1. Mustanski B, Andrews R, Puckett JA. The effects of cumulative victimization on mental health among lesbian, gay, bisexual, and transgender adolescents and young adults. *Am J Public Health*. 2016;106(3):527-533. doi:10.2105/AJPH.2015.302976

2. Merrick MT, Ford DC, Ports KA, Guinn AS. Prevalence of adverse childhood experiences from the 2011-2014 Behavioral Risk Factor Surveillance System in 23 states. *JAMA Pediatr*. 2018;172(11):1038-1044. doi:10.1001/jamapediatrics.2018.2537

3. Crouch E, Probst JC, Radcliff E, Bennett KJ, McKinney SH. Prevalence of adverse childhood experiences (ACEs) among US children. *Child Abuse Negl*. 2019;92:209-218. doi:10.1016/j.chiabu.2019.04.010

4. Centers for Disease Control and Prevention (CDC). Self-reported frequent mental distress among adults: United States, 1993-1996. *MMWR Morb Mortal Wkly Rep*. 1998;47(16):326-331. https://www.cdc.gov/mmwr/preview/mmwrhtml/00052469.htm

5. Purewal SK, Bucci M, Wang LG, et al. Screening for adverse childhood experiences (ACEs) in an integrated pediatric care model. *Zero Three*. 2016;36(3):10-17.

6. Substance Abuse and Mental Health Services Administration. LGBTQ+ Behavioral Health Equity Center of Excellence. Published 2021. Accessed October 14, 2021. https://www.samhsa.gov/lgbtq-plus-behavioral-health-equity

Evaluation of Increases in Drug Overdose Mortality Rates in the US by Race and Ethnicity Before and During the COVID-19 Pandemic

Drug overdose mortality rates have increased sharply in the US since the COVID-19 pandemic began in 2020.[1] Since 2015, overdose deaths have been rising most rapidly among Black and Hispanic and Latino communities.[2] The pandemic has since disproportionately worsened a wide range of health, social, and economic outcomes among racial and ethnic minoritized communities. Careful attention to examining these trends by race and ethnicity is therefore warranted. Here we evaluate increases in drug overdose mortality rates by race and ethnicity before and during the COVID-19 pandemic.

Supplemental content

Methods | This cross-sectional study used anonymized publicly available data and was therefore deemed exempt from review by the University of California, Los Angeles Institutional Review Board, and informed consent was waived. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We used data from the Centers for Disease Control and Prevention WONDER (Wide-Ranging Online Data for Epidemiologic Research) platform and the National Center for Health Statistics (NCHS) to calculate drug overdose death rates per 100 000 population by race and ethnicity for 1999 to 2020 (eMethods in the Supplement).[3] Drug overdose deaths were defined using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes for underlying cause of death, including unintentional, suicide, homicide, or undetermined intent (X40-44, X60-64, X85, or Y10-14, respectively). Race and ethnicity were used as defined in the WONDER and NCHS databases. Racial and ethnic groups were defined first by ethnicity (Hispanic or Latino) and subsequently by race (non-Hispanic American Indian or Alaska Native, non-Hispanic Black, and non-Hispanic White). Statistical analyses were conducted using R software version 4.0.3 (R Project for Statistical Computing).

Results | Overdose death rates per 100 000 among Black individuals increased from 24.7 in 2019 to 36.8 in 2020, which was 16.3% higher than that for White individuals (31.6) in 2020 (**Figure**). Thus, the 2020 overdose mortality rate among Black individuals was higher than that among White individuals for the first time since 1999. This is a reversal of the overdose mortality gap among Black and White individuals noted in 2010, when the rate per 100 000 among White individuals (15.8) was double (100.1% higher) that seen among Black individuals (7.9). These shifts reflect that Black communities have experienced higher annual percentage increases in overdose deaths compared with their White counterparts each year since 2012. In 2020, Black individuals had the largest percentage increase in overdose mortality (48.8%) compared with White individuals (26.3%).

The results also showed that American Indian or Alaska Native individuals experienced the highest rate of overdose mortality in 2020 (41.4 per 100 000), which was 30.8% higher than that for White individuals. Between 1999 and 2017, overdose mortality rates among American Indian or Alaska Native individuals were similar to those experienced by White individuals. Rates per 100 000 among American Indian or Alaska Native individuals first became disproportionately higher in 2019 (28.9) compared with White individuals (25.0).

