Research Paper

Fentanyl shock: The changing geography of overdose in the United States

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ABSTRACT

Background: Rapid increases in drug overdose deaths in the United States since 2014 have been highly regionally stratified, with the largest increases occurring in the eastern and northeastern states. By contrast, many western states saw overdose deaths plateau. This paper shows how the differential influx of fentanyl and fentanyl analogues in the drug supply has reshaped the geography and demography of the overdose crisis in the United States.

Methods: Using all state lab drug seizures obtained by Freedom of Information Act request, I analyze the regionally distinctive presence of fentanyl in the US drug supply with descriptive plots and statistical models. Main analyses explore state-year overdose trends using two-way fixed effects ordinary least squares (OLS) regression and two-stage least squares regression (2SLS) instrumenting for fentanyl exposure with state-longitude times a linear trend.

Results: First, fentanyl exposure is highly correlated with geography and only weakly explained by overdose rates prior to 2014. States in the east (higher degrees longitude) are much more heavily affected. Second, fentanyl exposure exhibits a statistically significant and important effect on overdose mortality, with model-predicted deaths broadly consistent with official death statistics. Third, fentanyl exposure explains most of the variation in increased overdose mortality between 2011 and 2017. Consequently, the epicenter of the overdose crisis shifted towards the eastern United States over these years.

Conclusion: These findings shed light on the "third-wave" of the overdose epidemic, characterized by rapid and geographically disparate changes in drug supply that heighten the risk of overdose. Above all, they underscore the urgency of adopting evidence-based policies to combat addiction in light of the rapidly changing drug environment.

Introduction

Life expectancy has declined in the United States as a "triple-epidemic" of prescription opioids, heroin, and fentanyl batters communities across the country (Ciccarone, 2019). Overdose deaths have climbed from 17,000 in 2000 to 38,000 in 2010 to more than 70,000 in 2017. But these differences were not equally distributed across the United States. Between 2014–2015 and 2015–2016, almost all states east of the Mississippi River experienced an increase in opioid overdose fatalities, while almost all states west of the Mississippi River did not experience an increase in overdose fatalities (CDC, 2018). There can be no doubt that social and economic determinants predispose individuals to addiction and overdose (Dasgupta, Beletsky, & Ciccarone, 2018; McLean, 2016; National Academies of Sciences Engineering & Medicine, 2017; Zoorob & Salemi, 2017). But the abrupt and geographically segmented explosion of overdose deaths during these years of economic recovery is not likely attributable to social determinants. Instead, changes in drug supply may play a primary role.

The drug environment – the availability, price, purity, and predictability of the drug supply – shapes the risks facing people who use drugs (Ruhm, 2019). Since 2013, the influx of synthetic opioids such as fentanyl and fentanyl analogs into the domestic heroin supply has reshaped the overdose epidemic in several ways. First, these more potent synthetic opioids increase the case-rate mortality risk for drug users (Ciccarone, 2017; Gladden, 2016). Between 2015 and 2016, the rate of overdose deaths attributed to synthetic opioids doubled, from 3.1 to 6.2 deaths per 100,000, eclipsing death rates attributed to heroin poisonings, which increased from 4.1 to 4.9 per 100,000 over the same period (Hedegaard, Warner, & Arialdi, 2017). Second, changes in the supply of drugs have altered the demographics of overdose mortality, with synthetic opioid deaths more prevalent in urban areas, nonwhites, and among Americans in their 20 s and 30 s (Gladden, 2016; Hedegaard et al., 2017). Consequently, the gap between whites and non-whites in the rate of drug poisoning mortality has narrowed, as rates of become more stable among whites while increasing substantially among Blacks and Hispanics (Seth, Scholl, Rudd, & Bacon, 2018), a trend that is most

obvious in high-fentanyl states (MA DPH, 2018). In light of the important roles played by regional and demographic context, some scholars conclude that the "opioid pill, heroin and fentanyl crises are intertwined yet increasingly have drivers and outcomes that support examining them as distinct" (Unick & Ciccarone, 2017). That is the approach taken by this paper, which examines the distinct role played by fentanyl and other synthetic opioids that have become an important fixture of the drug supply in the United States and elsewhere.

Leveraging unique data on US state-level fentanyl exposure obtained by a Freedom of Information Act request, I show that geographically segmented changes in the drug supply explain most of the rise in poisonings since 2013. These changes in drug supply overlap both with historical drug markets in the United States and recent increases in overdose mortality. These results have important implications for policymakers. First, it suggests that the drug environment is a critical component of the overdose epidemic (Ruhm, 2019), highlighting the need for uniform, timely access and monitoring of drug supply. Second, it underscores the urgency of states in which overdose deaths have plateaued to adopt robust regimes for managing addiction – such as removing barriers to medication assisted treatment and facilitating naloxone access – to prevent increases in overdose akin to those seen in other states.

