Has the United States Reached a Plateau in Overdoses Caused by Synthetic Opioids After the Onset of the COVID-19 Pandemic? Examination of Centers for Disease Control and Prevention Data to November 2021

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Background: Overdoses caused by synthetic mu-opioid receptor (MOR) agonists such as fentanyl are causing increasing mortality in the United States. The COVID-19 pandemic continues to have complex effects on public health, including opioid use disorders (OUD). It is unclear whether recent increases in mortality caused by synthetic opioids have reached a plateau (i.e., a stable period), after the onset of the COVID-19 pandemic.

Method: This study examined provisional overdose mortality data from the Centers for Disease Control and Prevention, for synthetic opioids excluding methadone (code T40.4; monthly data available from 39 States, plus New York City and Washington DC), for June 2019–November 2021. Data were first examined as crude mortality rates. The presence of a maximum plateau was analyzed for the last 4 months of available data. For authorities in which a plateau was detected, sigmoidal Boltzmann equations were used to model parameters of this phenomenon (e.g., level of the plateau).

Results: At the end of the study period, all but one authority (New Hampshire) reported increases in mortality rates for synthetic opioids, compared to the baseline month of June 2019 (range: 111–745% of baseline). A plateau was observed over the last 4 months of the study period (Aug 2021–Nov 2021) in 29 of the authorities. Ten other authorities had not reached a stable plateau at the end of the study period. For the authorities where a plateau was detected, sigmoidal Boltzmann equations were used to model parameters of this phenomenon (e.g., level of the plateau).
Discussion: There were increases in overdose mortality due to synthetic opioids across most states, ranging considerably in magnitude. A plateau in overdose mortality was detected at the end of the study period in most of these authorities. The reasons for these plateaus should be explored, in order to develop optimized public health interventions.

Keywords: COVID-19, overdose, opioid use disorder, fentanyl, plateau, opioid

INTRODUCTION

Starting with its global spread from early 2020, the COVID-19 pandemic has caused complex public health challenges. Most public health measures (e.g., lockdowns) in industrialized countries such as the United States commenced in March 2020 (1). Among the reported comorbidities with COVID-19 is opioid use disorder (OUD) (2). The COVID-19 pandemic could potentially affect different stages in the trajectory of OUD and its medical care (3–5). OUD is caused by self-exposure to mu-opioid receptor (MOR) agonists, such as fentanyl derivatives, heroin, and prescription opioids (e.g., oxycodone). MOR-agonist overdose causes mortality primarily by centrally mediated respiratory depression (6–9). Fentanyl analogs have other deleterious effects (e.g., chest rigidity and laryngospasm), which may further increase their potential to cause morbidity and mortality (10–13).

Even prior to the COVID-19 pandemic, increases in opioid-induced overdose mortality were reported (14–16). For example, a recent wave in 2014–2017 was thought to be due to fentanyl derivatives, heroin, and prescription opioids (17). The increasing presence of synthetic opioids in the illicit drug supply has resulted in a substantial increase in overdoses and mortality in the United States over the last several years (18–22). Consistent with this, data indicate that synthetic opioids (e.g., fentanyl derivatives), as opposed to other MOR-agonists such as heroin, are primarily responsible for the most recent increases in mortality in the United States, after the onset of COVID-19 (14, 23, 24).

The time-dependent increase in opioid-induced overdose deaths after the onset of COVID-19 was recently examined in 11 states (ending in August–December 2020) (25). This study reported heterogeneous profiles across these 11 states, for different kinds of opioids, including potential stabilizing trends in some states (i.e., tending toward a plateau). Another study reported on the increases in suspected opioid overdoses visits to ED in four states after onset of the COVID-19 lockdowns, ending in August 2020 (5). Other studies have also reported increases in all drug overdoses in individual states and counties in the onset of the COVID-19 pandemic (26–29).

