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Trends in Methadone Utilization for Opioid Use Disorder Treatment in the United States During the COVID-19 Pandemic

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Abstract

Objectives: Opioid use disorder (OUD) is a major public health concern in the United States (US), resulting in high rates of overdose and other negative outcomes. Methadone, an OUD treatment, has been shown to be effective in reducing the risk of overdose and improving overall health and quality of life. This study analyzed the distribution of methadone for the treatment of OUD across the US over the past decade and through COVID-19 pandemic.

Design: Retrospective observational study using secondary data analysis.

Setting: Data from the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System, Medicaid's State Drug Utilization Data, and the US Census Bureau for 2010 to 2021.

Participants: All US Opioid Treatment Programs (OTPs).

Primary and secondary outcome measures: The primary outcomes were the overall pattern in methadone distribution and the number of OTPs in the US per year. The secondary outcome was Medicaid prescriptions for methadone.

Results: Methadone distribution for OUD has expanded significantly over the past decade, with an average state increase of +96.96% from 2010 to 2020. There was a significant increase in overall distribution of methadone to OTP from 2010 to 2020 (+61.00%, $P \leq 0.001$) and from 2015 to 2020 (+26.22%, $P < 0.001$). However, the distribution to OTPs did not significantly change from 2019 to 2021 (-5.15%, $P = 0.491$). There was considerable state level variation in methadone prescribing to Medicaid patients with four states having no prescriptions.

Conclusions: There have been dynamic changes in methadone distribution for OUD. Furthermore, pronounced variation in methadone distribution among states were observed, with some states having no OTPs or Medicaid coverage. New policies are urgently needed to increase access to methadone treatment, address the opioid epidemic in the US, and reduce overdose deaths.

Article Summary: Strengths and limitations of this study

- ARCOS provides novel data on distribution and distributors of methadone for OTPs over the past decade, pre- and post-COVID-19
- ARCOS reports methadone distribution by weight, not by patient count or prescriptions, and doesn't differentiate pharmacological formulations
- Incorporating Medicaid data compensates for the absence of patient level methadone data in ARCOS

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Data Sharing Statement: Publicly available datasets were analyzed in this study. This data can be found here: [https://www.deadiversion.usdoj.gov/arcos/] [https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html].

Introduction

The United States (US) Food and Drug Administration (FDA) has approved methadone, buprenorphine, and naltrexone as treatments for Opioid Use Disorder (OUD) [1], but there have been several policy changes impacting OUD care during the COVID-19 pandemic. Methadone, a gold standard medication for OUD (MOUD), is a long-acting synthetic opioid administered via opioid treatment programs (OTP) [1-3]. In recent years, methadone take-home doses have been extended to 28 days for stable patients and 14 days for less stable patients, drug screening requirements have been relaxed, and telemedicine has been expanded for established patients [4, 5]. However, unlike for buprenorphine, starting methadone treatment requires an in-person visit. Prior to the pandemic, OUD methadone treatment also required the co-administration of counseling, however, these counseling requirements have also been relaxed as a result of the COVID-19 pandemic [5-7].

As an opioid, methadone has the potential to cause serious adverse effects including respiratory depression and cardiotoxicity [3, 8, 9]. An alternative gold standard MOUD, buprenorphine, has also raised safety concerns as well with rising respiratory depression fatalities after oral doses in both adult and pediatric patients, resulting in a total of 84 deaths from 2003–2019 [10]. In contrast, in 2021 alone, there were 106,699 overdose deaths in the US. Thus, it is important to weigh these potential concerns against the extremely high risk of respiratory depression associated with ongoing nonprescribed opioid use, a symptom of under or untreated OUD, and not withhold first line care unnecessarily. In regions where it is available, methadone is frequently used to treat the most severely ill OUD patients since it is a full mu receptor agonist and doses can be titrated up as needed, while buprenorphine is a partial mu receptor agonist with less higher end dosing flexibility. Methadone necessitates expert handling, especially in the early stages of treatment because of its full agonism properties combined with high lipophilicity, long serum half-life, and active metabolites [11]. Buprenorphine combined with naloxone may be becoming a more commonly prescribed option compared to methadone. A recent survey revealed 75% of emergency room physicians had a preference for buprenorphine over methadone [12]. However, buprenorphine was widely but inequitably unavailable from 2004 to 2015 due to factors such as systemic racism and discrimination based on socioeconomic status. In particular, Black patients had a lower probability of receiving a prescription [13]. Findings from a retrospective, cohort study from 1998 to 2014 suggest that patients on buprenorphine had a lower risk of drug-related poisoning mortality during treatment compared to those on methadone [14]. In contrast, treatment with methadone was superior to buprenorphine in reducing criminal activity, HIV infection, hepatitis, and overall mortality [2,15-18]. Additionally, a Cochrane meta-analysis concluded that methadone was superior to buprenorphine in retaining patients in treatment only if buprenorphine doses were 7mg per day or lower, but that methadone and buprenorphine were equivalent at higher doses (Supplemental Table 1) [19]. However, there is a nationwide lack of appropriate treatment with all potential medications for persons with OUD [20, 21]. Although studies have shown that

both treatments are effective, clinicians and patients should choose between buprenorphine and methadone treatment depending on their individual needs and circumstances, including the accessibility and availability of treatment programs in their area [2, 14-21].

There have been over one-million drug overdoses in the US since the start of the opioid epidemic [22]. The COVID-19 pandemic has placed tremendous stress on the healthcare system including the access to providers and availability of OUD treatments. Between 2019 and 2020, there was a +48.8% increase in overdose mortality among Black people, compared to +26.3% among White people [23]. Moreover, from April 2020 to April 2021, the number of drug overdoses in the US exceeded one-hundred thousand, a +28.5% increase over the previous year [24]. With a +60% rise in overdoses compared to the previous year, May 2020 became the deadliest month on record [25]. A cross-sectional study, conducted from May to June 2020 in the US and Canada, found that new patients wishing to initiate methadone treatment were faced with a barrier in 20% of clinics [26]. Similarly, prior to the pandemic, both methadone and buprenorphine-based OTPs were found to be effective in US jails and prisons. However, following the pandemic, some of these OTPs have been expanded while others were discontinued [27-29].

This study obtained data from the Drug Enforcement Administration's (DEA) Automated Reports and Consolidated Ordering System (ARCOS), a federal program established by the 1970 Controlled Substances Act, to monitor the distribution of DEA controlled substances from various sources including retail pharmacies, hospitals, practitioners, teaching institutions, mid-level practitioners, and OTPs. Previous pharmacoepidemiologic studies have also utilized the ARCOS database [30-34]. It is important to note that ARCOS does not provide information on the number of patients receiving methadone. This caveat is important because it prevents an accurate representation of the amount of methadone used for each OUD patient. However, federally funded OTPs record number of patients receiving treatment, which could be a useful resource in understanding the true scale of the OUD epidemic in the US and the effectiveness of treatment efforts. The Substance Abuse Mental Health Services Administration's (SAMHSA) National Survey of Substance Abuse Treatment Services' (N-SSATS) annual report provides national data regarding alcohol and drug abuse facilities [35]. The number of patients receiving methadone for OUD decreased by almost one-quarter (-23.7%) from 2019 (408,550) to 2020 (311,531) [35] (Supplemental Figure 1).

In addition to ARCOS, Medicaid's State Drug Utilization Data (SDUD) database was used in this study [36]. Medicaid is a program at the federal and state level which functions to aid in covering healthcare costs for patients with limited resources [37]. Medicaid.gov publishes all prescription drugs covered by Medicaid every year for all 50 states and the District of Colombia (DC) in the SDUD database. The State Health Official Letter, released on December 30, 2020, states that the SUPPORT Act of 2018

mandates the inclusion of Medicaid coverage for MOUD for all eligible patients with OUD. Subsequently, the Continuing Appropriations Act of 2021, which added to the SUPPORT Act, requires rebates on methadone and other MOUD starting from October 1, 2020 to September 30, 2025. [38, 39]. The use of both ARCOS and SDUD databases provide a comprehensive picture of the distribution and utilization of methadone for the OUD treatment over the past decade. Together, it is critical to examine the changes in methadone distribution during the COVID-19 pandemic and determine whether there are national or regional barriers to access this evidence-based pharmacotherapy.

Materials and Methods

The quantities of methadone distributed (in grams) were obtained from the ARCOS yearly drug summary reports for 2010, 2015, 2019, 2020 and 2021. Methadone distributed to OTPs was classified as an OUD treatment. The number of OTPs per state were also obtained from ARCOS for 2010, 2015, 2019, 2020 and 2021. The state population estimates, including DC, were derived from the US Census Bureau's Annual Estimates of the Resident Population for the US [40]. The US Territories were examined elsewhere and were not included in Figures 1-5 [41]. Data was collected for methadone covered by Medicaid in 2020 for all 50 states and DC using a filtered download from the SDUD [36]. National Drug Codes (NDC) of formulations that are primarily used for OUD are provided in the Supplemental Table 2. The number of methadone prescriptions per state was divided by the number of Medicaid enrollees per state in 2020. Three states—Virginia, Montana, and Iowa were excluded from the results due to being outliers (10-112K prescriptions/100K enrollees) which presumably reflected a Medicaid data error (mean 475.4 prescriptions/100K enrollees for the remaining 48 states). This study was approved by the institutional review boards of the University of New England and Geisinger.

The percent change in methadone distribution for OUD was compared between states for time spans of ten years, five years and one year respectively. Data were analyzed through one-way repeated measures ANOVA with Sidak corrections to examine the effects of OTPs per one million persons per state on 2010, 2015, 2020, 2021. Data were similarly to examine the effects of mg of methadone per person per state on 2010, 2015, 2019, 2020, and 2021. Heatmaps created using JMP version 16.2.0. Figures and data analysis completed using Microsoft Excel, GraphPad Prism version 9.4.0, and Systat version 13.1.

Results

ARCOS

Overall, the total volume of methadone distributed to OTPs in the US increased over the last decade from 8.62 metric tons in 2010 to 10.88 tons in 2015 (+26.3%), and to 13.03 tons in 2020 (+19.7%), reflecting an increase in distribution to the majority of states. Results of the one-way repeated measures ANOVA revealed a significant main effect of time on mg of methadone per person per state ($F(4, 200)=24.535$, $P < 0.001$). Specifically, the average percent change in state distribution of methadone for OUD from 2010 to 2020 significantly increased by +96.96% (SD=146.64%, Sidak post hoc $P < 0.001$), with forty-three states showing an increase, five states a decrease, and three states showing no change. There was also a significant increase in mg of methadone per person per state (+61.8%) from 2010 to 2019 ($P < 0.001$) and by +61.0% from 2010 to 2020 ($P < 0.001$). From 2010 to 2020, there was a large (> 1.5 SDs) increase in Vermont (+353.67%), and significant elevations (> 1.96 SDs, $P < 0.05$) in Alaska (+421.11%) and Montana (+897.02%) relative to the average (Figure 1).

Examination of 2015 relative to 2020 revealed the national average distribution for OUD increased significantly by +26.22% (SD = 50.38%, $P < 0.001$), with thirty-eight states increasing but eleven states decreasing. There were significant increases ($P < 0.05$) in Alaska (+135.34%) and Mississippi (+311.48%) relative to the national mean (Figure 2).

