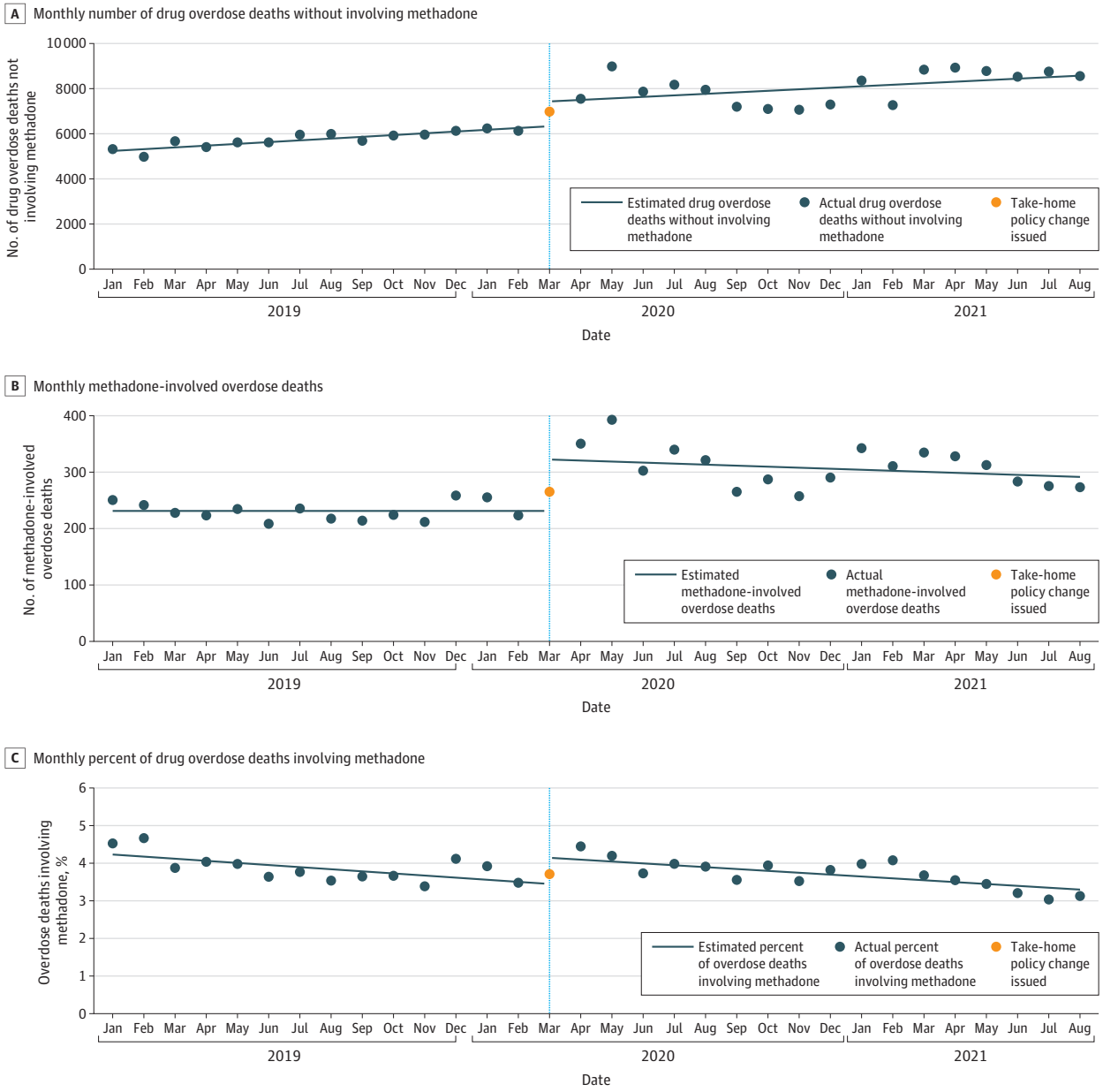
RESEARCH LETTER

Methadone-Involved Overdose Deaths in the US Before and After Federal Policy Changes Expanding Take-Home Methadone Doses From Opioid Treatment Programs

On March 16, 2020, to facilitate access to methadone treatment from opioid treatment programs (OTPs) during the COVID-19 pandemic, the Substance Abuse and Mental Health Services Administration allowed states to request blanket exceptions to provide up to 28 and 14 days of take-home methadone for stable and less stable patients, respectively; this signaled a shift in practice because most patients historically receive methadone daily from OTPs.[1]

Figure. Monthly Overdose Deaths With and Without Methadone, United States, January 2019 to August 2021



Opioid treatment program methadone take-home policy was released by the Substance Abuse and Mental Health Services Administration on March 16, 2020.
Source: National Vital Statistics System, Multiple-Cause-of-Death Final 2019-2020 Data and Provisional 2021 Data.

