Pronounced Declines in Licit Fentanyl Utilization and Changes in Prescribing and Reimbursement Practices in the United States, 2010-2019

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Abstract

Background: Fentanyl and its derivatives are highly utilized opioid-based analgesics provided to patients in various formulations. The evolving opioid crisis over the past decade has increased pressure on the health care industry to monitor opioid production. Different policies and procedures implemented to contain the crisis from a controlled substance standpoint have changed the utilization patterns of some opioids. A prior report identified 3-fold differences between states in fentanyl use. This study explored fentanyl distribution patterns from 2010 and 2019.

Methods: The amount of fentanyl base distributed from 2010 to 2019 was obtained from the Drug Enforcement Administration. Sufentanil, alfentanil, and remifentanil were also analyzed from 2010 to 2017, the most recent year reported. Prescriptions, units, and reimbursement for 2010 and 2019 were obtained from Medicaid and fentanyl prescriber specialty from Medicare Part D.

Results: There was a 65.5% decrease in the milligrams of fentanyl per person distributed when correcting for population. From a regional perspective, Ohio had the greatest decrease (-79.3%) while Mississippi saw the smallest (-44.5%). There was a 6.8-fold regional difference in the quantity of fentanyl distributed in 2019 from hospitals (South Dakota = 775.2, Alabama = 113.2 ug/person). The regional difference was also sizeable for pharmacies (6.2-fold, Mississippi = 1,025.3, Washington, D.C. = 165.6). Medicaid reimbursement in 2019 was $165 million for over eight hundred-thousand prescriptions with the majority for generic (99.7%) and injectable (77.6%) formulations. Interventional pain management and anesthesia were overrepresented, and hematology/oncology significantly underrepresented for fentanyl in Medicare.

Conclusion: The production and distribution of fentanyl-based substances decreased, although not uniformly, in the United States over the last decade. Additionally, the most prescribed formulations of fentanyl have transitioned away from transdermal, potentially in an effort to regulate its availability. Although impactful, overdose deaths attributed to synthetic opioid deaths continue to increase, highlighting the need for targeted public health interventions beyond the pharmaceutical and medical communities.

Introduction

The opioid crisis continues to plague healthcare in the United States (U.S.) despite legislation enacted by the government, scrutiny placed on pharmaceutical companies, and limitations restricting opioid prescribers. Fentanyl, a synthetic μ-receptor agonist, is employed as an analgesic administered in several formulations including injectable and transdermal patches (1). Fentanyl and its derivatives alfentanil, sufentanil, and remifentanil are most often utilized as intraoperative analgesics and in the management of chronic pain, particularly related to cancer and chemotherapies (1, 2). The potency of fentanyl, the diversity of administrative routes, and the low cost of its production have resulted in it becoming a frequently misused substance (2, 3).

Synthetic opioids pose risks beyond dependence. Commonly prescribed in chronic respiratory conditions (e.g., COPD), opioids treat pain, insomnia, and refractory respiratory symptoms (4). Potent derivatives like fentanyl increase risks of severe adverse effects contributing to the increased mortality due to respiratory complications such as pneumonia observed in this population (4). Additionally, opioid use during pregnancy has been linked to teratogenic effects and neonatal abstinence syndrome (NAS) (5). Estimated to have impacted one newborn per hour in 2009 in the U.S., the syndrome causes disruptions in brain development and is associated with cardiac defects, spina bifida, and gastroschisis (5–7).

The U.S. has a history of battling illicit substances and prescription drug misuse, but since the early 2000s the opioid crisis has been evolving. The steep increase in drug-related mortalities has been linked to two major factors: the over-prescription of opioids and the illegal manufacturing of fentanyl and fentanyl analogues (8–13). Over-prescribing began in the 1990s and accelerated in the 2000s. This led to an increase in opioid dependence among patients and increased the diversion and misuse of prescribed opioids in the street markets. The extent of this crisis gained national attention in 2016 when roughly 11 million people were estimated to have misused prescription opioids (14).

The initial focus of combating this growing epidemic was directed at regulating prescription fentanyl, specifically related to the apparent over-prescribing of opioids. Some of these measures included state legislation limiting the amount of

opioids prescribed, utilization of drug monitoring programs, and new prescribing guidelines (14–16). Despite some success, fentanyl-related deaths have continued to increase with a larger proportion related to illicit fentanyl.