However, based on a one-way repeated measures ANOVA with Sidak post hoc from 2019 to 2020 (i.e., pre- to post- COVID-19 pandemic), the distribution of methadone was stable (-0.091%, SD = 10.81%). Slightly over half (twenty-eight) of states showed an increase and twenty-two states exhibited a decrease. No significant ($P = 1.000$) differences were found between 2019 and 2020. Examination of specific states revealed an increase in Kentucky (+18.68%) and a significant increase ($P < 0.05$) in Ohio (+26.02%) relative to the national mean. In contrast, there were appreciable decreases in Nebraska (-16.6%), South Dakota (-17.27%), and Mississippi (-20.53%), and significant decreases ($P < 0.05$) in Alabama (-21.96%), New Hampshire (-24.13%) and Florida (-28.97%) relative to the national mean (Figure 3).

Examination of 2019 to 2021, a wider pre- to post COVID-19 pandemic timeline, the distribution of methadone to OTPs showed a decline (-5.15%, SD = 19.14%), but no significant difference ($P = 0.491$). Eighteen states showed an increase while thirty-one states showed a decrease. Ohio (+47.53%) had a significant increase ($P < 0.05$) relative to the national mean. In contrast, there was an appreciable decrease in Mississippi (-42.53%), and significant decreases ($P < 0.05$) in Alabama (-44.27%), Nebraska (-47.96), New Hampshire (-52.99%) and Florida (-54.61%) relative to the national mean (Figure 4). However, distribution in 2021 was -5.69% lower than 2019 and -5.71% lower than 2020 (Supplemental Figure 2A).

The average methadone distribution in the US for OUD was 43.75 mg/person (SD = 35.01) in 2021. There was significantly elevated methadone distributed in Rhode Island (155.13 mg/person), Delaware (147.27 mg/person), Connecticut (126.66 mg/person), and Vermont (125.06 mg/person) relative to the national mean (43.75, $P < 0.05$).

The total number of OTPs distributing methadone in the US increased +18.6% from 2010 (1,139) to 2015 (1,351) and peaked in 2021 (1,738, Supplemental Figure 2B). In comparison, the number of pharmacies distributing buprenorphine (49,041) was 43.1-fold greater than OTPs distributing methadone in 2010. However, this ratio decreased to 33.3-fold in 2021. Results of the repeated measures ANOVA revealed a significant interaction between time and OTPs per one million persons per state ($F(3, 150)=38.067$, $P < 0.000$). The number of OTPs per one million persons per state significantly increased ($P < 0.0001$) from 2010 to 2021. In addition, one-way repeated measures ANOVA with Sidak post hoc revealed 2010 to 2015 ($P < 0.0001$), 2010 to 2020 ($P < 0.0001$), 2015 to 2020 ($P < 0.0001$), and 2015 to 2021 ($P < 0.0001$) were each significantly different. The number of OTPs per 1 million persons per state in 2020 relative to 2021 did not significantly increase ($P = 0.683$). Twenty states had fewer OTPs in 2021 relative to 2010, 2015, or 2020 (Alabama, Florida, Georgia, Maine, Maryland, Minnesota, Mississippi, Montana, Nebraska, New Hampshire, New Mexico, New York, North Carolina, Oklahoma, South Carolina, South Dakota, Texas, Utah, Vermont, and Washington). One state (Wyoming) did not have a single OTP (Figure 5, Supplemental Table 3).

Medicaid

The SDUD database showed considerable variation in methadone prescribing between states and regions for patients covered under Medicaid (mean = 475.39, SD = 1097.78 with four states having values of 0). The top four states (Wisconsin, Tennessee, Oregon, and Vermont) accounted for 64.03% of all methadone covered by Medicaid in 2020 (Supplemental Figure 3).

Discussion

The key finding of this study was that the pronounced and significant increase in methadone distribution to OTPs for OUD over the past decade has reversed with non-significant decreases (-0.09%) from 2019 to 2020 and (-5.15%) from 2019 to 2021. There were significant increases in the number of OTPs per one million persons per state over the past decade, but no significant increases over the COVID-19 pandemic period from 2019 compared to 2021 [28]. These findings point to the necessity for more OTPs to combat the escalating OUD problem with this evidence-based pharmacotherapy [7]. Twenty states showed a reduction in OTPs from 2010 to 2021 which could be due to funding issues or policies for OTPs in these states [42].

Examination of how the COVID-19 pandemic affected OUD treatment from 2019 to 2021 revealed that methadone distribution to OTPs did not increase significantly. However, a subtle but statistically significant increase (+5.0%) was observed in the number of poison control reports of intentional methadone exposure during this period [43]. In addition, the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) reported that drug overdose mortality increased by +31% between 2019 and 2020. Nonetheless, the rate of methadone overdose deaths remained low with no significant increase in this report, suggesting no change in nonprescribed methadone use during the COVID-19 pandemic [44]. However, others have reached the opposite conclusion [9]. Since OTPs were not distributing additional methadone MMEs during the COVID-19 pandemic, and overdose rates continue to surge, this emphasizes the need for expanded access to methadone treatment and reduced treatment barriers. Individuals who overdose may be prime candidates for methadone treatment. Additional solutions can include allowing for earlier access to take home methadone from OTPs and allowing for patients to obtain methadone prescriptions from community pharmacies after a period of OUD stability, which is currently prohibited by law outside of an OTP [45]. Another uncommonly employed solution is to provide travelling methadone treatment on a daily route which can allow observed administration and decrease need for transportation to a further location [46]. This would be particularly beneficial for rural areas.

Despite methadone being an evidence-based treatment for OUD which is superior to buprenorphine for patient retention [7], only forty-one states in 2018 had methadone covered under Medicaid [47]. Twelve states located predominantly in the South and Midwest opted to not expand Medicaid, leaving patients in these areas vulnerable to inaccessible treatment for OUD and for pain [48, 49]. States where methadone was not covered included: Arkansas, Idaho, Kansas, Kentucky, Louisiana, Nebraska, North Dakota, South Carolina, Tennessee, and Wyoming [47]. It was also found that only four states with 5.40% of the US population, accounted for the preponderance (64.03%) of prescriptions. This pronounced disparity indicates that patients in certain states and regions have appreciably better access to this evidence-based treatment for OUD than others [2]. Moving forward, improvements in access to

methadone prescriptions and clinics for Medicaid patients need to be expanded in order to equalize treatment options for this large, but vulnerable, population. Having coverage for methadone under Medicaid in all fifty states will help combat the escalating opioid epidemic by expanding treatment of substance use disorder (SUD) and OUD [47]. In addition, there is also a need for grant funding request for proposals to specifically focus on programs aimed at increasing access to methadone, particularly in rural areas [51].

This study suggests the importance of policy change as there is a pressing need for additional access to OUD therapy, specifically methadone treatment, in the US. Over 400,000 people in the US received methadone from an OTP pre-pandemic, 2019, with over 90% located in urban areas, making it challenging for rural patients to make the daily trip to receive their medication [50, 51, 52]. SAMHSA released guidelines in March 2020 allowing the regulatory authorities of all states to request blanket exceptions to allow OTP patients to take home doses of methadone and buprenorphine [53]. These guidelines were extended in November 2021. However, the number of patients receiving methadone declined in the first year of the COVID-19 pandemic by one-quarter [35]. Many providers and public health researchers are calling for these take home dosage rules to be continued post-pandemic [54, 55], although others that evaluated the number of overdoses involving methadone are more cautious [9, 56]. The number of pharmacies which dispensed buprenorphine was 34-fold greater in 2021 than the number of OTPs that dispensed methadone, indicating that buprenorphine is more easily accessible and available than methadone. On the other hand, the volume of methadone distributed by weight from OTPs was 2.4-fold higher than buprenorphine from pharmacies, hospitals, and OTPs combined, (Supplemental Table 1). It is currently curious that there are more restrictions in the US for prescribing methadone than for other Schedule II substances like fentanyl or oxycodone. Overcoming the “Not in my Backyard” (NIMBY) stigma surrounding OTPs is not a trivial undertaking and is exacerbated by a common lack of understanding of OUD as a chronic disease [41]. It will require a paradigm shift to allow supervised administration in pharmacies, primary care offices, mobile units as are common in other Western nations, and even video observed therapy [15, 26, 57, 58]. Expanding the role of specialty trained pharmacists by expanding the MOUD regulations to allow provider-delegated induction with buprenorphine in pharmacies, can immediately increase access to MOUD [57-61]. According to the Consolidated Appropriations Act, 2023, which was passed on December 29, 2022, medical providers with a current DEA registration number are now able to prescribe buprenorphine for OUD without needing an X-DEA waiver if state law permits it [62]. Overall, this is important because it aims to remove existing barriers to OUD treatment and increase access to care for individuals who need it.

During the pandemic, daily visits to a methadone clinic were considered to be a health hazard and regulations governing the clinical work of methadone clinics were changed. Nonetheless, methadone remains more challenging for patients to access on many counts. Additionally, the regulatory burden surrounding methadone maintenance means that creating clinics requires substantially more time, money and effort than even

specialty addiction medicine clinics where buprenorphine can be prescribed. This means that there will always be fewer methadone clinics than buprenorphine prescribers. This difference between the two medications may account for some of the change in methadone use described in this article. With the removal of the X-DEA waiver requirement for buprenorphine prescription, and the expansion of the exception to the Ryan Haight law [63] which governs prescribing scheduled drugs over telemedicine, it is reasonable to expect that an increasing proportion of people who have OUD will receive buprenorphine rather than methadone. That being said, despite lack of robust head to head trials [7], methadone has long been considered to have utility when other MOUDs have been ineffective, and is recommended for patients who cannot tolerate initiation or ongoing treatment with buprenorphine. Thus, there remains a strong need for wide and equitable methadone availability during this ever-worsening opioid crisis [64].

The strengths of this report include novel and timely data from ARCOS which is comprehensive for both distribution and number of distributors. This investigation extends upon earlier research both pre [4] and post COVID-19 pandemic [33, 34]. Potential caveats and limitations stem from the fact that methadone distribution is reported in ARCOS by weight rather than prescriptions per individual at an OTP. It is notable that ARCOS reporting does not differentiate between pharmacological formulations. Further, this pharmacoepidemiological report does not contain detailed patient-level information including medical comorbidities or social determinants of health. These contributions should be further explored in future investigations with electronic medical records. Because SAMHSA's N-SSATS annual reports contain data on the total number of patients receiving methadone at OTPs, they could complement the ARCOS data and allow for a more detailed analysis of opioid prescribing patterns and patient outcomes (Supplemental Figure 1) [35]. Importantly, other pharmacoepidemiological research that compared another Schedule II substance from ARCOS to a state Prescription Drug Monitoring Program identified a high correspondence (r = +.985) [32]. The inclusion of Medicaid data also, at least partially, offsets this concern. The paucity of methadone OTPs across rural states like Wyoming (253k km^2), South Dakota (200k km^2), and Nebraska (200 km^2) is an important finding. However, prior research found that another rural state, Maine, which ranked tenth in the US, had three-OTPs in a single thirty-thousand-person city (Bangor) and none in other areas in northern Maine [51]. The non-homogenous distribution within states should also be a concern for policy makers. Providing funding opportunities to train Addiction Medicine Fellows who will focus on rural care post-graduation can result in a pipeline of addiction medicine leaders to many areas of the US which are most in need. The ARCOS database has limitations such as lack of differentiation between pharmacological formulations and absence of patient-level information which suggests the need for future investigations. Future research should also be focused on determining which patient subgroups were most impacted by the reversal in methadone distribution. As the number of pharmacies nationally distributing buprenorphine decreased (-4.7%) from 2019 to 2021, further research should evaluate if both

methadone and buprenorphine continue to be underutilized in the post-COVID-19 pandemic period [65] (Supplemental Table 1).