Table. Interrupted Time Series Analysis Estimates for Monthly Overdose Deaths With and Without Methadone, United States, January 2019 to August 2021

Factor	Estimate (95% CI)	*P* value
Overdose deaths without involving methadone		
Monthly No. of overdose deaths in January 2019	5227.2 (4993.92 to 5460.48)	<.001
Monthly trend (slope) prior to policy change in March 2020	78.12 (53.69 to 102.55)	<.001
Change in No. of overdose deaths at time of policy change in March 2020	1078.27 (410.08 to 1746.46)	.003
Monthly trend (slope) after policy change in March 2020 (compared with prior to policy change)	−9.05 (−67.98 to 49.88)	.76
Monthly change in No. of overdose deaths after March 2020	69.07 (15.45 to 122.70)	.01
Methadone-involved overdose deaths		
Monthly No. of overdose deaths in January 2019	230.66 (216.13 to 245.18)	<.001
Monthly trend (slope) prior to policy change in March 2020	−0.12 (−2.54 to 2.29)	.92
Change in No. of overdose deaths at time of policy change in March 2020	94.12 (45.38 to 142.86)	<.001
Monthly trend (slope) after policy change in March 2020 (compared with prior to policy change)	−1.79 (−6.11 to 2.54)	.41
Monthly change in No. of overdose deaths after March 2020	−1.91 (−5.50 to 1.68)	.29
Percent of overdose deaths involving methadone		
Monthly percent of overdose deaths involving methadone in January 2019	4.23 (3.90 to 4.56)	<.001
Monthly trend (slope) prior to policy change in March 2020	−0.06 (−0.10 to −0.01)	.02
Change in percent of overdose deaths involving methadone at time of policy change in March 2020	0.69 (0.22 to 1.15)	.006
Monthly trend (slope) after policy change in March 2020 (compared with prior to policy change)	0.01 (−0.05 to 0.06)	.82
Monthly change in percent of overdose deaths involving methadone after March 2020	−0.05 (−0.08 to −0.02)	.001

Prior research indicates most methadone-involved overdose deaths are due to methadone used for pain rather than opioid use disorder treatment.[2] It is unknown whether methadone-involved overdose deaths increased owing to expanded OTP take-home policies.

Methods | US Centers for Disease Control and Prevention National Vital Statistics System multiple cause of death 2019-2020 final and 2021 provisional data were used. Drug overdose deaths were those assigned an underlying cause of death (*ICD-10* codes X40-X44, X60-X64, X85, and Y10-Y14; methadone-involved deaths had *ICD-10* code T40.3). Overdose deaths could involve multiple drugs.

Monthly drug overdose deaths without involving methadone and methadone-involved and percentages of overdose deaths involving methadone during January 2019 to August 2021 were calculated. Interrupted time series analyses (ITSA) assessed changes in outcomes before/after the March 2020 methadone take-home policy. This study was exempt from institution review board review by regulation. Stata version 16 (StataCorp) ITSA program was used for analyses. *P* values less than .05 (2-sided) were considered statistically significant.

Results | ITSA-estimated monthly overdose deaths without involving methadone increased by 78.12 (95% CI, 53.69-102.55; *P* < .001) deaths per month before March 2020, by 1078.27 (95% CI, 410.08-1746.46; *P* = .003) deaths in March 2020, and by 69.07 (95% CI, 15.45-122.70; *P* = .01) deaths per month after March 2020 (**Figure** and **Table**). Trend slopes were similar before and after March 2020 (−9.05 [95% CI, −67.98 to 49.88]; *P* = .76).

Before March 2020, ITSA-estimated methadone-involved overdose deaths were stable (−0.12 [95% CI, −2.54 to 2.29; *P* = .92) (Figure and Table). Consistent with the increase in overdose deaths without involving methadone, methadone-involved overdose deaths increased by 94.12 (95% CI, 45.38-142.86; *P* < .001) deaths in March 2020. Monthly methadone-involved overdose deaths remained stable after March 2020 (−1.91 [95% CI, −5.50 to 1.68]; *P* = .29). Trend slopes were similar before and after March 2020 (−1.79 [95% CI, −6.11 to 2.54]; *P* = .41).

ITSA-estimated percentages of overdose deaths involving methadone declined 0.06% (95% CI, −0.10% to 0.01%; *P* = .02) per month before March 2020, increased by 0.69% (95% CI, 0.22%-1.15%; *P* = .006) in March 2020, and declined 0.05% per month (95% CI, −0.08% to 0.02%; *P* = .001) after March 2020. Trend slopes were similar before and after March 2020 (0.01% [95% CI, −0.05% to 0.06%]; *P* = .82).

Discussion | Findings provide insights about methadone-involved overdose deaths during COVID-19. In March 2020, overdose deaths both with and without methadone increased. After March 2020, overdose deaths not involving methadone continued to increase approximately 69 deaths per month, whereas methadone-involved overdose deaths remained stable. The percentage of overdose deaths involving methadone declined at similar rates, approximately 0.05% to 0.06%, before and after the take-home policy change, with 4.5% of overdose deaths involving methadone in January 2019 and declining to 3.2% by August 2021. These findings suggest the modest increase in methadone-involved overdose deaths in March 2020 was associated with the spike in overall drug overdose deaths driven by illicitly made fentanyl in the early months of the COVID-19 pandemic[3] rather than associated with OTP take-home policy changes.