The present study extends and complements the above reports by examining U.S. Centers for Disease Control and Prevention (CDC) data, for 12-month periods ending June 2019 to November 2021 (therefore, covering a period before and after the onset of COVID-19 in the United States). The selected starting month (June 2019) provided 8 months of pre-COVID-19 data, to characterize a potential minimum plateau, important for non-linear sigmoidal regression analyses. The selected ending month was the latest available at the time of download (20 April 2022; Vital Statistics Rapid Release).1 We examined data for the authorities that report overdose deaths caused by “synthetic opioid excluding methadone” (category T40.4) (23). This category contains primarily fentanyl and its analogs, and can potentially include MOR-agonists from other synthetic scaffolds (e.g., analogs of etonitazene and U47700), although the latter are thought to be less common (16, 24). All data from an authority was excluded from non-linear regressions if it had more than two consecutive missing monthly values, or if values for the baseline month (June 2019) were not available.

Data for each 12-month ending period were first plotted per authority over the study period, expressed as crude mortality rate/million of population (to the nearest 0.1 million, based on U.S. Census numbers). Data were not cumulated across authorities, due to the possibility of differences in reporting standards (35, 36). For better visualization, separate figures were plotted for the four Census regions (i.e., West, Midwest, South, and Northeast).

Absolute baseline values (June 2019) differed widely across authorities, and the remaining calculations were made after normalizing each data set’s monthly data as a percent of its baseline month. For each data set, a maximum plateau was defined to occur if each of values for the last 4 months (i.e.,

1https://www.cdc.gov/nchs/ivs/vsrr/drug-overdose-data.htm
August 2021–November 2021) was within ±5% of: (mean value for the last 4 months/baseline month). This therefore takes into account the differing magnitudes of increases relative to each authority’s baseline.

Sigmoidal Time/Mortality Curve
Sigmoidal equations (including the sigmoldal Boltzmann model) have been used for epidemiological and opioid clinical pharmacology studies (32, 37, 38). The sigmoidal Boltzmann model was used to fit minimum and maximum (i.e., bottom and top) plateaus for mortality due to synthetic opioids, and the midpoint of the rise in mortality (23, 25). Data sets from the 29 authorities which had a detected maximum plateau in the last 4 months of the study period (as defined above; Table 1) were entered in an overall Boltzmann sigmoidal equation model, using GraphPad Prism (V.9) software. The equation was: mortality = [lower plateau + (top plateau – bottom plateau)]/[1 + \exp \left[ \frac{(month of midpoint of top – bottom) – month}{slope}\right]]. The regression was weighted by 1/Y^2, to account for larger variation in the later months of the study period. The minimum plateau was constrained to be >0%. The main fitted values of interest were therefore the maximum plateau (±95%CI) and the month of the midpoint between the minimum and maximum plateau (i.e., to determine when the rise in mortality occurred). The minimum plateau is not reported here, as the values were normalized as percent of baseline. This overall sigmoidal model was followed by separate models for the states in the four Census regions, with identical methods.

RESULTS
Provisional overdose deaths due to synthetic opioids excluding methadone were analyzed, before and after the onset of COVID-19 in the United States (June 2019–November 2021). Monthly crude mortality rates/million are shown in Figure 1, separated by Census region. There was a considerable variation in baseline mortality rate (Table 1 and Figure 1). Of the 41 authorities studied, only New Hampshire showed a decrease in mortality rate over the study period (to 85% of baseline; Table 1). All other authorities reported an increase in mortality over the study period, and there was a considerable variation in the magnitude of time-dependent increases compared to each baseline (i.e., June 2019; Table 1 and Figure 1). Due to this variation, the potential sigmoidal profile of some curves is less easily discernable than others, on a common y-axis axis. As an illustration, the four States in the South census region with lower absolute values are replotted on a compressed y-axis (Figure 2, compare to Figure 1, lower right panel).