Conclusions

In conclusion, this study highlights the trend over the past decade of methadone distribution for OUD in the US and disparities in access to OTPs in rural and western states. The findings of this study have the potential to guide improvements in OUD treatment policies at the state level, by providing valuable information on disparities in access to OTPs that could lead to the implementation of more permanent solutions. The many policy accommodations to COVID-19 may present an important opportunity to determine which factors most impact the accessibility, adherence, safety, and efficacy of methadone. Policy solutions that increase access to MOUD are urgently needed in order to continue to address the ongoing opioid epidemic.

Figure Captions

Figure 1. Percent change from 2010 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+96.96%, SD = 146.64%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 2. Percent change from 2015 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+26.22%, SD = 50.38%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 3. Percent change from 2019 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-0.09%, SD 10.81), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 4. Percent change from 2019 to 2021 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-5.15%, SD 19.14), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 5. Number of opioid treatment programs per 1 million persons per state all significantly (P < 0.0001) different from 2010, 2015, 2020 and 2021. The twenty states that decreased in 2021 relative to 2010, 2015 or 2020 are indicated with a "d". DC: District of Columbia.

Supplemental Materials

Supplemental Figure 1. Number of patients receiving methadone for opioid use disorder in the United States per year as reported by Substance Abuse and Mental Health Services Administration's National Survey of Substance Abuse Treatment Services data. The years 2014 and 2018 were not available and were omitted.

Supplemental Figure 2. Distribution in kg (A) and number of buyers and registrants (B) in Opioid Treatment Programs (OTP) and pharmacies (pharm, buprenorphine only) for methadone and buprenorphine as reported to the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders system for the fifty states, Washington DC, and the US Territories. Methadone in 2021 (12.4 metric tons) was 5.69% lower than 2019 (13.1 metric tons) and 5.71% below 2020 (13.1 metric tons). Methadone by weight was 2.49-fold greater than buprenorphine from pharmacies and OTPs in 2021. The number of pharmacies distributing buprenorphine was 33.3 to 47.3-fold greater than the number of OTPs distributing methadone from 2010 to 2021.

Supplemental Figure 3. Methadone prescriptions, per 100K Medicaid patients, for 48 US states, and Washington DC.

Supplemental Table 1. Comparison of the pharmacological and therapeutic properties of methadone and buprenorphine.

	Methadone	Buprenorphine
Year developed	1937	1969
Opioid receptor activity	mu full-agonist	mu partial agonist
Other mechanism(s)	NMDA antagonist	non-selective for other opioid receptors
Potency (x morphine)	8 – 12	10
Metabolism	CYP2D6, CYP3A4	CYP3A4
Active metabolite(s)	none	norbuprenorphine
Half-life	8 – 59 hours for oral	24 – 48 hours for buccal
Formulation	mono	mono or combination with naloxone
Present in breast milk	yes, < 3% maternal dose	yes, < 1% maternal dose
Availability (US)	narcotic treatment programs	providers with an X-waiver
Schedule (US)	II	III
Crowdsource (price/mg)	$0.96	$2.13
Black box warnings	addiction, abuse, misuse, QT prolongation	addiction, abuse, misuse[1], child exposure can result in overdose
Opioid rank	#1	#4
2021 Distribution (US)	12.4 metric tons[3]	5.2 metric tons[4]
WHO Essential Medication[2]	yes	yes

[1]buccal formulation; [2]complimentary; [3]Opioid Treatment Programs (OTP); [4]total of pharmacies, hospitals, and OTP.

Supplementary Table 2. Medicaid's State Drug Utilization Data reported National Drug Codes (NDC) for methadone prescribed for opioid use disorder.

NDC
54039168
54039268
54355344
54355563
54421825
54421925
54453825

54457025

54457125

54855324

54855424

406052710

406054034

406254001

406575501

406575523

406575562

406577101

406577123

406577162

406872510

904653061

13107000000

17478000000

31722000000

42806000000

60687000000

63739000000

66689000000

67457000000

67877000000

68084000000

68462000000

Supplemental Table 3. Opioid treatment programs as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System per one million persons.

State	2010	2015	2020	2021
1. Rhode Island	16.1	16.1	21.0	24.6
2. Delaware	6.7	10.6	14.1	17.9
3. Maryland	9.9	11.4	14.4	14.3
4. Connecticut	10.1	10.3	11.9	14.1
5. Massachusetts	7.9	9.1	12.1	13.7
6. Vermont	11.2	14.4	12.4	12.4
7. New Mexico	4.8	6.7	11.3	9.5
8. Arizona	5.0	5.7	9.2	9.3
9. DC	8.3	5.9	7.3	9.0
10. Alaska	2.8	5.4	5.5	8.2
11. Maine	6.8	9.0	7.3	7.3
12. Illinois	5.1	5.6	7.2	7.2
13. Pennsylvania	5.4	5.8	6.9	7.0
14. Georgia	4.7	6.3	7.0	6.7
15. Kentucky	3.0	3.4	6.2	6.4
16. North Carolina	3.8	5.1	7.9	6.4
17. Iowa	1.3	2.2	5.6	6.0
18. New York	5.7	5.3	6.0	5.8
19. New Hampshire	4.6	6.0	7.3	5.8
20. Ohio	1.5	1.8	4.8	5.5
21. Oregon	3.4	3.7	5.2	5.4
22. Nevada	4.4	4.5	5.2	5.4
23. Utah	3.6	4.4	5.5	5.1
24. West Virginia	4.9	4.9	5.0	5.0
25. Oklahoma	3.7	3.6	5.3	5.0
26. Colorado	2.2	2.6	4.9	5.0
27. Michigan	3.3	4.3	4.5	4.8
28. New Jersey	0.11	3.7	4.7	4.7
29. Virginia	2.1	3.6	4.5	4.7
30. South Carolina	1.9	3.7	4.7	4.6
31. California	3.8	3.8	4.0	4.2
32. North Dakota	0.0	0.0	3.8	3.9
33. Wisconsin	2.3	3.0	3.7	3.7
34. Montana	2.0	2.9	3.7	3.6
35. Indiana	2.2	2.1	3.4	3.5
36. Washington	3.0	3.0	3.9	3.5
37. Alabama	2.9	4.5	4.6	3.2
38. Texas	3.3	3.2	3.3	3.1
39. Kansas	2.5	3.1	3.1	3.1
40. Minnesota	1.5	3.3	2.8	3.0
41. Missouri	1.7	2.5	2.6	2.9

42. Tennessee	1.9	1.8	2.3	2.9
43. Louisiana	1.8	2.1	2.2	2.8
44. Hawaii	2.9	2.8	2.8	2.8
45. Florida	1.3	2.6	2.9	2.5
46. Idaho	1.9	1.8	2.2	2.1
47. Arkansas	1.0	2.0	2.0	2.0
48. South Dakota	0.0	1.2	1.1	1.1
49. Nebraska	1.6	1.6	1.5	1.0
50. Mississippi	0.3	0.3	1.7	1.0
51. Wyoming	0.0	0.0	0.0	0.0
Mean	**3.8**	**4.6**	**5.7**	**5.9**
SEM	**0.4**	**0.5**	**0.6**	**0.6**

Author Contributions: Conceptualization, Amy Kennalley and Brian Piper; Data curation, Amy Kennalley and Jessica Fanelli; Formal analysis, Amy Kennalley; Investigation, Amy Kennalley; Methodology, Brian Piper; Project administration, Kenneth McCall; Supervision, Brian Piper; Visualization, Amy Kennalley; Writing – original draft, Amy Kennalley; Writing – review & editing, Jessica Fanelli, John Furst Jr., Nicholas Mynarski, Margaret Jarvis, Stephanie Nichols, Kenneth McCall and Brian Piper.

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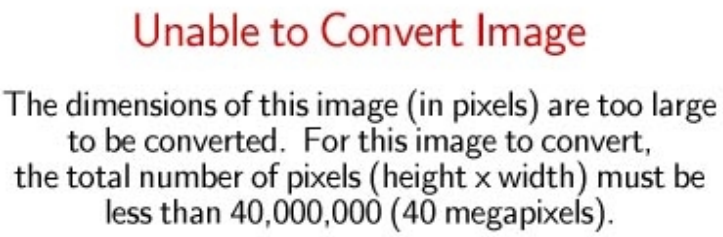

Figure 1. Percent change from 2010 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+96.96%, SD = 146.64%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

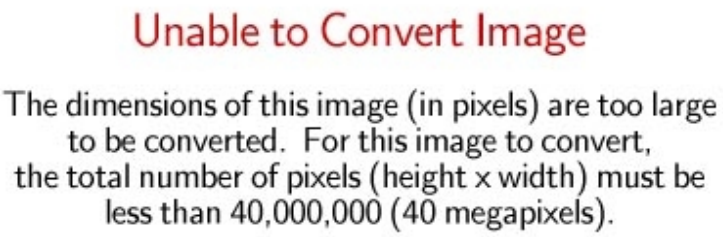

Figure 2. Percent change from 2015 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+26.22%, SD = 50.38%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

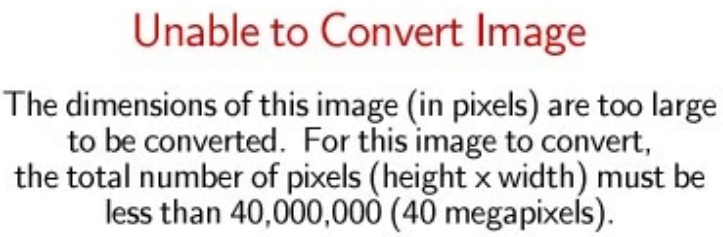

Figure 3. Percent change from 2019 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-0.09%, SD 10.81), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

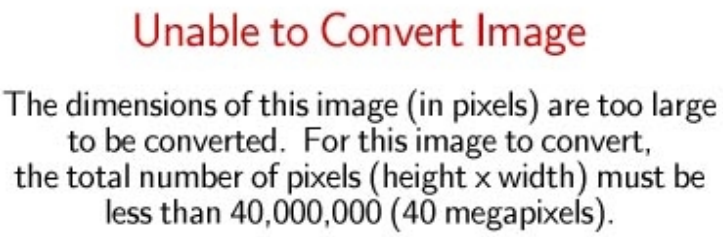

Figure 4. Percent change from 2019 to 2021 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-5.15%, SD 19.14), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

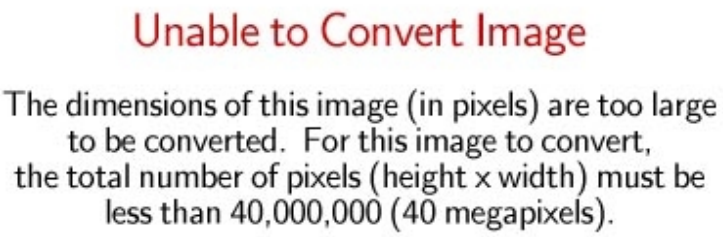

Figure 5. Number of opioid treatment programs per 1 million persons per state all significantly ($P < 0.0001$) different from 2010, 2015, 2020 and 2021. The twenty states that decreased in 2021 relative to 2010, 2015 or 2020 are indicated with a "d". DC: District of Columbia.