Drug overdose rates among Hispanic or Latino individuals remained the lowest among the groups assessed throughout the study period (17.3 per 100 000 in 2020). However, Hispanic or Latino individuals also experienced a large percentage increase in drug overdose rates in 2020 (40.1%).

For all racial and ethnic groups assessed, the relative increases in drug overdose mortality rates observed in 2020 were higher than any prior increase between 1999 and 2019.

Discussion | In this cross-sectional study, we observed that Black individuals had the largest percentage increase in overdose mortality rates in 2020, overtaking the rate among White individuals for the first time since 1999, and American Indian or Alaska Native individuals experienced the highest rate of overdose mortality in 2020 of any group observed.

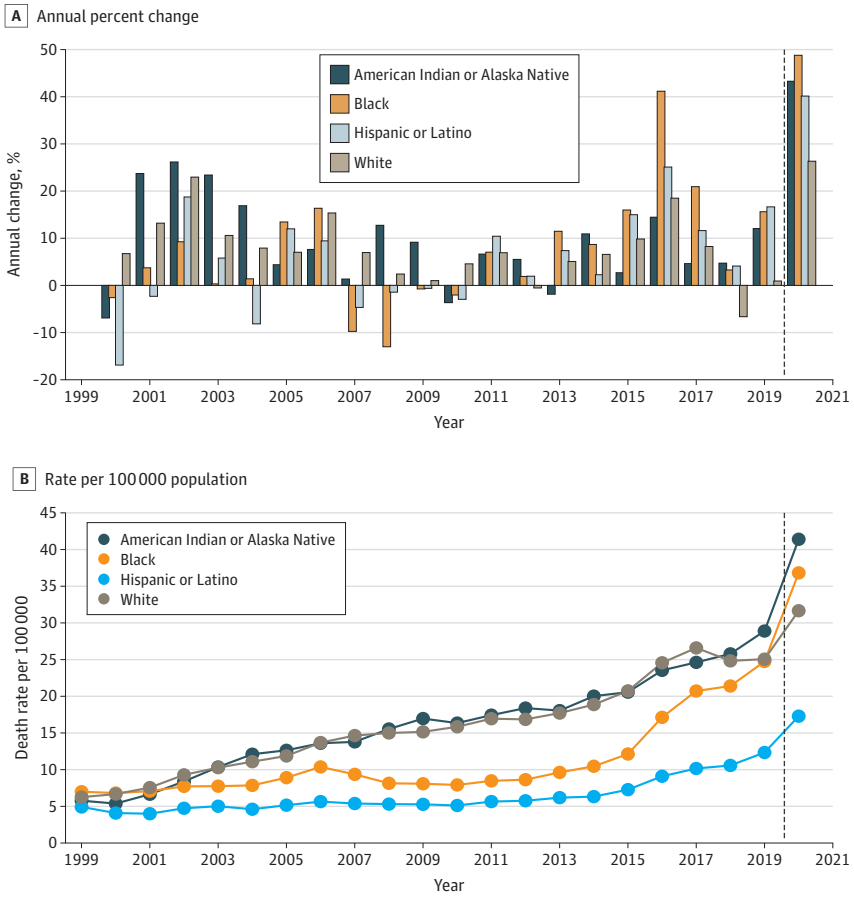
Recent studies suggest that an increasingly toxic illicit drug supply, characterized by polysubstance use of potent synthetic opioids and benzodiazepines as well as high-purity methamphetamine, is contributing to worsening of the US overdose crisis.[1,4] The high—and unpredictably variable—potency of the illicit drug supply may be disproportionately harming racial and ethnic minoritized communities, with deep-seated inequalities in living conditions (including stable housing and employment, policing and arrests, preventive care, harm reduction, telehealth, medications for opioid use disorder, and naloxone access) likely playing a role.[5,6]

The increasing toxicity of the drug supply has been associated with the increased lethality of recent incarceration as a risk factor for overdose mortality,[4] which may disproportionately affect American Indian or Alaska Native, Black, and Hispanic or Latino individuals as a result of structural racism in the criminal justice system. Recently incarcerated individuals have been consistently observed to have reduced opioid tolerance and less knowledge of shifts in drug potency.[4]

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Figure. Drug Overdose Mortality Rates by Race and Ethnicity, 1999 to 2020



A, Year-to-year percent change. B, Drug overdose mortality per 100 000 population. The vertical dashed lines separate the COVID-19 pandemic period from prior trends.