Normalized Mortality Rates
Crude mortality rates were then normalized as a percent of each data set’s baseline month (June 2019), and are presented in Table 1. As mentioned above, as of the final month of the study period (Nov 2021), only New Hampshire had a decrease (85% of baseline). All other data sets exhibited increases by the end of the study period, ranging in magnitude from 111 to 645% of baseline (New Jersey and Alaska, respectively).

Determination of Maximum Plateau in Overdose Mortality
The presence of a maximum plateau (i.e., a period of stability) in the last 4 months of the study period was examined for each data set. There were a total of 39 data sets which could be analyzed (New York City and Kansas were excluded due to missing data in some cells). Of these 39 data sets, 29 showed a maximum plateau as defined in the Methods (Table 1). By contrast, data sets from 10 states did not exhibit a maximum plateau in the last 4 months of the study; these were: Alaska, Colorado, Hawaii, Wyoming, Washington, South Dakota, Georgia, Oklahoma, Vermont, and Maine.

Sigmoidal Model of Data From States With a Maximum Plateau in Mortality
In order to examine the plateau phenomenon further, we entered data from the 29 authorities (28 states and Washington DC) with a detected maximum plateau (see Table 1) into an overall regression, as replicates. For this overall regression, the data fit a sigmoidal Boltzmann equation with a high weighted R^2 (0.99) (Figure 3, left panel). The fitted maximum plateau for this overall regression was 262% of baseline (95%CI: 255–271%) (Figure 3, left panel). The fitted mid-point between the minimum and maximum plateau was detected in September 2020 (Table 2). In a follow up analysis, we divided these 29 authorities into their four respective Census regions, and carried out separate regressions (Figure 3, right panel; Table 2). These four regressions revealed that the regions had different maximum plateau levels, based on lack of overlap in their weighted 95%CI (Table 2). The region with the highest plateau was the West, followed in descending order by the South, Midwest and Northeast. These region-specific regressions also exhibited high weighted R^2 (≈0.99).

DISCUSSION
Several studies have reported an increase in opioid-induced mortality after the onset of COVID-19 in the United States (commencing in March 2020), largely ascribed to synthetic MOR-agonists such as fentanyl analogs (10, 23, 24). Mortality had also been rising in prior years (e.g., a wave in 2014 onwards) due to synthetic MOR-agonists, heroin and prescription opioids (11, 14, 17, 23, 39).

As expected, nearly all of the 41 authorities under study exhibited an increase in mortality due to synthetic opioids after the onset of the COVID-19 lockdowns in March 2020. One authority only (New Hampshire) showed a decrease at the end of the study period. This study detected that 29 of these authorities exhibited a plateau in mortality caused by synthetic opioids, defined as stability in the last 4 months of this period (August 2021–November 2021). The data also show that 10 authorities had not exhibited such a plateau at the end of the study period.

https://www.graphpad.com/guides/prism/latest/curve-fitting/REG_Classic_Boltzmann.htm
A large variability in baseline mortality due to synthetic opioids and the magnitude of the post-COVID-19 increases was noted across authorities and regions. Overall, the highest plateau was observed in the West Census region, followed in descending order by South, Midwest and Northeast. Variability in these profiles is consistent with recent reports focusing on all opioid overdoses (i.e., not only those due to synthetic opioids), for selected states (25, 26, 40). Future studies could examine the relationship between different relative increases in mortality across regions and States, and diverse public health measures enacted after the onset of COVID-19. Pre-existing differences across regions and States could also be important factors, based