Methods

Testing results data

All test results for drug seizures between 2011 and 2016 recorded in the National Forensic Laboratory Information System were obtained by a Freedom of Information Act request, which was delivered via CD-ROM containing a Microsoft Access Database. States do not report data to the NFLIS in a uniform fashion. Twenty-two states report test-level data, with each row representing the test results of a drug. The remaining states, District of Columbia, and Puerto Rico report data, by state and year, for each drug. For the purposes of this paper, I count any test result which includes in any amount fentanyl or its analogues (acetyl-fentanyl, carfentanyl, etc) or the synthetic opioid U-47700 (a full list of the terms used to measure fentanyl exposure is included in the Appendix). I then aggregate the number of fentanyl tests for each state and year. To create a measure that is comparable across states of highly variable populations in regression analyses, I divide annual seizures by the state population in that year and take the natural logarithm (plus 1 to avoid an undefined logarithm of zero):

$$Fentanyl_{ij} = \log(\frac{S_{ij}}{P_{ij}} + 1)$$

where S_{ij} represents the number of tests containing fentanyl in state i, year j, and P_{ij} represents state-annual populations. This data allows me to quantify state-specific increases in the presence of fentanyl and other synthetic-opioids.

Mortality data

Age-adjusted mortality data for drug poisoning deaths for every state and year during the 2011–2017 period were obtained from the National Center for Health Statistics (NCHS), part of the US federal Centers for Disease Control and Prevention. Though fentanyl is a synthetic opioid, overdose mortality rates for all drug-poisonings are used as the main response variable due to demonstrated heterogeneity across states in categorizing opioid overdose deaths on death certificates (Ruhm, 2018).

Statistical analyses

To quantify the average treatment effect of fentanyl exposure on overdose, I estimate two statistical models of state-year age-adjusted overdose mortality as a function of fentanyl exposure. Each model includes two- way fixed effects for state and year, which, respectively, absorb time-invariant unobserved characteristics at the state-level and changes common to all states (Gunasekara, Richardson, Carter, & Blakely, 2013). Standard errors are two-way clustered by state and year and population weights are included. Model 1 (specified below) is thus an ordinary least squares equation with fixed effects for state α_i and year η_j:

$$Overdose_{ij} = \alpha_i + \eta_j + \beta_1 Fentanyl_{ij} + \varepsilon_{ij}$$

A remaining potential threat to inference is time-varying changes that vary across states. The models are insulated somewhat against such changes because state-specific changes in demographic correlates of overdose, such as race and ethnicity, educational attainment, and social capital are unlikely to change substantially between 2011 and 2017 (the drug environment, by contrast, has changed rapidly during this period). For additional analytic leverage (Rassen, Alan Brookhart, Glynn, Mittleman, & Schneeweiss, 2009), Model 2 employs an instrumental variables strategy to estimate the causal effect of fentanyl exposure. In the first stage, the state's centroid longitude multiplied by a linear time trend is used to instrument for fentanyl exposure. In other words, I use the variation in fentanyl exposure explained by a state's geographic orientation. This is a good instrument because a state's position on the earth's surface is plausibly uncorrelated with any other rapidly-changing determinants of overdose but is highly correlated with fentanyl exposure. Because this measure varies over time, it is not absorbed by the state and fixed effects. Model 2, estimated via two-stage least squares, is specified below:

$$Fent\hat{a}nyl_{ij} = \alpha_i + \eta_j + \beta_1 (Longitude_i \cdot Year_j) + \varepsilon_{ij}$$
$$Overdose_{ij} = \alpha_i + \eta_j + \beta_2 Fent\hat{a}nyl_{ij} + \varepsilon_{ij}$$

Results

Geography of fentanyl

Fentanyl and its analogues rapidly entered the US drug supply in the early 2010s. The number of forensic tests reporting fentanyl has increased enormously in recent years, from about 400 in 2011 to 35,000 in 2016 to 80,000 in 2017 (Appendix Fig. A1). But this increase has been highly unequal across the country, with some regions experiencing marked increases while others relatively unscathed, as illustrated in Fig. 1, which shows the annual number of test results containing fentanyl, per 1000 residents, in all states during this period, with states arranged to reflect roughly their spatial arrangement in the United States. This figure highlights the drastically unequal presence of fentanyl across American states. Seizures are much more common in the northeast of the country, sweeping from New England through Pennsylvania down to Illinois. Ohio, New Hampshire, and Massachusetts lead the country with the highest levels of fentanyl exposure. In states outside of this region, there were substantially fewer fentanyl seizures detected. Given the high prevalence of synthetic-opioids like fentanyl in the drug supply of British Columbia (Irvine et al., 2018), the most western province of Canada, the absence of significant fentanyl in adjacent parts of the United States, such as Washington state, is striking, suggesting that illicit drug suppliers in western Canada differ from those in the Pacific Northwest of the United States.