A limitation of this study is that records from 2020 were provisional and may underestimate final mortality rates. Additional methodologic considerations are discussed in the Supplement.

Drug overdose mortality is increasingly becoming a racial justice issue in the US. Our results suggest that drug overdose mortality has been exacerbated during the COVID-19 pandemic. Providing individuals with a safer supply of drugs, closing gaps in health care access (eg, harm reduction services and medications for opioid use disorder), ending routine incarceration of individuals with substance use disorders, and addressing the social conditions of people who use drugs represent urgently needed, evidence-based strategies that can be used to reduce increasing inequalities in overdose rates.

Joseph R. Friedman, MPH
Helena Hansen, MD, PhD

Author Affiliations: Medical Scientist Training Program, University of California, Los Angeles (Friedman); Center for Social Medicine and Humanities, University of California, Los Angeles (Friedman, Hansen).

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Corresponding Author: Joseph R. Friedman, MPH, Medical Scientist Training Program, University of California, Los Angeles, B7-435, UCLA Semel Institute, PO Box 951759, Los Angeles, CA 90095 (joseph.robert.friedman@gmail.com).

Author Contributions: Mr Friedman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Friedman.
Drafting of the manuscript: Friedman.
Critical revision of the manuscript for important intellectual content: Hansen.
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1. Friedman J, Akre S. COVID-19 and the drug overdose crisis: uncovering the deadliest months in the United States, January–July 2020. *Am J Public Health*. 2021;111(7):1284-1291. doi:10.2105/AJPH.2021.306256

2. Hoopsick RA, Homish GG, Leonard KE. Differences in opioid overdose mortality rates among middle-aged adults by race/ethnicity and sex, 1999-2018. *Public Health Rep*. 2021;136(2):192-200. doi:10.1177/0033354920968806

3. National Center for Health Statistics. Provisional drug overdose deaths by quarter and demographics—2019 to 2020. Accessed October 23, 2021. https://www.cdc.gov/nchs/data/health_policy/Provisional-Drug-Overdose-Deaths-by-Quarter-and-Demographic-Characteristics-2019-to-2020.pdf

4. Brinkley-Rubinstein L, Macmadu A, Marshall BDL, et al. Risk of fentanyl-involved overdose among those with past year incarceration: findings

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from a recent outbreak in 2014 and 2015. *Drug Alcohol Depend*. 2018;185:189-191. doi:10.1016/j.drugalcdep.2017.12.014

5. Lagisetty PA, Ross R, Bohnert A, Clay M, Maust DT. Buprenorphine treatment divide by race/ethnicity and payment. *JAMA Psychiatry*. 2019;76(9):979-981. doi:10.1001/jamapsychiatry.2019.0876

6. Park JN, Rouhani S, Beletsky L, Vincent L, Saloner B, Sherman SG. Situating the continuum of overdose risk in the social determinants of health: a new conceptual framework. *Milbank Q*. 2020;98(3):700-746. doi:10.1111/1468-0009.12470

COMMENT & RESPONSE

Do Not Rule Out Double-blind Placebo Run-in Periods for Randomized Clinical Trials

To the Editor In their systematic review and meta-analysis, Scott and colleagues[1] concluded that the practice of placebo run-in (PRI) periods in randomized clinical trials (RCTs) of antidepressants should be discontinued. They examined 174 studies of major depressive disorder that used single-blind PRI designs and found less robust within-group changes in both the experimental drug and placebo groups and equivalence in the drug-placebo outcome differences compared with studies that did not use PRI designs.

The systematic review and meta-analysis offers contemporary documentation that single-blind PRI designs do not effectively mitigate high placebo responses.[1,2] However, in summarily dismissing all PRI designs, the authors did not mention the potential utility of double-blind PRI designs. This omission is understandable, given that few studies have used this strategy.