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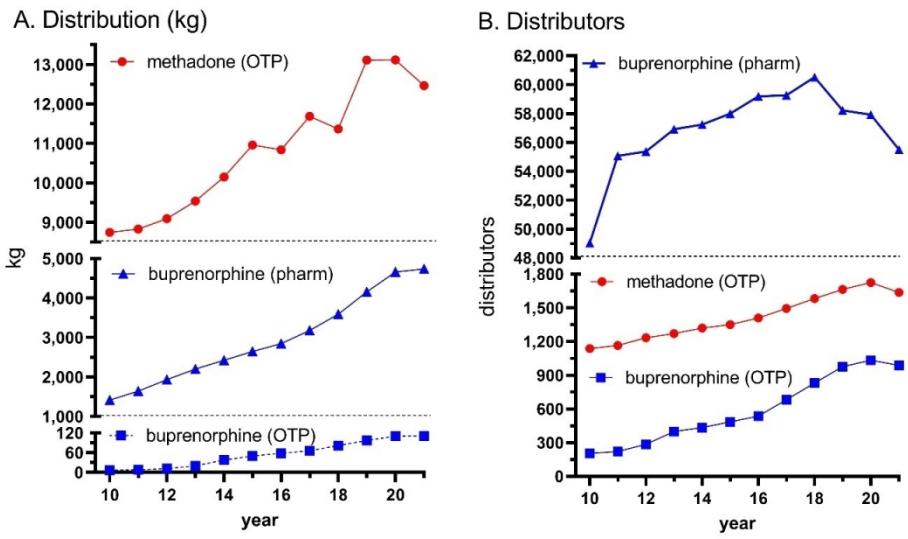

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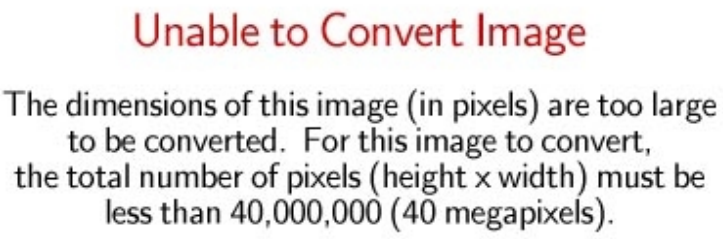
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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9, 10, 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Dynamic Changes in Methadone Utilization for Opioid Use Disorder Treatment: A Retrospective Observational Study During the COVID-19 Pandemic

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Abstract

Objectives: Opioid use disorder (OUD) is a major public health concern in the United States (US), resulting in high rates of overdose and other negative outcomes. Methadone, an OUD treatment, has been shown to be effective in reducing the risk of overdose and improving overall health and quality of life. This study analyzed the distribution of methadone for the treatment of OUD across the US over the past decade and through COVID-19 pandemic.

Design: Retrospective observational study using secondary data analysis of Drug Enforcement Administration and Medicaid databases.

Setting: United States.

Participants: Patients who were dispensed methadone at US Opioid Treatment Programs (OTPs).

Primary and secondary outcome measures: The primary outcomes were the overall pattern in methadone distribution and the number of OTPs in the US per year. The secondary outcome was Medicaid prescriptions for methadone.

Results: Methadone distribution for OUD has expanded significantly over the past decade, with an average state increase of +96.96% from 2010 to 2020. There was a significant increase in overall distribution of methadone to OTP from 2010 to 2020 (+61.00%, $P \leq 0.001$) and from 2015 to 2020 (+26.22%, $P < 0.001$). However, the distribution to OTPs did not significantly change from 2019 to 2021 (-5.15%, $P = 0.491$). There was considerable state level variation in methadone prescribing to Medicaid patients with four states having no prescriptions.

Conclusions: There have been dynamic changes in methadone distribution for OUD. Furthermore, pronounced variation in methadone distribution among states were observed, with some states having no OTPs or Medicaid coverage. New policies are urgently needed to increase access to methadone treatment, address the opioid epidemic in the US, and reduce overdose deaths.

Article Summary: Strengths and limitations of this study

- ARCOS provides novel data on distribution and distributors of methadone for OTPs over the past decade, pre- and post-COVID-19
- ARCOS reports methadone distribution by weight, not by patient count or prescriptions, and doesn't differentiate pharmacological formulations
- Incorporating Medicaid data compensates for the absence of patient level methadone data in ARCOS

Introduction

The United States (US) Food and Drug Administration (FDA) has approved methadone, buprenorphine, and naltrexone as treatments for Opioid Use Disorder (OUD) [1], but there have been several policy changes impacting OUD care during the COVID-19 pandemic. Methadone, considered a gold standard medication for OUD (MOUD), is a long-acting synthetic opioid administered via opioid treatment programs (OTP) [1-3]. Since 2021, it has been revealed that only 27.8% of individuals with OUD have actually received MOUD treatment [4].

Over recent years, methadone take-home doses have been extended to 28 days for stable patients and 14 days for less stable patients, drug screening requirements have been relaxed, and telemedicine has been expanded for established patients [5, 6]. However, unlike for buprenorphine, starting methadone treatment requires an in-person visit. Prior to the pandemic, OUD methadone treatment also required the co-administration of counseling, and these counseling requirements have also been relaxed due to the COVID-19 pandemic [6-8].

Despite its effectiveness, methadone carries the potential for serious adverse effects including respiratory depression and cardiotoxicity [3, 9, 10]. An alternative gold standard MOUD, buprenorphine, has also raised safety concerns, with rising respiratory depression fatalities associated with oral doses in both adult and pediatric patients, resulting in a total of 84 deaths from 2003–2019 [11]. However, it is important to note that in 2021 alone, there were 106,699 overdose deaths in the US emphasizing the urgency of providing first-line care [12].

In regions where available, methadone is frequently used for severe OUD cases due to its full mu receptor agonist properties and its doses can be titrated up as needed. Buprenorphine is a partial mu receptor agonist with less higher end dosing flexibility [13]. Methadone necessitates expert handling, especially in the early stages of treatment because of its full agonism properties combined with high lipophilicity, long serum half-life, and active metabolites [14].

Due to its pharmacokinetic and pharmacodynamic properties [11], buprenorphine combined with naloxone may be becoming a more commonly prescribed option compared to methadone. A recent survey revealed 75% of emergency room physicians preferred buprenorphine over methadone [15]. Buprenorphine was inequitably available from 2004 to 2015 driven by systemic racism and discrimination based on socioeconomic status. In particular, Black patients had a lower probability of receiving a prescription [16]. Findings from a retrospective, cohort study from 1998 to 2014 suggest that patients treated with buprenorphine had a lower risk of drug-related poisoning mortality during treatment compared to those on methadone [17].

Compared to buprenorphine, treatment with methadone was more effective in reducing criminal activity, HIV infection, hepatitis, and overall mortality [2,18-21]. Additionally, a Cochrane meta-analysis concluded that methadone was better for

retaining patients in OUD treatment only if buprenorphine doses were 7mg per day or lower, but both methadone and buprenorphine were equivalent at higher doses (Supplemental Table 1) [22]. However, there is a nationwide accessibility problem for treatment with all potential MOUD [23, 24]. Although studies have shown that both treatments are effective, clinicians and patients should choose between MOUD treatments depending on their individual needs and circumstances, including the accessibility and availability of treatment programs in their area [2, 17-24].

Methadone is a safe and effective treatment for OUD in fentanyl users and is the preferred medication over buprenorphine in this population. Methadone treatment is associated with a significant decrease in illicit drug use, including fentanyl. However, it is important to start with a higher dose of methadone than in people who are not using fentanyl [25, 26]. Patients with OUD who are using fentanyl are at increased risk of overdose and relapse, but methadone treatment can significantly reduce this risk. Additionally, patients who test positive for fentanyl use at the start of methadone treatment are just as likely to achieve remission as patients who test negative for fentanyl use. Methadone may also be protective against fentanyl overdose deaths [27]. These findings suggest that methadone is a valuable tool for treating OUD in fentanyl users.

There have been over one-million drug overdoses in the US since the start of the opioid epidemic [28]. The COVID-19 pandemic has placed tremendous stress on the healthcare system including the access to providers and availability of OUD treatments. Between 2019 and 2020, there was a +48.8% increase in overdose mortality among Black people, compared to +26.3% among White people [29]. Moreover, from April 2020 to April 2021, the number of drug overdoses in the US exceeded one-hundred thousand, a +28.5% increase over the previous year [30]. With a +60% rise in overdoses compared to the previous year, May 2020 became the deadliest month on record [31].

A cross-sectional study, conducted from May to June 2020 in the US and Canada, found that new patients wishing to initiate methadone treatment were faced with a barrier in 20% of clinics [32]. Similarly, prior to the pandemic, both methadone and buprenorphine-based OTPs were found to be effective in US jails and prisons. However, following the pandemic, some of these OTPs have been expanded while others were discontinued [33-35].

This study obtained data from the Drug Enforcement Administration's (DEA) Automated Reports and Consolidated Ordering System (ARCOS), a federal program established by the 1970 Controlled Substances Act, to monitor the distribution of DEA controlled substances from various sources including retail pharmacies, hospitals, practitioners, teaching institutions, mid-level practitioners, and OTPs [36]. Previous pharmacoepidemiologic studies have also utilized the ARCOS database [37-41]. It is important to note that ARCOS does not provide information on the number of patients receiving methadone. This caveat is important because it prevents an accurate

representation of the amount of methadone used for each OUD patient. However, federally funded OTPs record number of patients receiving treatment, which could be a useful resource in understanding the true scale of the OUD epidemic in the US and the effectiveness of treatment efforts. The Substance Abuse Mental Health Services Administration's (SAMHSA) National Survey of Substance Abuse Treatment Services' (N-SSATS) annual report provides national data regarding alcohol and drug abuse facilities [42]. The number of patients receiving methadone for OUD decreased by almost one-quarter (-23.7%) from 2019 (408,550) to 2020 (311,531) [42] (Supplemental Figure 1).

In addition to ARCOS, Medicaid's State Drug Utilization Data (SDUD) database was used in this study [43]. Medicaid is a program at the federal and state level which functions to aid in covering healthcare costs for patients with limited resources [44]. Medicaid.gov publishes all prescription drugs covered by Medicaid every year for all 50 states and the District of Colombia (DC) in the SDUD database. The State Health Official Letter, released on December 30, 2020, states that the SUPPORT Act of 2018 mandates the inclusion of Medicaid coverage for MOUD for all eligible patients with OUD. Subsequently, the Continuing Appropriations Act of 2021, which added to the SUPPORT Act, requires rebates on methadone and other MOUD starting from October 1, 2020, to September 30, 2025. [45, 46]. However, not all states have equal coverage of medications, which can lead to discrepancies in the prescription numbers reflected by the SDUD. There is variation among states regarding methadone coverage, which in turn affects prescribing methadone patterns [47].

This manuscript aims to address the paucity of research on methadone for OUD treatment over the past decade and during the COVID-19 pandemic. The impact of COVID-19-related policies on individuals with OUD is poorly understood, and this manuscript seeks to shed light on this important area of research. The use of both ARCOS and SDUD databases provide a comprehensive picture of the distribution and utilization of methadone for the OUD treatment over the past decade. Together, it is critical to examine the changes in methadone distribution during the COVID-19 pandemic to determine whether there are national or regional barriers to accessing this evidence-based pharmacotherapy.