### Table 1: Mortality rate for overdoses caused by synthetic opioids, before and after the onset of COVID-19.

| Census region | Crude mortality rate for synthetic opioids excluding methadone (category T40.4 in CDC Data) |
|---------------|------------------------------------------------------------------------------------------------|
| Authority     | Death rate/Million | Ending month as % of baseline month | Mean of last 4 months as % of baseline month | Maximum plateau detected in the last 4 months of study period? |
|---------------|---------------------|------------------------------------|---------------------------------------------|-------------------------------------------------|
| West          |                     |                                    |                                             |                                                 |
| California (CA) | 29.7 | 148.4 | 498.8 | 492.8 | $Y$                   |
| Alaska (AK)   | 27.4 | 204.1 | 745.0 | 667.5 | $N$                   |
| Arizona (AZ)  | 85.9 | 239.3 | 278.6 | 275.1 | $Y$                   |
| New Mexico (NM) | 55.7 | 271.0 | 486.3 | 466.2 | $Y$                   |
| Colorado (CO) | 26.6 | 163.6 | 616.2 | 587.2 | $N$                   |
| Hawaii (HI)   | 12.7 | 29.3  | 231.6 | 211.8 | $Y$                   |
| Nevada (NV)   | 34.5 | 117.7 | 341.1 | 330.1 | $Y$                   |
| Oregon (OR)   | 20.5 | 103.8 | 507.0 | 506.1 | $Y$                   |
| Utah (UT)     | 25.6 | 59.4  | 231.7 | 220.7 | $Y$                   |
| Wyoming (WY)  | 16.7 | 56.7  | 340.0 | 325.0 | $N$                   |
| Washington (WA) | 34.9 | 150.0 | 430.2 | 403.6 | $N$                   |
| Iowa (IA)     | 23.8 | 61.3  | 257.9 | 269.7 | $Y$                   |
| Illinois (IL) | 125.2| 209.4 | 167.2 | 164.2 | $Y$                   |
| Indiana (IN)  | 110.1| 290.6 | 263.8 | 255.6 | $Y$                   |
| Missouri (MO) | 137.4| 232.6 | 169.2 | 165.6 | $Y$                   |
| Ohio (OH)     | 257.7| 357.0 | 138.5 | 139.8 | $Y$                   |
| South Dakota (SD) | 12.2 | 37.8 | 309.1 | 277.3 | $N$                   |
| Wisconsin (WI) | 92.9 | 210.2 | 226.2 | 224.4 | $Y$                   |
| South          |                     |                                    |                                             |                                                 |
| Texas (TX)    | 10.7 | 59.0  | 553.4 | 529.0 | $Y$                   |
| Maryland (MD) | 300.2| 372.3 | 124.0 | 127.6 | $Y$                   |
| Kansas (KS)   | Missing$^c$        | 117.6 | N/A   | N/A   | N/A                   |
| Delaware (DE) | 311.0| 381.0 | 122.5 | 118.2 | $Y$                   |
| Georgia (GA)  | 31.4 | 118.9 | 378.4 | 360.8 | $N$                   |
| Kentucky (KY) | 165.8| 384.4 | 231.9 | 228.3 | $Y$                   |
| Mississippi (MS) | 31.7 | 135.0 | 426.3 | 428.2 | $Y$                   |
| North Carolina (NC) | 126.4 | 256.9 | 205.4 | 203.3 | $Y$                   |
| Oklahoma (OK) | 15.0 | 64.8  | 431.7 | 408.8 | $N$                   |
| South Carolina (SC) | 98.7 | 282.3 | 286.2 | 279.0 | $Y$                   |
| Tennessee (TN) | 147.5| 407.2 | 276.1 | 267.3 | $Y$                   |
| Virginia (VA) | 107.6| 220.6 | 204.9 | 207.5 | $Y$                   |
| Washington DC (DC) | 277.1 | 532.9 | 192.3 | 193.3 | $Y$                   |
| West Virginia (WV) | 297.2 | 637.8 | 214.6 | 219.8 | $Y$                   |
| Northeast      |                     |                                    |                                             |                                                 |
| New York City (NYC) | 101.3 | 222.4$^d$ | 219.5$^d$ | 226.0 | N/A                   |
| New York State (NYS)$^d$ | 117.6 | 196.6 | 167.2 | 169.5 | $Y$                   |
| Connecticut (CT) | 232.8| 359.7 | 154.5 | 151.9 | $Y$                   |
| New Jersey (NJ) | 237.8| 264.3 | 111.2 | 111.5 | $Y$                   |
| Massachusetts (MA) | 259.6 | 304.6 | 117.4 | 116.3 | $Y$                   |
| Vermont (VT) | 145.0| 343.3 | 236.8 | 225.6 | $N$                   |
| Rhode Island (RI) | 200.9 | 286.4 | 142.5 | 139.7 | $Y$                   |
| New Hampshire (NH) | 260.0 | 222.1 | 85.4 | 86.1 | N/A$^e$                  |
| Maine (ME)    | 167.9| 347.9 | 207.2 | 194.8 | $N$                   |