Fentanyl distribution throughout the country has changed according to reports using similar methods to this study and others using associations between overdose deaths and underlying causative substances (9,11,16–18). One study noted an 18% reduction in licit fentanyl distribution in 2016; however, less is known about more recent use or trends over the last decade. A 3.5-fold regional difference in prescription fentanyl per state was identified between Oregon (1,718 µg/person) and Alaska (418.2 µg/person) (16). Between 2011 and 2017, states in the northeastern U.S. experienced an increase in fentanyl-related overdoses with an associated increase in seizures of diverted substances (9,11,18). New England states reported that 60–90% of overdose deaths were attributed to fentanyl (9,11). In contrast, states west of the Mississippi River reached a plateau in fentanyl deaths during that same period (18). States like Ohio, West Virginia, and Wisconsin reported that only 30–55% of deaths were associated with fentanyl (9,11). Despite these apparent trends, it was concluded that the distribution of fentanyl across the U.S. was significantly variable (18).

The objective of this study was to explore the trends in prescription fentanyl and select fentanyl derivatives distribution throughout the U.S. over the last decade (2010–2019); further, to examine prescriber preferences for fentanyl formulations in Medicare during the same period.

Methods

Procedures

Distributions of fentanyl base and select fentanyl derivatives in the U.S. were obtained from the Drug Enforcement Administration's (DEA) Automated Reports and Consolidated Ordering System (ARCOS) from 2010 to 2019. As a result of the 1970 Controlled Substance Act, this program mandates that the federal government track the distribution of controlled substances in grams by pharmacies, hospitals, providers, and treatment programs. This database has been used in previous research analyzing trends in controlled substance distribution (16). The last year where the fentanyl derivatives were reported by ARCOS was 2017. The total amounts for the drugs of interest were reported on the annual summary reports in grams from each of the U.S. states and territories. To normalize the data across the different states and years, population data were obtained from the American Community Survey and U.S. Census Bureau. The type of fentanyl or fentanyl citrate formulation and number of prescriptions for each of the formulations was obtained from Medicaid (19, 20). Formulations were categorized by National Drug Codes as generic versus brand and by route of administration. Fentanyl prescribers reporting to Medicare Part D were examined, specifically the number of prescribers in each specialty and the number of claims (including refills) per specialty (21). The methods used in this study using claims were similar to a previous study (22). Procedures were approved as exempt by the IRB of the University of New England.

Data analysis

The following analyses were completed: (1) total distributed amounts of fentanyl base and select fentanyl derivatives (i.e., alfentanil, remifentanil, and sufentanil) for each state; (2) the percent change of the distributed amount from 2010 to 2019 for each state per person; (3) ratio of highest to lowest in population corrected use per state; (4) a 95% confidence interval with states outside this range interpreted as significantly different from the mean; (5) the total number of prescriptions and total reimbursement for Medicaid in 2010 and 2019; (6) ratio of prescribers in specific specialties compared to the total number of prescribers to the number of claims per specialties in Medicare Part D in 2018. Data analysis and figures were completed using Microsoft Excel and GraphPad Prism, Version 8.4.2. Heat maps were generated with JMP Statistical Software version 15.2.1.

Results

From 2010 to 2019, the amount of fentanyl distributed declined from 1,689.9 µg/person to 583.9 µg/person, which was a -65.5% overall decrease across the U.S. (Figure 1). Further examination was completed by business activity. Hospitals showed a -63.4% decrease which was similar (-64.5%) among pharmacies (Figure 2).