Materials and Methods

The quantities of methadone distributed (in grams) per state were obtained from the ARCOS yearly drug summary reports for the years 2010, 2015, 2019, 2020 and 2021. Methadone distributed to OTPs, in the ARCOS database, was classified as an OUD treatment which excluded all methadone for pain. The number of OTPs per state were also obtained from ARCOS for 2010, 2015, 2019, 2020 and 2021. The state population estimates, including DC, were derived from the US Census Bureau's Annual Estimates of the Resident Population for the US [48]. The US Territories were examined elsewhere and were not included in Figures 1-5 [49]. Medicaid data was collected in the year 2020 for all 50 states and DC using a filtered download from the SDUD [43]. This data from Medicaid was the methadone reimbursements for use for OUD. National Drug Codes (NDC) of formulations that are primarily used for OUD are provided in the Supplemental Table 2. The number of methadone prescriptions per state was divided by the number of Medicaid enrollees per state in 2020. Three states—Virginia, Montana, and Iowa were excluded from the results due to being outliers (10-112K prescriptions/100K enrollees) which presumably reflected a Medicaid data error (mean 475.4 prescriptions/100K enrollees for the remaining 48 states). This study was approved by the institutional review boards of the University of New England and Geisinger.

The percent change in methadone distribution for OUD was compared between states for time spans of ten years, five years and one year respectively. For all 50 states, the milligrams of methadone per person for the years 2010, 2015, 2020 was calculated. This this calculation is the “amount distributed” per year in the following equation: percentage change = (Amount distributed in later year - Amount distributed in earlier year) / Amount distributed in earlier year * 100. Data were analyzed through one-way repeated measures ANOVA with Sidak corrections to examine the effects of OTPs per one million persons per state in 2010, 2015, 2020, 2021. Data were similarly analyzed to examine the effects of mg of methadone per person per state in 2010, 2015, 2019, 2020, and 2021. Heatmaps were created using JMP version 16.2.0. Figures and data analysis were completed using Microsoft Excel, GraphPad Prism version 9.4.0, and Systat version 13.1.

Patient and Public Involvement

None.

Results

ARCOS

Overall, the total volume of methadone distributed to OTPs in the US increased over the last decade from 8.62 metric tons in 2010 to 10.88 tons in 2015 (+26.3%), and to 13.03 tons in 2020 (+19.7%), reflecting an increase in distribution to the majority of

states. Results of the one-way repeated measures ANOVA revealed a significant main effect of time on mg of methadone per person per state ($F(4, 200)=24.535$, $P < 0.001$). Specifically, the average percent change in state distribution of methadone for OUD from 2010 to 2020 significantly increased by +96.96% (SD=146.64%, Sidak post hoc $P < 0.001$), with forty-three states showing an increase, five states a decrease (DC, Florida, Maine, Tennessee, and West Virginia), and three states showing no change (North Dakota, South Dakota, and Wyoming). There was also a significant increase in mg of methadone per person per state (+61.8%) from 2010 to 2019 ($P < 0.001$) and by +61.0% from 2010 to 2020 ($P < 0.001$). From 2010 to 2020, there was a large (> 1.5 SDs) increase in Vermont (+353.67%), and significant elevations (> 1.96 SDs, $P < 0.05$) in Alaska (+421.11%) and Montana (+897.02%) relative to the average (Figure 1). These findings show that methadone distribution in the US has increased significantly over the past decade, with most states showing increases.

Examination of 2015 relative to 2020 revealed the national average distribution of methadone for OUD increased significantly by +26.22% (SD = 50.38%, $P < 0.001$), with thirty-eight states increasing but eleven states decreasing (Alabama, Florida, Georgia, Kansas, Maine, Minnesota, Missouri, Nebraska, New Hampshire, South Dakota, and Texas). There were significant increases ($P < 0.05$) in Alaska (+135.34%) and Mississippi (+311.48%) relative to the national mean (Figure 2). In conclusion, methadone distribution increased from 2015 to 2020, with significant increases in most states.

Based on a one-way repeated measures ANOVA with Sidak post hoc from 2019 to 2020 (i.e., pre- to post- COVID-19 pandemic), the distribution of methadone was stable (-0.091%, SD = 10.81%). Slightly over half (twenty-eight) of states showed an increase and twenty-two states exhibited a decrease. No significant ($P = 1.000$) differences were found between 2019 and 2020. Examination of specific states revealed an increase in Kentucky (+18.68%) and a significant increase ($P < 0.05$) in Ohio (+26.02%) relative to the national mean. In contrast, there were appreciable decreases in Nebraska (-16.6%), South Dakota (-17.27%), and Mississippi (-20.53%), and significant decreases ($P < 0.05$) in Alabama (-21.96%), New Hampshire (-24.13%) and Florida (-28.97%) relative to the national mean (Figure 3). Overall, the distribution in was stable from 2019 to 2020, with significant increases in two states and decreases in three states.

Examination of 2019 to 2021, a wider pre- to post COVID-19 pandemic timeline, the distribution of methadone to OTPs showed a decline (-5.15%, SD = 19.14%), but no significant difference ($P = 0.491$). Eighteen states showed an increase while thirty-one states showed a decrease. Ohio (+47.53%) had a significant increase ($P < 0.05$) relative to the national mean. In contrast, there was an appreciable decrease in Mississippi (-42.53%), and significant decreases ($P < 0.05$) in Alabama (-44.27%), Nebraska (-47.96), New Hampshire (-52.99%) and Florida (-54.61%) relative to the national mean (Figure 4). However, distribution in 2021 was -5.69% lower than 2019 and -5.71% lower

than 2020 (Supplemental Figure 2A). In summary, methadone distribution declined from 2019 to 2021, with significant decreases in four states and increase in one state.

The average methadone distribution in the US for OUD was 43.75 mg/person (SD = 35.01) in 2021. There was significantly elevated methadone distributed in Rhode Island (155.13 mg/person), Delaware (147.27 mg/person), Connecticut (126.66 mg/person), and Vermont (125.06 mg/person) relative to the national mean (43.75, $P < 0.05$). Therefore, the distribution was relatively uniform in 2021, with significant elevations in Rhode Island, Delaware, Connecticut, and Vermont.

The total number of OTPs distributing methadone in the US increased +18.6% from 2010 (1,139) to 2015 (1,351) and peaked in 2021 (1,738, Supplemental Figure 2B). In comparison, the number of pharmacies distributing buprenorphine (49,041) was 43.1-fold greater than OTPs distributing methadone in 2010. However, this ratio decreased to 33.3-fold in 2021. Results of the repeated measures ANOVA revealed a significant interaction between time and OTPs per one million persons per state ($F(3, 150)=38.067$, $P < 0.000$). The number of OTPs per one million persons per state significantly increased ($P < 0.0001$) from 2010 to 2021. In addition, one-way repeated measures ANOVA with Sidak post hoc revealed 2010 to 2015 ($P < 0.0001$), 2010 to 2020 ($P < 0.0001$), 2015 to 2020 ($P < 0.0001$), and 2015 to 2021 ($P < 0.0001$) were each significantly different. The number of OTPs per 1 million persons per state in 2020 relative to 2021 did not significantly increase ($P = 0.683$). Twenty states had fewer OTPs in 2021 relative to 2010, 2015, or 2020 (Alabama, Florida, Georgia, Maine, Maryland, Minnesota, Mississippi, Montana, Nebraska, New Hampshire, New Mexico, New York, North Carolina, Oklahoma, South Carolina, South Dakota, Texas, Utah, Vermont, and Washington). One state (Wyoming) did not have a single OTP (Figure 5, Supplemental Table 3). To sum up, the number of OTPs distributing methadone increased significantly from 2010 to 2021 but plateaued in 2021. The number of OTPs per million persons per state also increased significantly, but there was no significant increase from 2020 to 2021.

Medicaid

The SDUD database showed considerable variation in methadone prescribing between states and regions for patients covered under Medicaid (mean = 475.39, SD = 1097.78 with four states having values of 0). The top four states (Wisconsin, Tennessee, Oregon, and Vermont) accounted for 64.03% of all methadone covered by Medicaid in 2020 (Supplemental Figure 3). Four states reporting zero values suggest that some data may be missing from the SDUD database. In conclusion, methadone prescribing for Medicaid patients varied widely across states, with the top four states disproportionally accounting for over 60% of all prescriptions.

Discussion

The key finding of this study was that the pronounced and significant increase in methadone distribution to OTPs for OUD over the past decade has reversed with non-significant decreases (-0.09%) from 2019 to 2020 and (-5.15%) from 2019 to 2021. There were significant increases in the number of OTPs per one million persons per state over the past decade, but no significant increases over the COVID-19 pandemic period from 2019 compared to 2021 [34]. These findings point to the necessity for more OTPs to combat the escalating OUD problem with this evidence-based pharmacotherapy [8]. Twenty states showed a reduction in OTPs from 2010 to 2021 which could be due to funding issues or policies for OTPs in these states [50].

Examination of how the COVID-19 pandemic affected OUD treatment from 2019 to 2021 revealed that methadone distribution to OTPs did not increase significantly. However, a subtle but statistically significant increase (+5.0%) was observed in the number of poison control reports of intentional methadone exposure during this period [51]. In addition, the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) reported that drug overdose mortality increased by +31% between 2019 and 2020. Nonetheless, the rate of methadone overdose deaths remained low with no significant increase in this report, suggesting no change in nonprescribed methadone use during the COVID-19 pandemic [52]. Conversely, others have reached the opposite conclusion [10].

Since OTPs were not distributing additional methadone MMEs during the COVID-19 pandemic, and overdose rates continue to surge, this emphasizes the need for expanded access to methadone treatment and reduced treatment barriers. Individuals who overdose on illicit and prescription opioids including heroin and fentanyl may be prime candidates for methadone treatment. Additional solutions can include allowing for earlier access to take home methadone from OTPs and allowing for patients to obtain methadone prescriptions from community pharmacies after a period of OUD stability, which is currently prohibited by law outside of an OTP [53]. Another uncommonly employed solution is to provide travelling methadone treatment on a daily route which can allow observed administration and decrease need for transportation to a further location [54]. This would be particularly beneficial for rural areas but also useful for zip codes with a limited number of methadone programs.

Despite methadone being an evidence-based treatment for OUD with better patient retention compared to buprenorphine [8], only forty-one states in 2018 had methadone covered under Medicaid [47]. Twelve states located predominantly in the South and Midwest opted to not expand Medicaid, leaving patients in these areas vulnerable to inaccessible treatment [55, 56]. States where methadone was not covered included: Arkansas, Idaho, Kansas, Kentucky, Louisiana, Nebraska, North Dakota, South Carolina, Tennessee, and Wyoming [47]. It was also found that only four states with 5.40% of the US population, accounted for the preponderance (64.03%) of prescriptions. Although this lab has prior experience with Medicaid in various capacities

(clozapine, esketamine, etc.) the data acquired should be viewed with substantial skepticism unless subsequently verified by others, as some states may not have uploaded all their methadone data [57, 58]. This pronounced disparity indicates that patients in certain states and regions have appreciably better access to this evidence-based treatment for OUD than others [2].