$^a$A maximum plateau is detected if each of the last 4 months of the study period (August 2021–November 2021) are within ±5% of (mean of last 4 months/baseline month).  
$^b$June–July 2019 data missing.  
$^c$Ending month (November 2021) missing; data shown with October 2021 as ending month.  
$^d$New York State excluding New York City.  
$^e$New Hampshire showed a decrease in mortality rate due to synthetic opioids over this period.
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FIGURE 1 | Crude monthly mortality rate (per million), due to “synthetic opioids excluding methadone,” for June 2019–November 2021. X-axes: month; Y-axes: mortality rate (per million population). Different panels show data separated by Census region (Midwest, Northeast, West and South). Note different Y-axis scale in the panel for the South region (lower right). Labels for each authority are placed near the ending month data for each curve, to aid visualization. Abbreviations for authorities are defined in Table 1.

FIGURE 2 | Re-plot of crude mortality rate of the four states from the South census region with the lowest absolute values (i.e., see Figure 1, lower right panel, for comparison). Note compressed Y-axis range; all other details as in Figure 1.

on variations in health systems, socioeconomics, demographics and frequency of illicit synthetic opioids in the drug supply (41–46).

Using the pre-pandemic period from June 2019 as baseline, the sigmoidal regression models in this study document an increase in mortality due to synthetic opioids in the United States after the onset of COVID-19 (in March 2020 onwards). For the overall regression, the midpoint of this increase was detected in September 2020, approximately 6 months after the onset of the lockdowns in the United States. The increase of such overdoses during the early pandemic may have been due to changes in supply, distribution or demand, for illicit opioids and other drugs (41, 47). Increased adulteration with fentanyl analogs in different types of illicit drug products (including both opioid and non-opioid compounds) is another potential cause of this trend (39, 45, 48). Behavioral changes in the early pandemic period, such as injecting alone, or refusal of transport to the ED may have also contributed to this rise in mortality (5, 49).

The presence of plateaus in epidemiological studies has been ascribed to different phenomena, including the presence of a “continuing common source,” which in this case could be the extensive penetration of synthetic opioids in the illicit drug supply (30, 39). Other factors that have been recently examined in such plateaus include behaviorally based heterogeneity within populations, and behavioral change due to awareness of risk (31, 34).
Limitations and Methodological Considerations

It cannot be excluded that the plateaus observed at the end of the study period in 29 authorities are temporary, and that further increases may occur in the future (17, 31, 34, 50). Only one state examined here, New Hampshire, showed a decrease in mortality due to synthetic opioids, compared to baseline. A slight time-dependent decrease was also observed for New Hampshire for mortality due to all opioids (T40.0–T40.4, T40.6), not only synthetic opioids studied here (not shown).

The analysis for “synthetic opioids excluding methadone” (category T40.4) did not include all States, as some do not report this category separately. Nevertheless, this study included a large sample of reporting authorities, representing all census regions in the United States. These CDC mortality data are considered provisional, and have lag times for reporting (51); there are also potential differences in reporting standards across authorities (36), further justifying normalization by the local baseline. However, completeness is relatively high, and these data are among the most timely indicators of overdose mortality across the United States (see text footnote 1).