This study has limitations. Approximately 5% of death certificates did not list specific drugs involved in the

overdose. Provisional data for 2021 may minimally underestimate overdose deaths owing to delayed reporting. OTP take-home policy changes occurred in the context of other policy changes and secular trends that could influence treatment and harms for people with opioid use disorder.

Coupled with research demonstrating improved patient satisfaction, treatment access, and engagement from these policies,[1,4-6] these findings can inform decisions about permanently expanding take-home methadone.

Christopher M. Jones, PharmD, DrPH
Wilson M. Compton, MD, MPE
Beth Han, MD, PhD, MPH
Grant Baldwin, PhD, MPH
Nora D. Volkow, MD

Author Affiliations: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia (Jones, Baldwin); National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland (Compton, Han, Volkow).

Corresponding Author: Christopher M. Jones, PharmD, DrPH, National Center for Injury Prevention and Control, 4770 Buford Highway NE, Atlanta, GA 30341 (fjr0@cdc.gov).

Accepted for Publication: May 16, 2022.

Published Online: July 13, 2022. doi:10.1001/jamapsychiatry.2022.1776

Author Contributions: Dr Jones 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: Jones, Compton, Volkow.
Acquisition, analysis, or interpretation of data: Jones, Compton, Han, Baldwin.
Drafting of the manuscript: Jones, Baldwin.
Critical revision of the manuscript for important intellectual content: Compton, Han, Baldwin, Volkow.
Statistical analysis: Jones.
Administrative, technical, or material support: Jones, Volkow.
Supervision: Volkow.

Conflict of Interest Disclosures: Dr Compton reported long-term stock holdings from General Electric Co, 3M Companies, and Pfizer Inc outside the submitted work. No other disclosures were reported.

Funding/Support: This study was sponsored by the US Centers for Disease Control and Prevention and the National Institutes of Health.

Role of the Funder/Sponsor: The sponsors supported the authors who were responsible for preparation, review, and approval of the manuscript and the decision to submit the manuscript for publication. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The sponsors reviewed and approved the manuscript.

Disclaimers: The findings and conclusions of this study are those of the authors and do not necessarily reflect the views of the National Institute on Drug Abuse of the National Institutes of Health, the Centers for Disease Control and Prevention, and the US Department of Health and Human Services.

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COMMENT & RESPONSE

Cerebrovascular Disease and Sleep-Disordered Breathing Need to Be Accounted for in Cognitive Impairment Following COVID-19

To the Editor Nersesjan et al[1] report on cognitive and neuropsychiatric outcomes in COVID-19 survivors vs control individuals. Their study is a robust foray into the neurocognitive sequalae of COVID-19 that provides both follow-up and control data for comparison and context. However, there are 2 critical caveats that may impair generalizability: sleep-disordered breathing and cerebrovascular disease as drivers of cognitive impairment in both patients with COVID-19 and control individuals without COVID-19. The former caveat stems from screening that was not included in the authors measurements; the latter is a direct generalization of their results and may also imply other confounders, such as medication status.

A systematic review and meta-analysis in *JAMA Neurology*[2] pooling 4 million participants denotes a 26% increase in risk of developing cognitive impairment and specifically executive dysfunction associated with sleep-disordered breathing compared with control individuals. Notably, dysexecutive syndromes also appear to manifest secondary to COVID-19, as another report indicates.[3] Aside from its prevalence in the general population (ie, estimated as high as 17% of US adults[4]), sleep-disordered breathing and comorbidities, such as hypertension and cardiovascular disease, exhibit a bidirectional association.[2,4] These comorbidities are among the control variables selected by Nersesjan et al,[1] yet the presence of sleep-disordered breathing itself is not accounted for by the authors via formal measures. Potential sleep disturbances—only a single item—probes sleep disturbances in the authors' sample but, defined as such, this variable relies on patients being aware of said sleep disturbance; it therefore cannot account for unconscious arousals that would otherwise disturb sleep architecture without being identified by the patient.

Aside from sleep-disordered breathing as a variable that has not been accounted for, the authors' results from the limited number of participants who underwent magnetic resonance imaging (ie, 5 patients with COVID-19 and 4 control individuals) indicate that 4 of 5 patients with COVID-19 exhibited cerebrovascular disease and hydrocephalus that could, on their own, account for secondary cognitive impairment.[5] Furthermore, despite including participants without COVID-19 with small vessel disease and stroke risk factors (ie, hypertension and cardiovascular disease), there was little evidence of structural brain damage in that group. This could be because of low sample size, the protective effect of agents already administered for such disease (eg, statins, antiplatelets, or anticoagulants), or both. It also presents a critical limitation for the generalizability of the