This study suggests the importance of policy change as there is a pressing need for additional access to OUD therapy, specifically methadone treatment, in the US. Over 400,000 people in the US received methadone from an OTP pre-pandemic, 2019, with over 90% located in urban areas, making it challenging for rural patients to receive their medication [58-61]. SAMHSA released guidelines in March 2020 allowing the regulatory authorities of all states to request blanket exceptions to allow OTP patients to take home doses of methadone and buprenorphine [62]. These guidelines were extended in November 2021. However, the number of patients receiving methadone declined in the first year of the COVID-19 pandemic by one-quarter [35]. Many providers and public health researchers are calling for these take home dosage rules to be continued post-pandemic [63, 64], although others that evaluated the number of overdoses involving methadone are more cautious [10, 65].

The number of pharmacies which dispensed buprenorphine was 34-fold greater in 2021 than the number of OTPs that dispensed methadone, indicating that buprenorphine is more easily accessible and available than methadone. On the other hand, the volume of methadone distributed by weight from OTPs was 2.4-fold higher than buprenorphine from pharmacies, hospitals, and OTPs combined, (Supplemental Table 1). It is currently curious that there are more restrictions in the US for prescribing methadone than for other Schedule II substances like fentanyl or oxycodone. Overcoming the “Not in my Backyard” (NIMBY) stigma surrounding OTPs is not a trivial undertaking and is exacerbated by a common lack of understanding of OUD as a chronic disease [48]. It will require a paradigm shift to allow supervised administration in pharmacies, primary care offices, mobile units as are common in other Western nations, and even video observed therapy [18, 32, 66, 67].

Expanding the role of specialty trained pharmacists by expanding the MOUD regulations to allow provider-delegated induction with buprenorphine in pharmacies, can immediately increase access to MOUD [66-70]. According to the Consolidated Appropriations Act, 2023, which was passed on December 29, 2022, medical providers with a current DEA registration number are now able to prescribe buprenorphine for OUD without needing an X-DEA waiver if state law permits it [71]. Overall, this is important because it aims to remove existing barriers to OUD treatment and increase access to care for individuals who need it.

During the pandemic, daily visits to a methadone clinic were a health hazard and regulations governing the clinical work of methadone clinics were changed. Nonetheless, methadone remains more challenging for patients to access on many counts. Additionally, the regulatory burden surrounding methadone maintenance means

that creating clinics requires substantially more time, money, and effort than even specialty addiction medicine clinics where buprenorphine can be prescribed. This means that there will always be fewer methadone clinics than buprenorphine prescribers. This difference between the two medications may account for some of the change in methadone use described in this article. With the removal of the X-DEA waiver requirement for buprenorphine prescription, and the expansion of the exception to the Ryan Haight law [72] which governs prescribing scheduled drugs over telemedicine, it is reasonable to expect that an increasing proportion of people who have OUD will receive buprenorphine rather than methadone. Despite lack of robust head-to-head trials [8], methadone has long been considered to have utility when other MOUDs have been ineffective and is recommended for patients who cannot tolerate initiation or ongoing treatment with buprenorphine. Thus, there remains a strong need for wide and equitable methadone availability during this ever-worsening opioid crisis [73].

The non-homogenous distribution within states should also be a concern for policy makers. The paucity of methadone OTPs across rural states like Wyoming (253k km^2), South Dakota (200k km^2), and Nebraska (200 km^2) is an important finding. However, prior research found that another rural state, Maine, which ranked tenth in the US, had three-OTPs in a single thirty-thousand-person city (Bangor) and none in other areas in northern Maine [60]. Providing funding opportunities to train Addiction Medicine Fellows who will focus on rural care post-graduation can result in a pipeline of addiction medicine leaders to many areas of the US which are most in need.

The strengths of this report include novel and timely data from ARCOS which is comprehensive for both distribution and number of distributors. This investigation extends upon earlier research both pre [5] and post COVID-19 pandemic [40, 41]. Potential caveats and limitations stem from the fact that methadone distribution is reported in ARCOS by weight rather than prescriptions per individual at an OTP. It is notable that ARCOS reporting does not differentiate between pharmacological formulations. Further, this pharmacoepidemiological report does not contain detailed patient-level information including medical comorbidities or social determinants of health. These contributions should be further explored in future investigations with electronic medical records. Because SAMHSA's N-SSATS annual reports contain data on the total number of patients receiving methadone at OTPs, they could complement the ARCOS data and allow for a more detailed analysis of opioid prescribing patterns and patient outcomes (Supplemental Figure 1) [42]. Importantly, other pharmacoepidemiological research that compared another Schedule II substance from ARCOS to a state Prescription Drug Monitoring Program identified a high correspondence (r = +.985) [39]. The inclusion of Medicaid data also, at least partially, offsets this concern. However, the substantial state-level inhomogeneity of methadone as reported by Medicaid should be viewed carefully and warrants further study. A reported value of zero for four state could possibly be explained by factors such as states not reporting data or changes in how states report this data over time. Future

research should also be focused on determining which patient subgroups were most impacted by the reversal in methadone distribution. As the number of pharmacies nationally distributing buprenorphine decreased (-4.7%) from 2019 to 2021, further research should evaluate if both methadone and buprenorphine continue to be underutilized in the post-COVID-19 pandemic period [74] (Supplemental Table 1). This research is essential to guide policy and practice efforts to ensure that all individuals with OUD have access to effective MOUD treatment options.

Conclusions

In conclusion, this study highlights the trend over the past decade of methadone distribution for OUD in the US and disparities in access to OTPs in rural and western states. The findings of this study have the potential to guide improvements in OUD treatment policies at the state level, by providing valuable information on disparities in access to OTPs that could lead to the implementation of more permanent solutions. The many policy accommodations to COVID-19 may present an important opportunity to determine which factors most impact the accessibility, adherence, safety, and efficacy of methadone. Policy solutions that increase access to MOUD are urgently needed to continue to address the ongoing opioid epidemic.

Figure Captions

Figure 1. Percent change from 2010 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+96.96%, SD = 146.64%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 2. Percent change from 2015 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+26.22%, SD = 50.38%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 3. Percent change from 2019 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-0.09%, SD 10.81), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 4. Percent change from 2019 to 2021 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-5.15%, SD 19.14), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

Figure 5. Number of opioid treatment programs per 1 million persons per state all significantly (P < 0.0001) different from 2010, 2015, 2020 and 2021. The twenty states that decreased in 2021 relative to 2010, 2015 or 2020 are indicated with a "d". DC: District of Columbia.

Supplemental Materials

Supplemental Figure 1. Number of patients receiving methadone for opioid use disorder in the United States per year as reported by Substance Abuse and Mental Health Services Administration's National Survey of Substance Abuse Treatment Services data. The years 2014 and 2018 were not available and were omitted.

Supplemental Figure 2. Distribution in kg (A) and number of buyers and registrants (B) in Opioid Treatment Programs (OTP) and pharmacies (pharm, buprenorphine only) for methadone and buprenorphine as reported to the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders system for the fifty states, Washington DC, and the US Territories. Methadone in 2021 (12.4 metric tons) was 5.69% lower than 2019 (13.1 metric tons) and 5.71% below 2020 (13.1 metric tons). Methadone by weight was 2.49-fold greater than buprenorphine from pharmacies and OTPs in 2021. The number of pharmacies distributing buprenorphine was 33.3 to 47.3-fold greater than the number of OTPs distributing methadone from 2010 to 2021.

Supplemental Figure 3. Methadone prescriptions, per 100K Medicaid patients, for 48 US states, and Washington DC.

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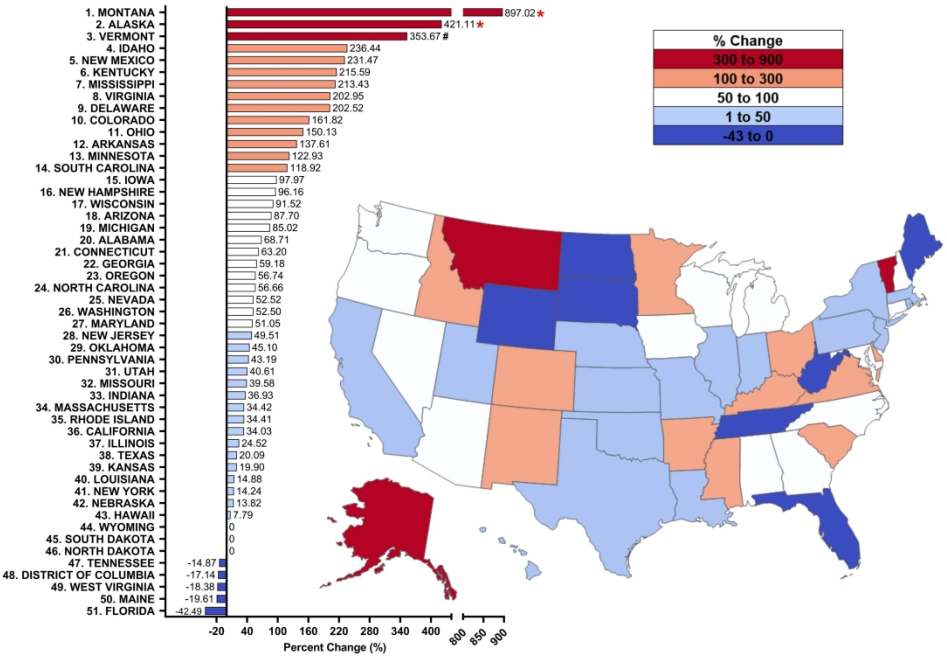
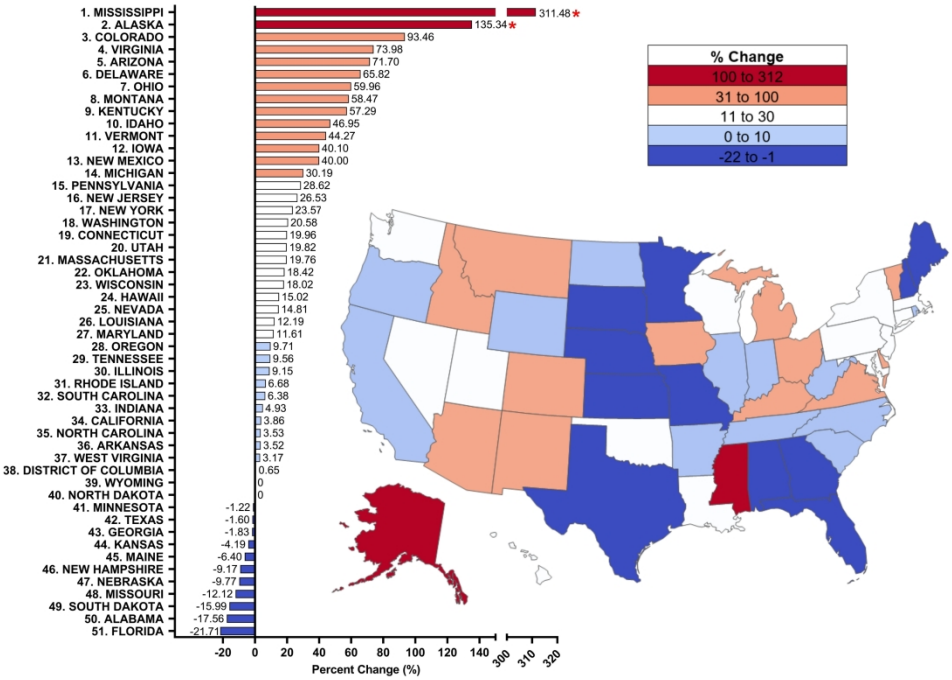