Interestingly, overdose mortality prior to the fentanyl shock does not explain a large amount of the variability in subsequent fentanyl exposure. However, geography appears to be highly predictive of the fentanyl shock. In bivariate regressions, the degree Longitude (where more positive values indicate an eastern location on the earth's surface) of a state's central point explains about 55% of the state-level variation in the intensity of fentanyl exposure in 2017 ($R^2 = 0.55$), up

Drug Seizures with Fentanyl (2011-2017)
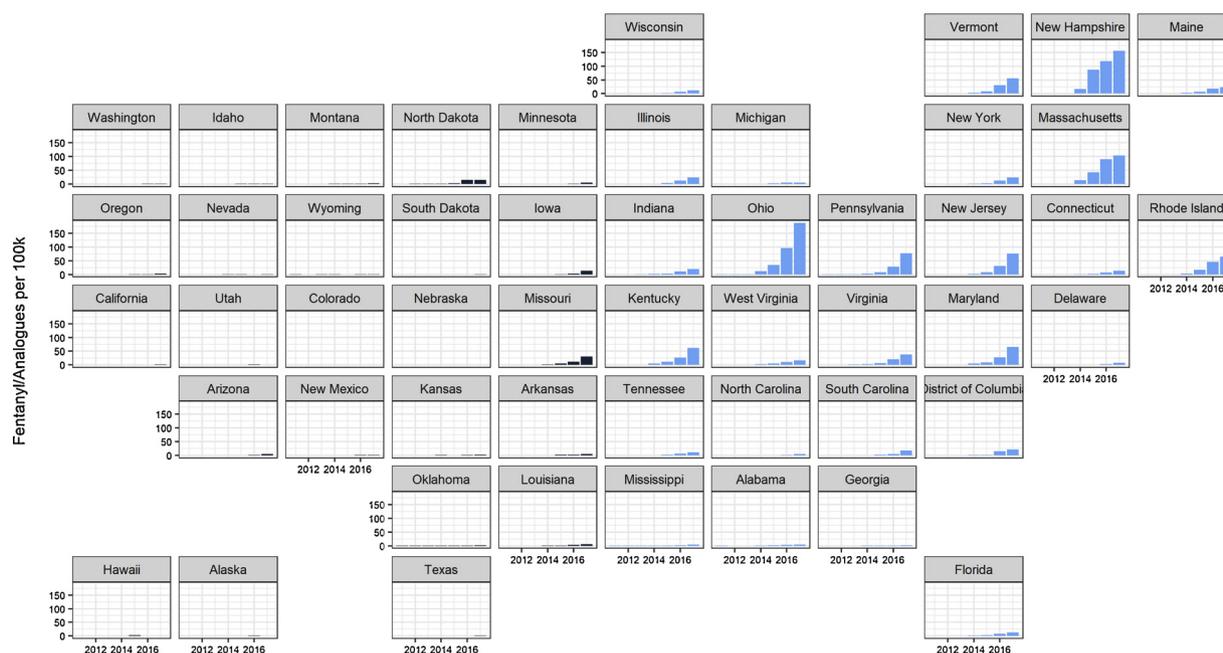
Source: National Forensic Laboratory Information System (NFLIS)

Fig. 1. States are arranged roughly according to their geography, with bar graphs for each state showing annual test results containing fentanyl, per 1000 residents (Top). States east of the Mississippi River are colored light blue, while states west of the Mississippi River are colored dark blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Statistical Models of Fentanyl Exposure.

	Dependent variable: Fentanyl Tests per 100,000 (log)				
	(2013)	(2014)	(2015)	(2016)	(2017)
Longitude	0.002	0.019***	0.030***	0.044***	0.053***
	(0.002)	(0.004)	(0.006)	(0.006)	(0.007)
Latitude	0.008	0.025*	0.017	0.049**	0.037*
	(0.005)	(0.013)	(0.020)	(0.020)	(0.021)
Overdose Mortality (2013)	− 0.003	0.034**	0.035	0.033	0.028
	(0.006)	(0.014)	(0.022)	(0.022)	(0.023)
Constant	0.241	0.985	2.853**	3.498***	5.338***
	(0.290)	(0.679)	(1.070)	(1.084)	(1.130)
Observations	51	51	51	51	51
R^2	0.076	0.406	0.366	0.536	0.590
F Statistic (df = 3; 47)	1.286	10.706***	9.029***	18.110***	22.591***

*$p < 0.1$.
**$p < 0.05$.
***$p < 0.01$.

substantially from 2014 ($R^2 = 0.273$). Prior to 2014, there was little evidence of a significant geographical component to fentanyl reporting (2013: $R^2 = 0.023$; 2012: $R^2 = 0.006$). Degrees Latitude (north/south distance) does not explain much variation in fentanyl exposure, with less than 1% of the variation in fentanyl exposure ($R^2 < 0.01$) for any year explained by Latitude. Omitting Alaska and Hawaii (geographic outliers) yields the same conclusions. As Table 1 indicates, the explanatory power of degrees Longitude has grown over time, while prior levels of overdose mortality and degree latitude remain uninformative of fentanyl exposure. Appendix Fig. A2 shows the increasing geographic structure to fentanyl exposure since 2014 – but not heroin exposure, which is not explained well by degree longitude.