Scott and colleagues[1] acknowledged that the success of blinding during single-blind PRI periods and whether participants are truly masked is not known. It is known that site-based clinicians are not blinded to the enrollment criteria in single-blind PRI designs and therefore are not unbiased assessors.[2] In contrast, in double-blind PRI designs, neither the potential study participant nor the site clinician knows about the existence of the PRI period and when the true randomization visit will occur.[2-4]

Double-blind PRI periods generate higher rates of placebo response than single-blind PRI. For instance, Faries and colleagues[3] reported that 28% of individuals with major depressive disorder were responsive to placebo during a double-blind PRI compared with fewer than 10% from 2 single-blind PRI studies they conducted. In another study, Targum and colleagues[4] noted that 85% of individuals who were responsive to placebo during a 2-week double-blind PRI sustained these responses after 6 weeks of additional blinded placebo treatment, and 68% of these individuals were in remission. If sustained, early placebo responses may impede signal detection.

RCTs attempt to ascertain the true drug effect of an experimental intervention vs placebo. Scott and colleagues[1] noted that single-blind PRI designs yield less robust symptomatic changes regardless of treatment assignment owing to the mitigation of additive placebo and nonspecific effects. A lower overall placebo response achieved from more reliable measurements reduces the sample size necessary to achieve sufficient power for signal detection.[2,5] Hence, rather than add expense, a well-designed double-blind PRI design may be cost-effective.

Although it is true that PRI periods are deceptive, it is also true that all double-blind placebo-controlled studies are inherently deceptive experiments. In sum, the potential utility of a double-blind PRI design ought not be dismissed without further consideration.

Steven D. Targum, MD

Author Affiliation: Signant Health, Boston, Massachusetts.

Corresponding Author: Steven D. Targum, MD, Signant Health, 505 Tremont St, Ste 907, Boston, MA 02116 (sdtargum@yahoo.com).

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1. Scott AJ, Sharpe L, Quinn V, Colagiuri B. Association of single-blind placebo run-in periods with the placebo response in randomized clinical trials of antidepressants: a systematic review and meta-analysis. *JAMA Psychiatry*. 2022;79(1):42-49. doi:10.1001/jamapsychiatry.2021.3204

2. Fava M, Evins AE, Dorer DJ, Schoenfeld DA. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3):115-127. doi:10.1159/000069738

3. Faries DE, Heiligenstein JH, Tollefson GD, Potter WZ. The double-blind variable placebo lead-in period: results from two antidepressant clinical trials. *J Clin Psychopharmacol*. 2001;21(6):561-568. doi:10.1097/00004714-200112000-00004

4. Targum SD, Cameron BR, Ferreira L, MacDonald ID. Early score fluctuation and placebo response in a study of major depressive disorder. *J Psychiatr Res*. 2020;121:118-125. doi:10.1016/j.jpsychires.2019.11.014

5. Perkins DO, Wyatt RJ, Bartko JJ. Penny-wise and pound-foolish: the impact of measurement error on sample size requirements in clinical trials. *Biol Psychiatry*. 2000;47(8):762-766. doi:10.1016/S0006-3223(00)00837-4

In Reply We thank Targum for his interest in our systematic review and meta-analysis[1] on placebo run-in periods (PRI) in antidepressant trials for depression. We identified 348 double-blind randomized clinical trials (RCTs), 174 of which used a single-blind PRI. We found no difference in the drug-placebo difference between trials with and without a PRI. Targum does not question this finding, but argues that it may not extend to double-blind PRIs. As Targum notes, few double-blind PRI trials exist. None were identified in our systematic review and meta-analysis. Clearly, there is limited evidence to judge whether double-blind PRIs influence the drug-placebo difference. However, there are reasons to suspect such influence is unlikely. Even if small differences emerged, double-blind PRIs would not likely be problematic.

Targum cites an article[2] reporting on 4 RCTs—2 using single-blind PRIs and 2 using double-blind PRIs.[2] In that article, Faires et al[2] found a much higher rate of response to placebo in the double-blind PRI trials (28% and 26%) than in the single-blind PRI trials (4.2% and 16.4%). Further, in the first double-blind PRI trial, the drug-placebo difference was significant when excluding individuals responsive to placebo but not when including individuals responsive to placebo. While these findings are interesting, there are several problems with generalizing from this study. First, as Targum notes, the drug-placebo difference was not statistically significant in the second double-blind PRI trial even when excluding individuals responsive to placebo. Second, the size of the drug-placebo

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