Percent change from 2010 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+96.96%, SD = 146.64%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

141x102mm (600 x 600 DPI)



Percent change from 2015 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (+26.22%, SD = 50.38%), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

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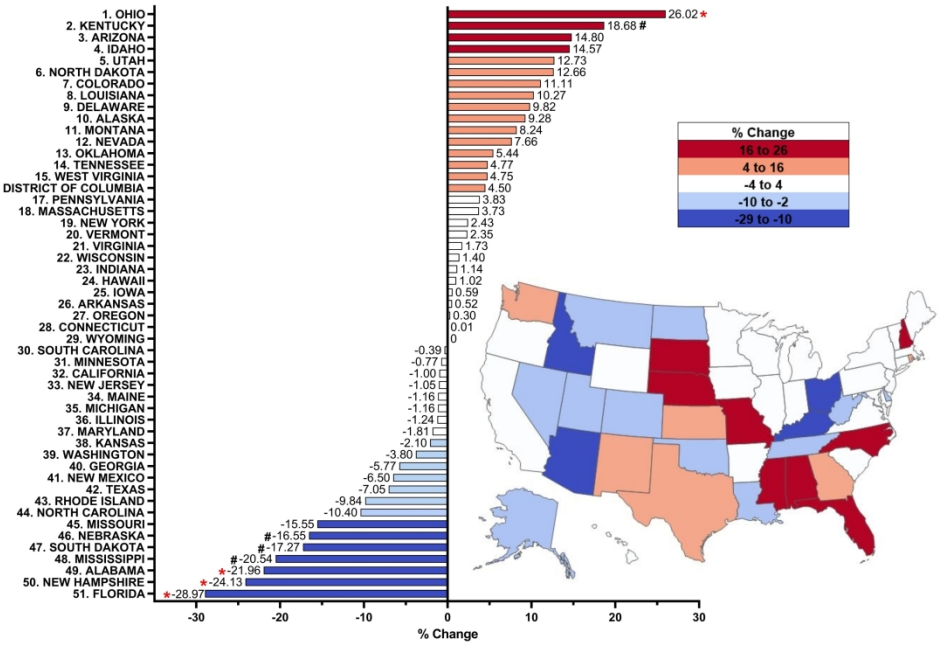

Percent change from 2019 to 2020 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-0.09%, SD 10.81), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

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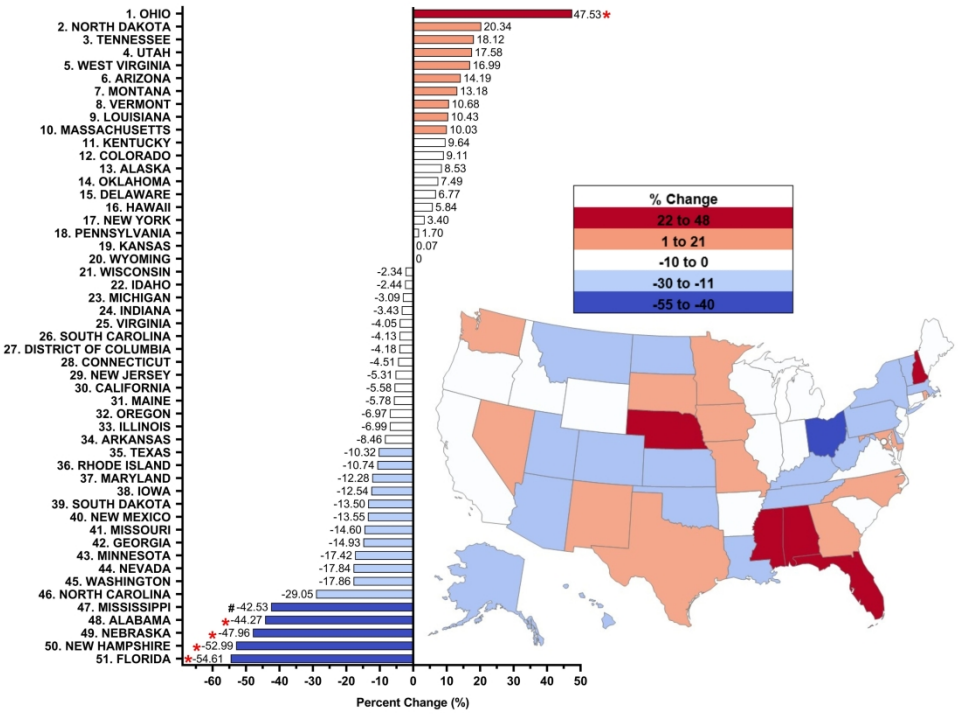

Percent change from 2019 to 2021 in methadone distribution as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System for Opioid Use Disorder. Percent change between 1.5 SDs and 1.959 SDs from the mean (-5.15%, SD 19.14), indicated with a #. Percent change > ±1.96 SD from the mean was considered significant (*P < 0.05).

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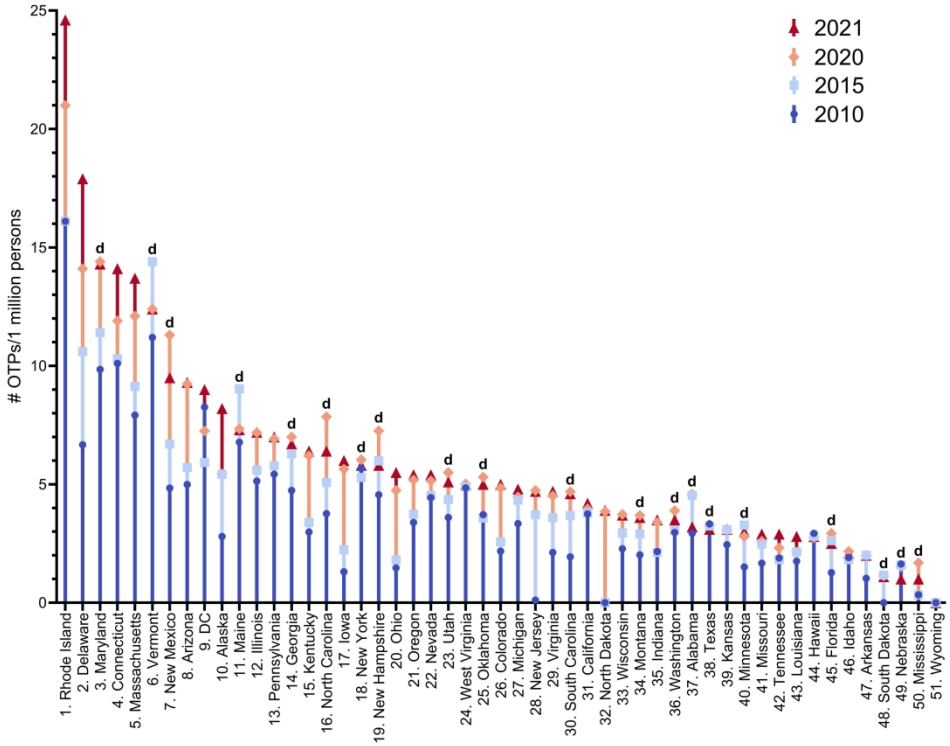

Number of opioid treatment programs per 1 million persons per state all significantly ($P < 0.0001$) different from 2010, 2015, 2020 and 2021. The twenty states that decreased in 2021 relative to 2010, 2015 or 2020 are indicated with a "d". DC: District of Columbia.