An increasingly synthetic-opioid crisis

The geography of fentanyl seizures closely matches that of recent skyrocketing overdose death rates, as Fig. 2 shows. In states like Ohio, Pennsylvania, Maryland, and Massachusetts – all of which are in the Northeastern part of the United States – overdose deaths increased exponentially since 2014, while in the states in the west of the country, deaths mostly plateaued. On average, states east of the Mississippi River (colored light blue) tend to have greater fentanyl exposure and much steeper increases in overdose death than those west of the Mississippi River (dark blue).

Fig. 3 plots fentanyl exposure and overdose mortality for each year between 2012 and 2017, illustrating the massive increases in overdose mortality as a function of fentanyl exposure after the fentanyl shock occurred in 2014. The intensity of the fentanyl shock is highly informative of whether a state experienced a substantial increase in overdoses since 2011. In 2011, when overdose deaths had already reached "crisis-levels" exceeding car crash fatalities, New Mexico and Nevada experienced much higher rates of overdose mortality than Massachusetts, New Hampshire, and Maine. By the end of this time series, this was no longer true, as overdose death rates were much higher in the New England states. Moreover, over this period, states east of the Mississippi River (light blue) became the places with the highest rates of overdose deaths. State-level variation in the intensity of fentanyl exposure explains most of the variation in the change in overdose mortality between 2011 and 2017 (Fig. 4: $R^2 \approx 0.60$).

To rigorously evaluate the effect of fentanyl exposure on overdose, I estimate two panel regression models of state-year age-adjusted overdose mortality as a function of fentanyl exposure (model specifications indicated earlier in the paper). Table 2 reports the results of these analyses. In Model 1, only state and year fixed effects are included, along with the fentanyl exposure metric. Controlling for unobservable,

Trend in Overdose Mortality (2011-2017)
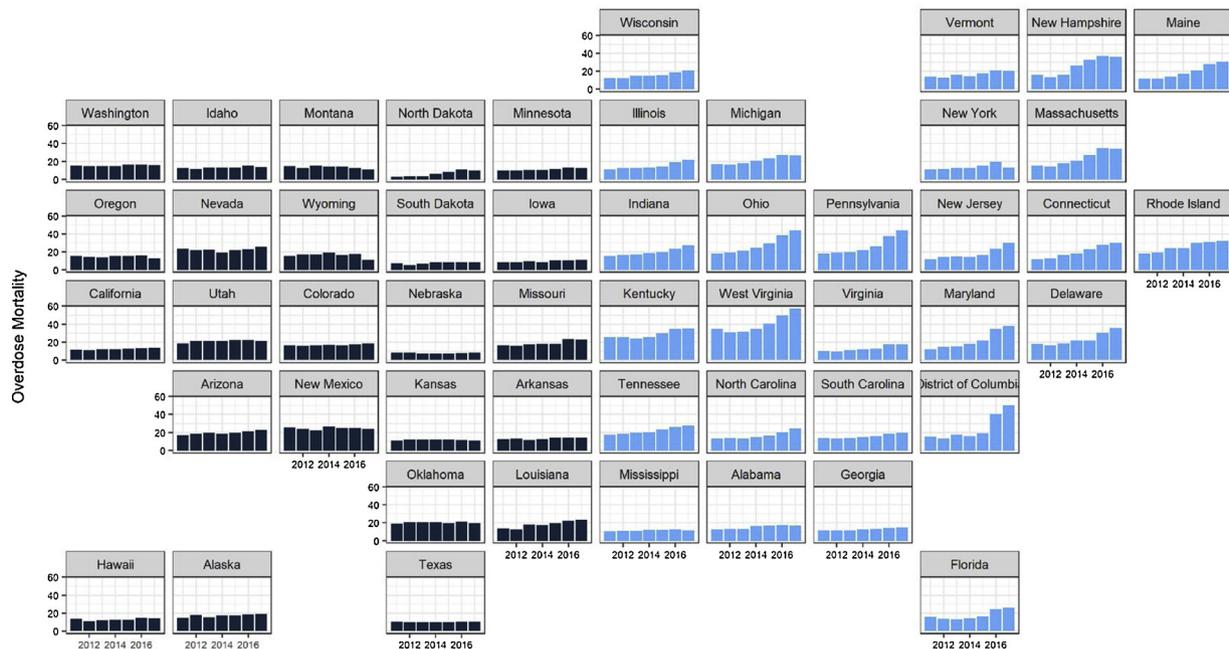
Source: CDC WONDER