The available data do not allow differentiation of which specific synthetic opioid (e.g., fentanyl or an analog thereof) was detected (24). Also, these data sets do not imply that “synthetic opioids other than methadone” were the only drugs detected in the decedents (52). However synthetic opioids are thought to be the compounds primarily underlying the increases in mortality observed after the onset of COVID-19 (14, 41). For illustration, California (the most populous State) had a decrease in overdose mortality with heroin (T40.1) in the last month of the study period compared to baseline (to 80.9% of baseline; not shown). By contrast, there had been a robust increase in overdose mortality with “synthetic opioids other than methadone” (i.e., 498.8% of baseline; Table 1).

Because there was a broad variation across authorities in the crude mortality rate at baseline (i.e., June 2019), data were normalized data as percent of each baseline, for sigmoidal non-linear regressions. However a similar sigmoidal curve could also be fit on crude mortality rates (not shown), therefore the models shown here were not simply an artifact of normalization. Modeling of these monthly data with a sigmoidal Boltzmann equation was justified based on the observed profiles in most of the authorities in this study, and has been used to examine other epidemiological variables (32, 37). Nevertheless, equations other than the sigmoidal Boltzmann could be used in the future to explore this potential plateau phenomenon. In the

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**TABLE 2** | Non-linear sigmoidal regressions for overdose mortality caused by synthetic opioids.

| Sigmoidal non-linear regressions for normalized data (expressed as % of baseline month)\(^a\) | Maximum plateau as \(^%\) of baseline (weighted ± 95%CI)\(^b\) | Midpoint between minimum and maximum plateau\(^c\) |
|---|---|---|
| 29 U.S. Authorities combined | 262% (255–271) | September 2020 |
| Separate census regions | | |
| West region | 409% (392–433) | October 2020 |
| South region | 262% (256–268) | August 2020 |
| Midwest region | 204% (199–209) | May 2020 |
| Northeast region | 149% (147–152) | May 2020 |

\(^a\)Includes data from 29 authorities which showed a stable maximum plateau in the last 4 months of the study period (described in Table 1).

\(^b\)These data describe the maximum (top) plateau as fitted with the sigmoidal Boltzmann regression from June 2019 to November 2021. This does not necessarily imply that these plateaus will be the maximum for the future (see section “Discussion; Limitations and methodological considerations”).

\(^c\)To the nearest whole month.
sigmoidal models shown here, we included only authorities that had individually shown a stable maximum plateau in the last 4 months of the study period. As a follow-up, we also carried out a further Boltzmann model including all data sets without exclusion. Results of this equation were also fit to a sigmoidal model with high R², and yielded similar maximum plateau to that reported above (not shown). Therefore, the fitted sigmoidal models here were not likely to be an artifact of the exclusion of the data sets that had not individually reached a plateau.

CONCLUSION

The COVID-19 pandemic has potentially affected different stages in OUD, including initiation, escalation, overdoses, and engagement with clinical care (3, 5, 21). We confirm here increases in mortality rates due to synthetic opioids after the onset of COVID-19 in the United States, which varied considerably in magnitude across census regions and the broad array of states examined here. This study shows that most, but not all, of the authorities had reached a stable plateau in August to November 2021. The magnitude of the observed plateau was the highest for the West census region, followed in descending order by South, Midwest and Northeast. Differing plateau levels in specific parts of the United States may be due to patterns of opioid initiation and use, but also use of other drugs, as in specific parts of the United States may be due to patterns of opioid initiation and use, but also use of other drugs, as illicit synthetic opioids can be mixed in the drug supply for ostensible non-opioid drugs (14, 39, 53). The lack of observable plateaus at the end of the study period in 10 of the states studied here is also worthy of investigation, given the potential risk of further increases. Overall, future studies should explore the reasons underlying these divergent plateau profiles across states, as a potential guide for locally optimized prevention, mitigation and intervention approaches.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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