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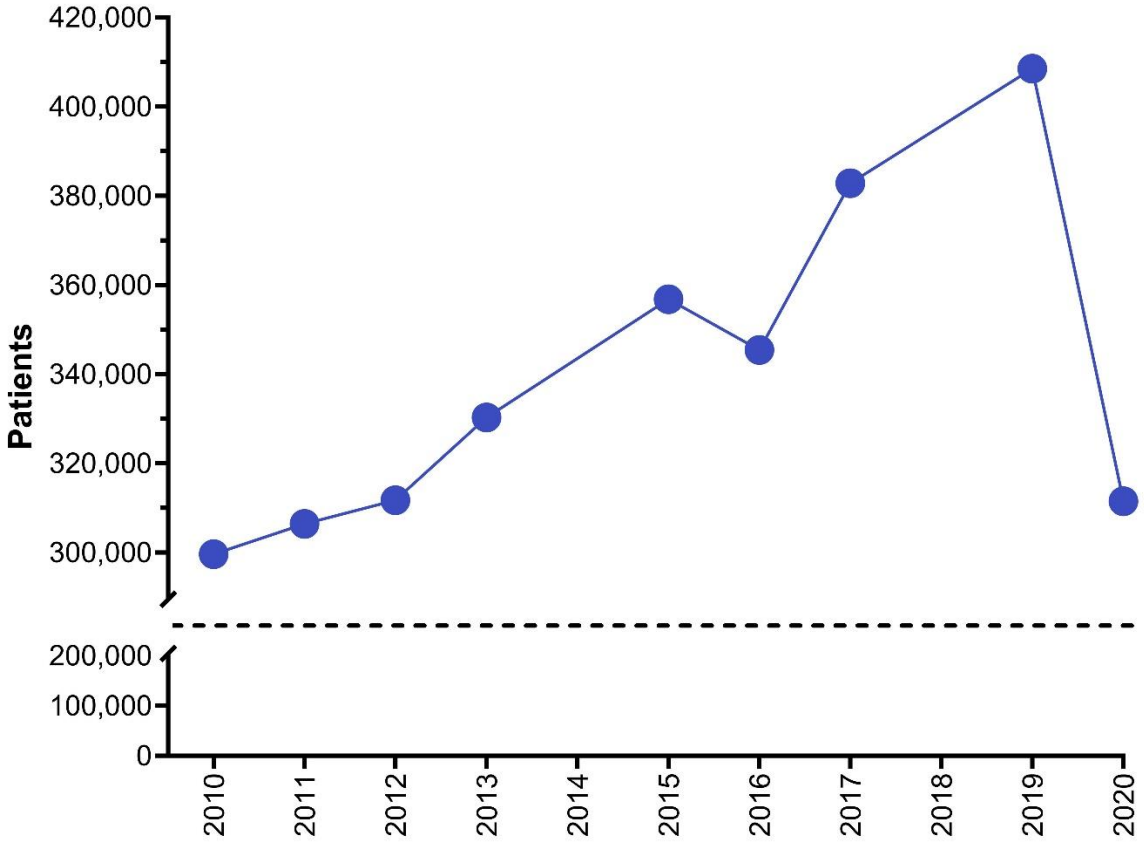
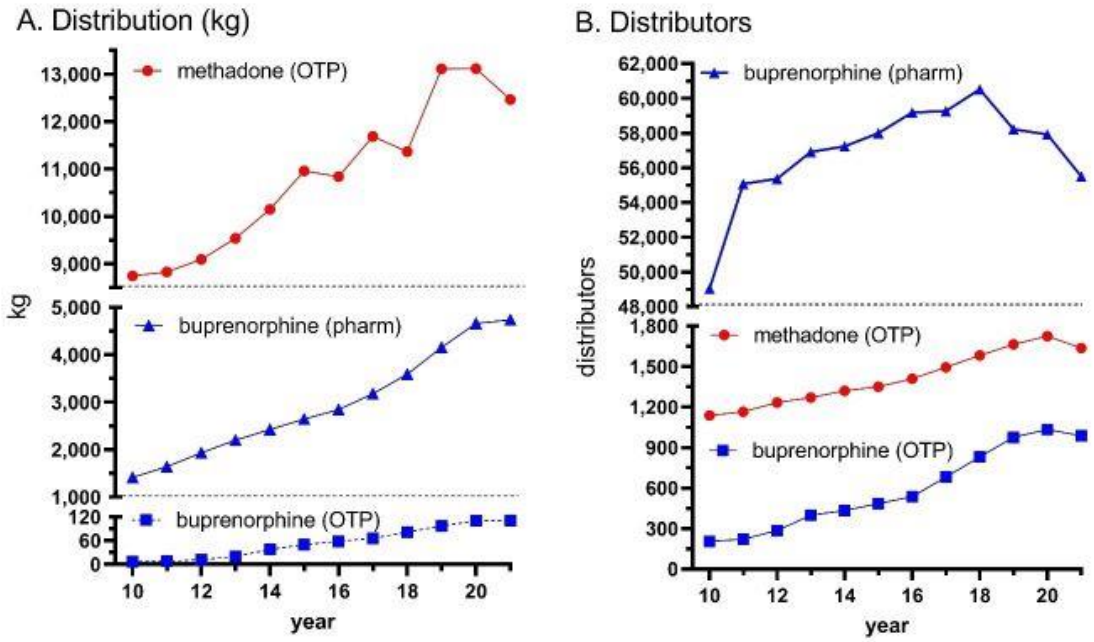
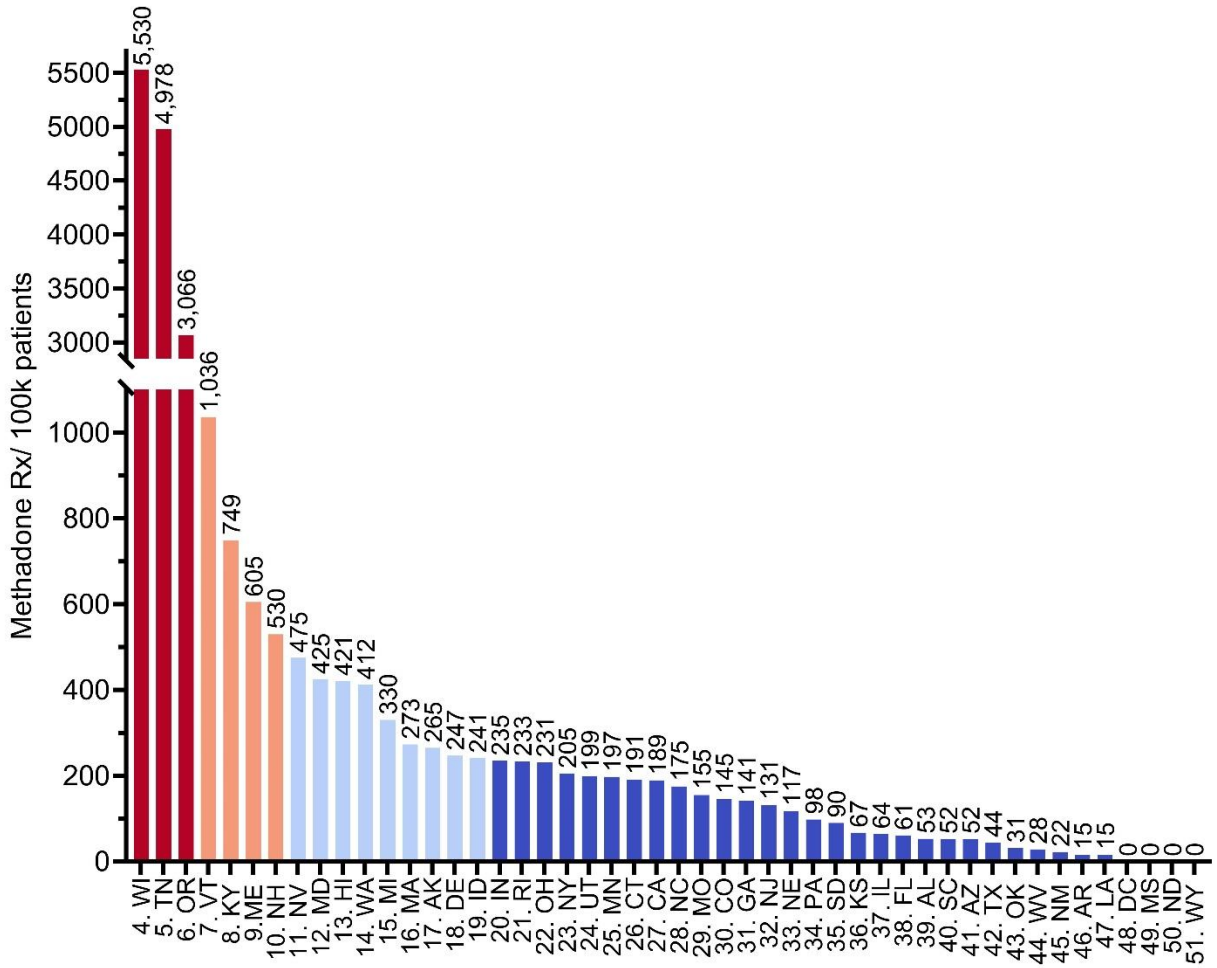


Supplemental Figure 1. Number of patients receiving methadone for opioid use disorder in the United States per year as reported by Substance Abuse and Mental Health Services Administration's National Survey of Substance Abuse Treatment Services data. The years 2014 and 2018 were not available and were omitted.



Supplemental Figure 2. Distribution in kg (A) and number of buyers and registrants (B) in Opioid Treatment Programs (OTP) and pharmacies (pharm, buprenorphine only) for methadone and buprenorphine as reported to the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders system for the fifty states, Washington DC, and the US Territories. Methadone in 2021 (12.4 metric tons) was 5.69% lower than 2019 (13.1 metric tons) and 5.71% below 2020 (13.1 metric tons). Methadone by weight was 2.49-fold greater than buprenorphine from pharmacies and OTPs in 2021. The number of pharmacies distributing buprenorphine was 33.3 to 47.3-fold greater than the number of OTPs distributing methadone from 2010 to 2021.



Supplemental Figure 3. Methadone prescriptions, per 100K Medicaid patients, for 48 US states, and Washington DC.

Supplemental Table 1. Comparison of the pharmacological and therapeutic properties of methadone and buprenorphine.

	Methadone	Buprenorphine
Year developed	1937	1969
Opioid receptor activity	mu full-agonist	mu partial agonist
Other mechanism(s)	NMDA antagonist	non-selective for other opioid receptors
Potency (x morphine)	8 – 12	10
Metabolism	CYP2D6, CYP3A4	CYP3A4
Active metabolite(s)	none	norbuprenorphine
Half-life	8 – 59 hours for oral	24 – 48 hours for buccal
Formulation	mono	mono or combination with naloxone
Present in breast milk	yes, < 3% maternal dose	yes, < 1% maternal dose
Availability (US)	narcotic treatment programs	providers with an X-waiver
Schedule (US)	II	III
Crowdsource (price/mg)	$0.96	$2.13
Black box warnings	addiction, abuse, misuse, QT prolongation	addiction, abuse, misuse[1], child exposure can result in overdose
Opioid rank	#1	#4
2021 Distribution (US)	12.4 metric tons[3]	5.2 metric tons[4]
WHO Essential Medication[2]	Yes	yes

[1]buccal formulation; [2]complimentary; [3]Opioid Treatment Programs (OTP); [4]total of pharmacies, hospitals, and OTP.

Supplementary Table 2. Medicaid's State Drug Utilization Data reported National Drug Codes (NDC) for methadone prescribed for opioid use disorder.

NDC
54039168
54039268
54355344
54355563
54421825
54421925
54453825
54457025
54457125
54855324
54855424
406052710
406054034
406254001
406575501
406575523
406575562
406577101
406577123
406577162
406872510
904653061
13107000000
17478000000
31722000000

42806000000

60687000000

63739000000

66689000000

67457000000

67877000000

68084000000

68462000000

Supplemental Table 3. Opioid treatment programs as reported to the Drug Enforcement Administration's Automated Reports and Consolidated Orders System per one million persons.

State	2010	2015	2020	2021
1. Rhode Island	16.1	16.1	21.0	24.6
2. Delaware	6.7	10.6	14.1	17.9
3. Maryland	9.9	11.4	14.4	14.3
4. Connecticut	10.1	10.3	11.9	14.1
5. Massachusetts	7.9	9.1	12.1	13.7
6. Vermont	11.2	14.4	12.4	12.4
7. New Mexico	4.8	6.7	11.3	9.5
8. Arizona	5.0	5.7	9.2	9.3
9. DC	8.3	5.9	7.3	9.0
10. Alaska	2.8	5.4	5.5	8.2
11. Maine	6.8	9.0	7.3	7.3
12. Illinois	5.1	5.6	7.2	7.2
13. Pennsylvania	5.4	5.8	6.9	7.0
14. Georgia	4.7	6.3	7.0	6.7
15. Kentucky	3.0	3.4	6.2	6.4
16. North Carolina	3.8	5.1	7.9	6.4
17. Iowa	1.3	2.2	5.6	6.0
18. New York	5.7	5.3	6.0	5.8
19. New Hampshire	4.6	6.0	7.3	5.8
20. Ohio	1.5	1.8	4.8	5.5
21. Oregon	3.4	3.7	5.2	5.4
22. Nevada	4.4	4.5	5.2	5.4
23. Utah	3.6	4.4	5.5	5.1
24. West Virginia	4.9	4.9	5.0	5.0
25. Oklahoma	3.7	3.6	5.3	5.0
26. Colorado	2.2	2.6	4.9	5.0
27. Michigan	3.3	4.3	4.5	4.8
28. New Jersey	0.11	3.7	4.7	4.7
29. Virginia	2.1	3.6	4.5	4.7
30. South Carolina	1.9	3.7	4.7	4.6
31. California	3.8	3.8	4.0	4.2
32. North Dakota	0.0	0.0	3.8	3.9
33. Wisconsin	2.3	3.0	3.7	3.7
34. Montana	2.0	2.9	3.7	3.6
35. Indiana	2.2	2.1	3.4	3.5
36. Washington	3.0	3.0	3.9	3.5
37. Alabama	2.9	4.5	4.6	3.2
38. Texas	3.3	3.2	3.3	3.1
39. Kansas	2.5	3.1	3.1	3.1
40. Minnesota	1.5	3.3	2.8	3.0
41. Missouri	1.7	2.5	2.6	2.9

42. Tennessee	1.9	1.8	2.3	2.9
43. Louisiana	1.8	2.1	2.2	2.8
44. Hawaii	2.9	2.8	2.8	2.8
45. Florida	1.3	2.6	2.9	2.5
46. Idaho	1.9	1.8	2.2	2.1
47. Arkansas	1.0	2.0	2.0	2.0
48. South Dakota	0.0	1.2	1.1	1.1
49. Nebraska	1.6	1.6	1.5	1.0
50. Mississippi	0.3	0.3	1.7	1.0
51. Wyoming	0.0	0.0	0.0	0.0
Mean	**3.8**	**4.6**	**5.7**	**5.9**
SEM	**0.4**	**0.5**	**0.6**	**0.6**

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7
		Cross-sectional study—Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7, 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9, 10, 11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.