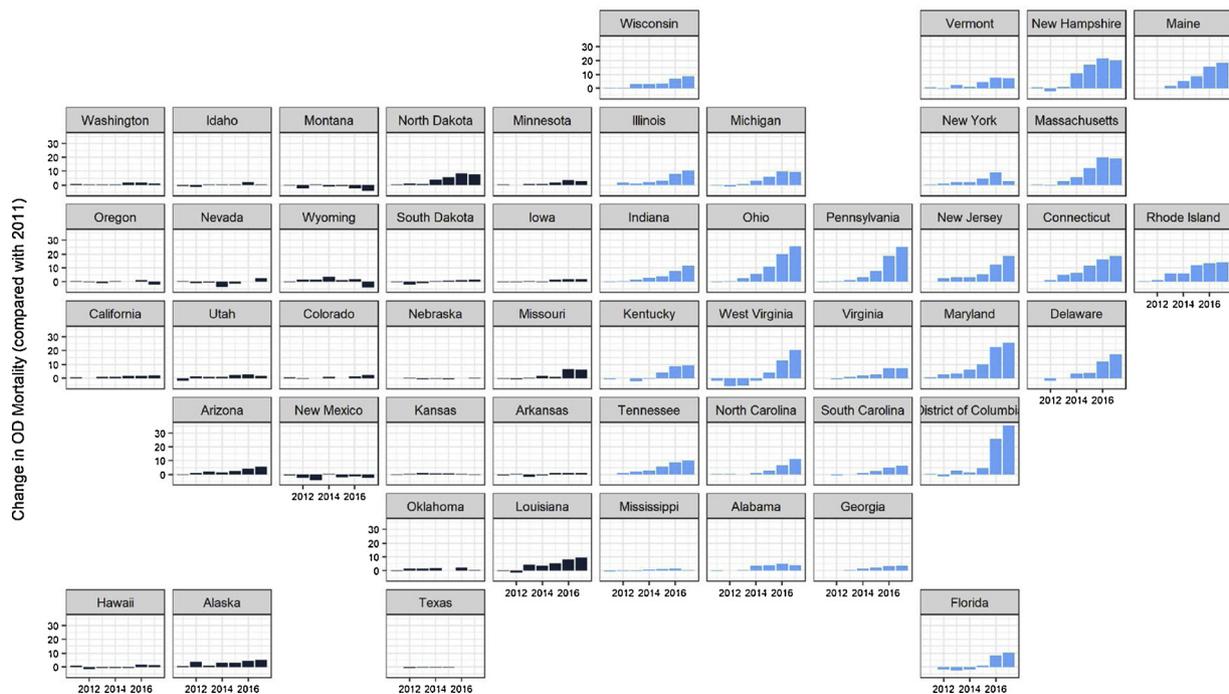## Regionality of Changing Overdose Mortality

Fig. 2. States are arranged roughly according to their geography, with bar graphs for each state showing annual overdose mortality (Top) and the change in annual overdose mortality since 2011 (Bottom). States east of the Mississippi River are colored light blue, while states west of the Mississippi River are colored dark blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

time- invariant state characteristics and shocks common to all states, Model 1 indicates that Fentanyl Exposure has a positive and statistically significant association with overdose mortality rates. Furthermore, the estimated association is substantively large ($\beta \approx 4.0$; $p < 0.001$). Model 2 employs an instrumental variables strategy to estimate the

