2019.3505> PMID: 30990541
30. Todd KH, Deaton C, D’Adamo AP, Goe L. Ethnicity and analgesic practice. *Ann Emerg Med.* 2000; 35(1):11–6. [https://doi.org/10.1016/s0196-0644\(00\)70099-0](https://doi.org/10.1016/s0196-0644(00)70099-0) PMID: 10613935
31. Ng B, Dimsdale JE, Rollnik JD, Shapiro H. The effect of ethnicity on prescriptions for patient-controlled analgesia for post-operative pain. *Pain.* 1996; 66(1):9–12. [https://doi.org/10.1016/0304-3959\(96\)02955-7](https://doi.org/10.1016/0304-3959(96)02955-7) PMID: 8857626
32. Bernabei R, Gambassi G, Lapane K, Landi F, Gatsonis C, Dunlop R, et al. Management of pain in elderly patients with cancer. SAGE Study Group. Systematic Assessment of Geriatric Drug Use via Epidemiology. *JAMA.* 1998; 279(23):1877–82. <https://doi.org/10.1001/jama.279.23.1877> PMID: 9634258
33. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ.* 2017; 357: j1550. <https://doi.org/10.1136/bmj.j1550> PMID: 28446428
34. Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, et al. Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. *Ann Intern Med.* 2018; 169(3):137–45. <https://doi.org/10.7326/M17-3107> PMID: 29913516
35. Malta M, Varatharajan T, Russell C, Pang M, Bonato S, Fischer B. Opioid-related treatment, interventions and outcomes among correctional populations: a systematic review. *PLoS Med.* Forthcoming 2019
36. Robertson AM, Garfein RS, Wagner KD, Mehta SR, Magis-Rodriguez C, Cuevas-Mota J, et al. Evaluating the impact of Mexico’s drug policy reforms on people who inject drugs in Tijuana, B.C., Mexico, and San Diego, CA, United States: a binational mixed methods research agenda. *Harm Reduct J.* 2014; 11:4. <https://doi.org/10.1186/1477-7517-11-4> PMID: 24520885
37. Cheng T, Small W, Nosova E, Hogg B, Hayashi K, Kerr T, et al. Nonmedical prescription opioid use and illegal drug use: initiation trajectory and related risks among people who use illegal drugs in Vancouver, Canada. *BMC Res Notes.* 2018; 11(1):35. <https://doi.org/10.1186/s13104-018-3152-9> PMID: 29338770
38. Morris MD, Brouwer KC, Lozada RM, Gallardo M, Vera A Strathdee SA. “Injection first”: a unique group of injection drug users in Tijuana, Mexico. *Am J Addict.* 2012; 21(1):23–30. <https://doi.org/10.1111/j.1521-0391.2011.00194.x> PMID: 22211343
39. Marks C, Borquez A, Jain S, Sun X, Strathdee SA, Garfein RS, et al. Opioid agonist treatment scale-up and the initiation of injection drug use: A dynamic modeling analysis. *PLoS Med.* 2019; 16(11): e1002973. <https://doi.org/10.1371/journal.pmed.1002973>
40. US Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville: Center for Behavioral Health Statistics and Quality, U.S. Substance Abuse and Mental Health Services Administration; 2019.
41. Yedinak JL, Goedel WC, Paull K, Lebeau R, Krieger M, Thompson C, et al. Defining a recovery-oriented cascade of care for opioid use disorder: A community-driven, statewide cross-sectional assessment. *PLoS Med.* 2019; 16(11):e1002963. <https://doi.org/10.1371/journal.pmed.1002963>

42. Eisenberg JM, Power EJ. Transforming insurance coverage into quality health care: voltage drops from potential to delivered quality. *JAMA*. 2000; 284(16):2100–7. <https://doi.org/10.1001/jama.284.16.2100> PMID: 11042759
43. Giordano TP, Suarez-Almazor ME, Grimes RM. The population effectiveness of highly active antiretroviral therapy: are good drugs good enough? *Curr HIV/AIDS Rep*. 2005; 2(4):177–83. <https://doi.org/10.1007/s11904-005-0013-7> PMID: 16343375
44. Stringer JS, Sinkala M, Maclean CC, Levy J, Kankasa C, Degroot A, et al. Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. *AIDS*. 2005; 19(12):1309–15. <https://doi.org/10.1097/01.aids.0000180102.88511.7d> PMID: 16052086
45. Pence BW, O'Donnell JK, Gaynes BN. Falling through the cracks: the gaps between depression prevalence, diagnosis, treatment, and response in HIV care. *AIDS*. 2012; 26(5):656–8. <https://doi.org/10.1097/QAD.0b013e3283519aae> PMID: 22398574
46. Williams AR, Nunes EV, Bisaga A, Levin FR, Olfson M. Development of a Cascade of Care for responding to the opioid epidemic. *Am J Drug Alcohol Abuse*. 2019; 45(1):1–10. <https://doi.org/10.1080/00952990.2018.1546862> PMID: 30675818
47. Lake S, Walsh Z, Kerr T, Cooper ZD, Buxton J, Wood E, et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal analysis. *PLoS Med*. 2019; 16(11):e1002967. <https://doi.org/10.1371/journal.pmed.1002967>
48. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Int Med*. 2014; 174(10):1668–73. <https://doi.org/10.1001/jamainternmed.2014.4005> PMID: 25154332
49. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*. 2018; 58:29–42. <https://doi.org/10.1016/j.jhealeco.2017.12.007> PMID: 29408153
50. Marshall BD, Milloy MJ, Wood E, Montaner JS, Kerr T. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: a retrospective population-based study. *Lancet*. 2011; 377(9775):1429–37. [https://doi.org/10.1016/S0140-6736\(10\)62353-7](https://doi.org/10.1016/S0140-6736(10)62353-7) PMID: 21497898
51. Caulkins JP, Pardo B, Kilmer B. Supervised consumption sites: a nuanced assessment of the causal evidence. *Addiction*. Epub 2019 Jul 16. <https://doi.org/10.1111/add.14747> PMID: 31309637
52. Kennedy MC, Hayashi K, Milloy M-J, Wood E, Kerr T. Supervised injection facility use and all-cause mortality among people who inject drugs in Vancouver, Canada: A cohort study. *PLoS Med*. 2019; 16(11):e1002964. <https://doi.org/10.1371/journal.pmed.1002964>
53. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci U S A*. 2015; 112(49):15078–83. <https://doi.org/10.1073/pnas.1518393112> PMID: 26575631
54. Pitt AL, Humphreys K, Brandeau ML. Modeling health benefits and harms of public policy responses to the US opioid epidemic. *Am J Public Health*. 2018; 108(10):1394–400. <https://doi.org/10.2105/AJPH.2018.304590> PMID: 30138057
55. Chen Q, Larochelle MR, Weaver DT, Lietz AP, Mueller PP, Mercaldo S, et al. Prevention of prescription opioid misuse and projected overdose deaths in the United States. *JAMA Netw Open*. 2019; 2(2):e187621. <https://doi.org/10.1001/jamanetworkopen.2018.7621> PMID: 30707224
56. Tsai AC, Kiang MV, Barnett ML, Beletsky L, Keyes KM, McGinty EE, et al. Stigma as a fundamental hindrance to the United States opioid overdose crisis response. *PLoS Med*. 2019; 16(11):e1002969. <https://doi.org/10.1371/journal.pmed.1002969>
57. McKetta S, Keyes KM. Heavy and binge alcohol drinking and parenting status in the United States from 2006 to 2018: An analysis of nationally representative cross-sectional surveys. *PLoS Med*. 2019; 16(11):e1002954. <https://doi.org/10.1371/journal.pmed.1002954>
58. Besbris M, Faber JW, Rich P, Sharkey P. Effect of neighborhood stigma on economic transactions. *Proc Natl Acad Sci U S A*. 2015; 112(16):4994–8. <https://doi.org/10.1073/pnas.1414139112> PMID: 25848041
59. Hasin DS, Shmulewitz D, Keyes K. Alcohol use and binge drinking among U.S. men, pregnant and non-pregnant women ages 18–44: 2002–2017. *Drug Alcohol Depend*. 2019; 205:107590. <https://doi.org/10.1016/j.drugalcdep.2019.107590> PMID: 31600616
60. Harris S, Dykxhoorn J, Hollander A-C, Dalman C, Kirkbride JB. Substance use disorders in refugee and migrant groups in Sweden: A nationwide cohort study of 1.2 million people. *PLoS Med*. 2019; 16(11):e1002944. <https://doi.org/10.1371/journal.pmed.1002944>
61. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017; 167(4):268–74. <https://doi.org/10.7326/M16-2607> PMID: 28693043

62. Fatseas M, Serre F, Alexandre JM, Debrabant R, Auriacombe M, Swendsen J. Craving and substance use among patients with alcohol, tobacco, cannabis or heroin addiction: a comparison of substance- and person-specific cues. *Addiction*. 2015; 110(6):1035–42. <https://doi.org/10.1111/add.12882> PMID: 25688760
63. Humphreys K, Blodgett JC, Wagner TH. Estimating the efficacy of Alcoholics Anonymous without self-selection bias: an instrumental variables re-analysis of randomized clinical trials. *Alcohol Clin Exp Res*. 2014; 38(11):2688–94. <https://doi.org/10.1111/acer.12557> PMID: 25421504
64. Cerdá M, Diez-Roux AV, Tchetgen ET, Gordon-Larsen P, Kiefe C. The relationship between neighborhood poverty and alcohol use: estimation by marginal structural models. *Epidemiology*. 2010; 21(4):482–9. <https://doi.org/10.1097/EDE.0b013e3181e13539> PMID: 20498603
65. Carpenter C, Dobkin C. The effect of alcohol consumption on mortality: regression discontinuity evidence from the minimum drinking age. *Am Econ J Appl Econ*. 2009; 1(1):164–82. <https://doi.org/10.1257/app.1.1.164> PMID: 20351794
66. Maclean JC, Saloner B. Substance use treatment provider behavior and healthcare reform: evidence from Massachusetts. *Health Econ*. 2018; 27(1):76–101. <https://doi.org/10.1002/hec.3484> PMID: 28224675
67. Hansen H, Lopez-Iftikhar MM, Alegria M. The economy of risk and respect: accounts by Puerto Rican sex workers of HIV risk taking. *J Sex Res*. 2002; 39(4):292–301. <https://doi.org/10.1080/00224490209552153> PMID: 12545412
68. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain Med*. 2007; 8(2):171–83. <https://doi.org/10.1111/j.1526-4637.2006.00255.x> PMID: 17305688
69. Ritter A. Studying illicit drug markets: Disciplinary contributions. *Int J Drug Policy*. 2006; 17(6):453–63