causal effect of fentanyl exposure. The first-stage relationship between this geographic instrument and fentanyl exposure is strong ($F \approx 21$), confirming the strong association between state geography and rising fentanyl exposure. The Local Average Treatment Effect – the marginal effect of fentanyl exposure only due to geography – is similarly positive,
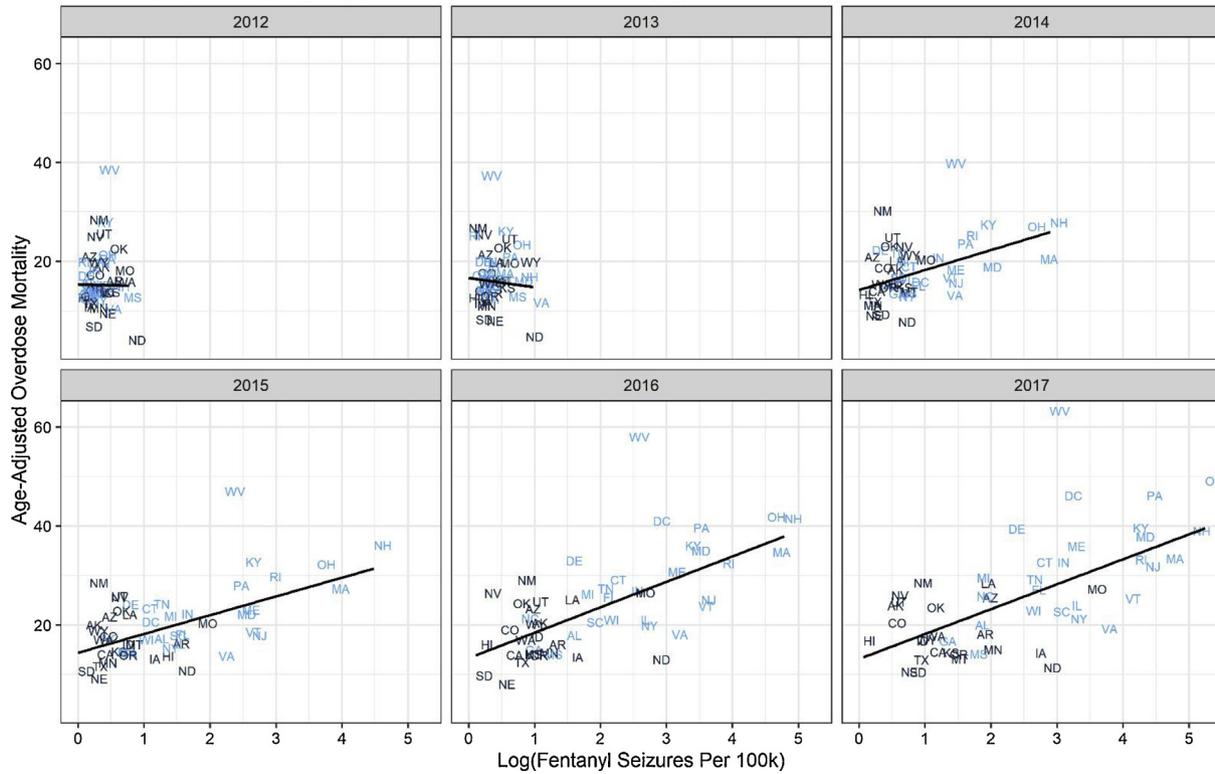
Fig. 3. Plots show, by year, the bivariate relationship between fentanyl shock exposure and overdose mortality in states. States east of the Mississippi River are colored light blue, while states west of the Mississippi River are colored dark blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

statistically and substantively significant ($\beta \approx 4.73$; $p < 0.001$). Robustness tests in the appendix indicate that omitting Hawaii and Alaska (non-contiguous states which are outliers on the geographic variables) does not substantively alter the results (Table A1). Other sensible strategies for measuring fentanyl exposure – such as the proportion of all drug seizures in a given state year which are for fentanyl or other synthetic opioids – produces similar estimates (Table A2).

I use Models 1 and 2 to generate back-of-the-envelope estimates of the total number of overdose deaths attributable to fentanyl and other synthetic opioids. To do this, I first multiply the parameter estimate for fentanyl by the measure of fentanyl exposure in each state year, which yields the effect for each state in terms of a rate per 100,000 people.
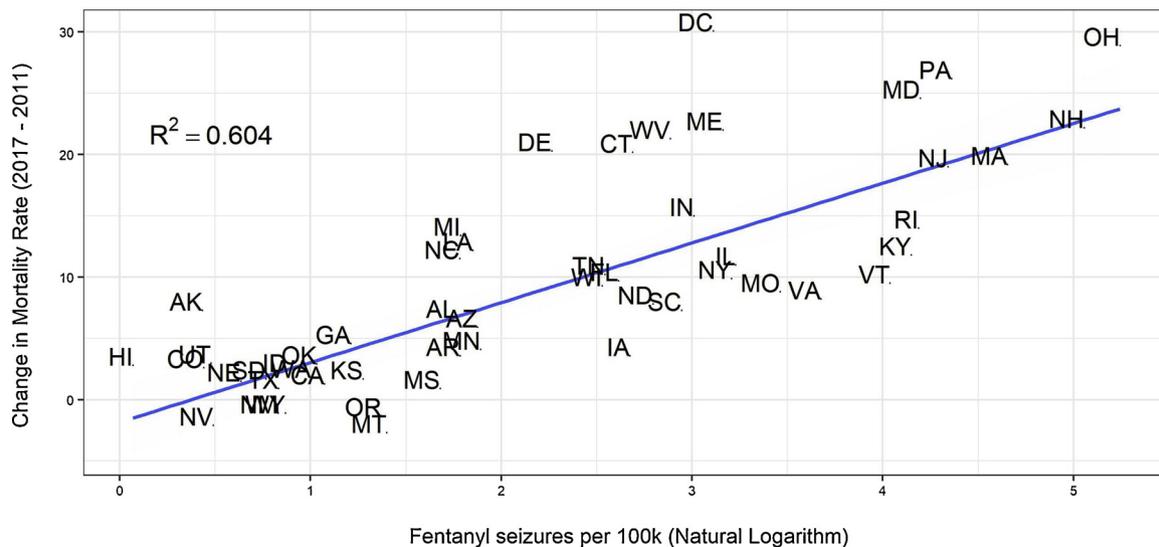
Fig. 4. Fentanyl Exposure and State-Level changes in overdose rate between 2017 and 2011 (Bottom).

Table 2
The top table shows the parameters of two statistical Models of Overdose &
Fentanyl Exposure, an ordinary least square model (OLS) and the second stage
of a two-stage least squares model (2SLS). The second table reports the total
estimated deaths per year attributable to fentanyl according to each statistical
model.

A: Statistical Models of Fentanyl & Overdose

Dependent variable: Age-Adjusted Mortality Rate

	(Model 1, OLS)	(Model 2, 2SLS)
Fentanyl Exposure	4.495***	5.426***
	(0.687)	(0.717)
State Fixed Effects	Y	Y
Year Fixed Effects	Y	Y
Population Weights	Y	Y
Observations	357	357
Adjusted R^2	0.915	0.909
First-Stage F		31.6

B: Total Estimated Deaths Attributable to Fentanyl by Model.

	Model 1 Deaths	Model 2 Deaths
2011	2,295	2,705
2012	2,365	2,788
2013	3,312	3,904
2014	8,870	10,458
2015	15,446	18,211
2016	23,188	27,339
2017	30,398	35,841

* $p < 0.1$.
** $p < 0.05$.
*** $p < 0.01$.

Next, I multiply this rate by the population of that state year to cal-
culate the number of deaths attributable to fentanyl in each state and
year. Finally, I sum the number of deaths for all states in that year. The
results, rounded to the nearest integer, are summarized in panel B of
Table 2. In 2016, about 23,500 deaths were attributable to fentanyl
according to Model 1, up from 14,700 in 2015 and just 2300 in 2011.
Model 2-based estimates were very similar, though slightly higher, than
those from Model 1. These estimates are broadly consistent with official
mortality statistics; in 2016, about 19,400 overdose death certificates
listed synthetic opioids–primarily illicit fentanyl–as present (NIDA,
2018). However, depending on the year, between 15% and 25% of
death certificates for drug overdose deaths did not list any specific
drugs (Hedegaard et al., 2017, 6). The estimate in Model 1 of 23,500
deaths in 2016 is about 20% higher than the synthetic opioid number
reported by the CDC, consistent with underreporting produced by the
omission of implicated drugs on this fraction of death certificates.

Discussion

Structural features of drug markets have long been known to shape
the risks facing people who use drugs. That prior overdose mortality is
not very predictive of fentanyl exposure – while geography is highly
predictive is consistent with the idea of a regional (and exogenous)
"supply-shock" tracking drug market boundaries (Gladden, 2016). That
is, fentanyl was imposed by drug suppliers, not induced by the demand
of drug users (Mars et al., 2018). The geographic variation in the new
synthetic opioid epidemic elaborated on in this paper is consistent with
historic geographic segmentation of the heroin market in the United
States, with injected, white-powder heroin typically sold east of the
Mississippi River and smoked, black-tar heroin west of the Mississippi
River (Ciccarone, 2005, 2009; Ciccarone, Unick, Cohen, Mars, &
Rosenblum, 2016; Gladden, 2016). Fentanyl is more easily mis-
represented in powdered heroin, compared to tar (Ciccarone, 2017).
This is reflected in state-level data about substances frequent in

overdose deaths. In Massachusetts, more than 90% of overdose fatal-
ities contained fentanyl by the end of 2017 (MA DPH, 2018). In con-
trast, in New Mexico, fentanyl was present in less than a quarter of
overdose fatalities (O'Donnell, Halpin, Mattson, Goldberger, & Matthew
Gladden, 2017). However, recent reports note that fentanyl and fen-
tanyl analogs are spreading into the southern and western United
States, though it remains much more prevalent in eastern US states
where heroin tends to be sold as a white powder (Springer, 2019).

These findings may elaborate and clarify a provocative recent
county-level analysis of so-called "deaths-of- despair" which found that
changes in the drug environment account for the bulk of the increase in
drug poisonings and that correlations with economic decline may be
spurious (Ruhm, 2019). But given the apparent failure of traditional
supply-side interventions (Hadland & Beletsky, 2018) such as curtailing
opioid prescribing, tamper-resistant formulations of oxycodone, and
drug arrests to stem the tide of overdose deaths, criminal sanction is
unlikely to provide a durable solution to the fentanyl crisis – and may
have accelerated the transformation of opioid supply into more potent
forms that are easier to conceal (the "Iron Law of Prohibition")
(Beletsky & Davis, 2017). Instead, policymakers might consider evi-
dence-based therapies that reduce drug taking among people who are
addicted to opioids.

Medication treatment for people who are addicted to opioids, in-
cluding methadone, buprenorphine, and naltrexone can help crave
cravings and reduce the risk of risky injection drug use. Such therapy
has been shown to cause significant improvements in clinical and social
outcomes (Volkow & Wargo, 2018). Providing medication treatment
such as methadone to patients who have experienced nonfatal over-
doses has been associated with significantly reduced mortality, even in
a state (Massachusetts) with very high exposure to the fentanyl shock
(Larochelle et al., 2018). Such medications remain underutilized due to
stigma and onerous prescribing requirements. Indeed, doctors in some
European countries have for decades prescribed pharmaceutical-grade
heroin to long-term heroin users refractory to other treatments (Strang
et al., 2015). Though politically unimaginable in the United States, the
practice does mitigate the overdose risk caused by adulterated drug
supply (Glasser, 2017). Finally, it should be noted that overdose is only
one of many harms caused by addiction, a learning disorder char-
acterized by compulsive drug taking that manifests from genetic pre-
disposition, environmental stressors, and maladaptive coping
(Szalavitz, 2016). Addressing the structural and root causes of this
disease – including depressed economic opportunity, isolation, and
declining social capital (Dasgupta et al., 2018) – is a necessary com-
ponent of a comprehensive response to the current drug crises and
prevention of future epidemics.

Limitations

Measurement error is a concern to bear in mind. The NFLIS data
contains observations of drug seizures, which may differ systematically
from the overall drug supply. Moreover, quantity and purity are not
reported consistently in the NFLIS data; consequently, I use only the
presence of synthetic opioids in the drug test. This is another source of
measurement error. Given increased media attention to fentanyl in re-
cent years, it is possible that testing laboratories have become more
likely to test for fentanyl, an effect which could be unevenly geo-
graphically concentrated. Moreover, while I have utilized multiple
techniques to reduce the risk of confounding, it remains possible that
estimates of the fentanyl are biased by the presence of some omitted
variable. Finally, there may be some unmodeled spatial dependence in
these data with drug seizures in one state intended for an adjacent state;
for example, drug seizures in Baltimore, Maryland may reflect drugs
intended to be sold in nearby Washington DC.

Conclusion

As scholars have noted, there is no single, static overdose epidemic; there are many epidemics, including and morphing from prescription opioids and benzodiazepines (Zoorob, 2018), heroin (Quinones, 2015), and most recently fentanyl and its analogues (Beletsky & Davis, 2017; Ciccarone, 2017). These epidemics are interconnected and cumulative, but they are not identical. As of 2017, fentanyl remained extremely unevenly distributed across the United States. Some states – like New Mexico, Nevada, and Washington experienced significant increases in overdose morbidity and mortality from prescription opioids and from heroin, but not from fentanyl. Other areas, like Maryland and Washington DC, were spared the earlier epidemics but hard-hit by the influx of fentanyl into the heroin supply. West Virginia, the state with the highest overdose mortality rate, was battered sequentially by each epidemic. Here again, it is worth reiterating the iterative nature of the "triple-epidemic" of opiates in the United States. The third wave of the opioid crisis – the fentanyl and synthetic opioid shock – has substantially exacerbated overdose mortality in some regions of the country, while leaving other places relatively unscathed, at least so far. Speaking only of this third-wave of the overdose epidemic, the most plausible explanation for the regionally stratified spike in mortality is that geographically-concentrated, abrupt changes in the drug supply heightened the risk of overdose mortality among people who use drugs.

These findings, taken together, portray this most recent face of the mutating overdose crisis as one of drug supply. These findings suggest that policymakers should consider how to facilitate timely surveillance of drug supply to researchers as well as to drug users, some of whom may well wish to avoid ingesting a deadly batch of carfentanil if they can help it (Ciccarone, Ondocsin, & Mars, 2017; Krieger et al., 2018). Enhancing the accessibility of fentanyl field tests – sometimes called fentanyl strips – could thus attenuate the risk of overdose, in the same way that syringe distribution reduces the transmission of hepatitis (Peiper et al., 2018). But above all, these results underscore the need for urgent implementation of evidence-based policies to mitigate overdose in all states. Places where drug overdoses have not increased since 2011 are not necessarily immune to spikes of the kind seen in other regions of the country; they were not spared the quadrupling of overdose fatalities in the subsequent five years because their populations were bereft of despair or their public health policies amply responsive to addiction and overdose. They were spared by vagaries of drug markets that are liable to rapid change.

Conflict of interest statement

No conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.04.010.

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