The heat map shows that all states had a reduced utilization of prescription fentanyl with the greatest overall decrease in Ohio (-79.3%), whereas Mississippi had the smallest decline (-44.4%, Figure 3). These regional differences were further explored by business activity. The states with the largest pharmacy reduction were Ohio (-80.7%), Oregon (-75.7%), and Nevada (-74.4%). In contrast, Idaho (-49.1%), Kansas (-48.9%), and Mississippi (-41.9%) experienced the smallest declines (Figure 4). Among hospitals, Vermont (-84.5%), South Dakota (-84.0%), and Connecticut (-80.5%) experienced the greatest fentanyl

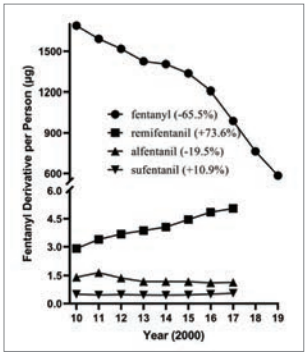


Figure 1. Distribution of fentanyl base and fentanyl derivatives (sufentanil, remifentanil, and alfentanil) in micrograms per person as reported by the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders System from 2010 to 2019. Values in parentheses indicated percent change from 2010.

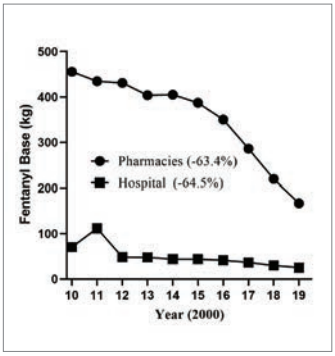


Figure 2. Fentanyl base (kilograms) distributed to pharmacies and hospitals across the United States from 2010 to 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System.

	2010	2019	Percent change
Prescriptions (total)	695,653	864,156	+24.2%
% generic	86.2%	99.7%	+13.5%[D]
% transdermal	67.2%	22.3%	-44.9%[D]
% injectable	32.4%	77.6%	+45.2%[D]
% other	0.5%	0.0%	-0.5%[D]
Units	6,814,928	4,791,673	-29.7%
Units per prescription	9.80	5.51	-43.8%
Reimbursement (millions)			
Total	149.2	165.0	+10.6%
Medicaid	146.3	124.0	-15.2%
Non-Medicaid	2.9	41.0	+1,313.8%
Enrollees (millions)	51.5	71.1[C]	+38.1%

[D]difference in % between 2019 and 2010, [C]includes Children's Health Insurance Program.

Table 1. Medicaid utilization of fentanyl formulations in 2010 and 2019.

reduction. Nevada (-47.5%), Delaware (-43.6%) and Alabama (-31.6%) had the smallest reductions (Figure 5, see also Figures 6–7).

Further assessing potential regional differences, pharmacies in Mississippi distributed a significantly greater amount of fentanyl than average while Washington, D.C., distributed significantly less. However, regional differences in 2019 were non-significant (Figure 6). In contrast to the pharmacies, fentanyl distribution to hospitals was significantly greater in South Dakota, Montana, and North Dakota in 2010. Similarly, hospitals in North Dakota and Montana in 2019 were elevated relative to the mean (Figure 7).

Alfentanil had a -19.5% decrease relative to 2010 (Figure 1). In contrast, sufentanil had a modest (+10.9%) change while remifentanil had an appreciable (+73.6%) increase. It is important to note that alfentanil, sufentanil, and remifentanil were not reported by ARCOS beyond 2017.

Next, Medicaid prescriptions and expenditures were examined. Table 1 shows that the intravenous/intramuscular (IV/IM) formulations accounted for one-third of the approximately 700,000 fentanyl prescriptions in 2010, but three-quarters of those in 2019. Conversely, transdermal formulations fell from two-thirds to less than one-quarter of prescriptions. Tablets became much more common (0.2% to 3.0%), and lozenges doubled (0.2% to 0.5%). Brand name formulations were responsible for 13.8% of prescriptions in 2010, and this declined to 0.3% in 2019. Units of fentanyl from 2010 to 2019 decreased by 30% while enrollment increased by 38.1%.

Finally, analyses were completed on fentanyl formulations in Medicare. A ratio of fentanyl (generic and brand name) prescribers to all claims was created with values greater than one indicating overrepresentation and values less than 1 were underrepresentation. Figure 8 shows that interventional pain management (2.85), anesthesiology (2.07), pain management (2.04), and physical medicine and rehabilitation (1.66) were among those specialties significantly overrepresented, while family practice (0.80), internal medicine (0.78), and hematology-oncology (0.64) were underrepresented in their prescriptions of fentanyl.

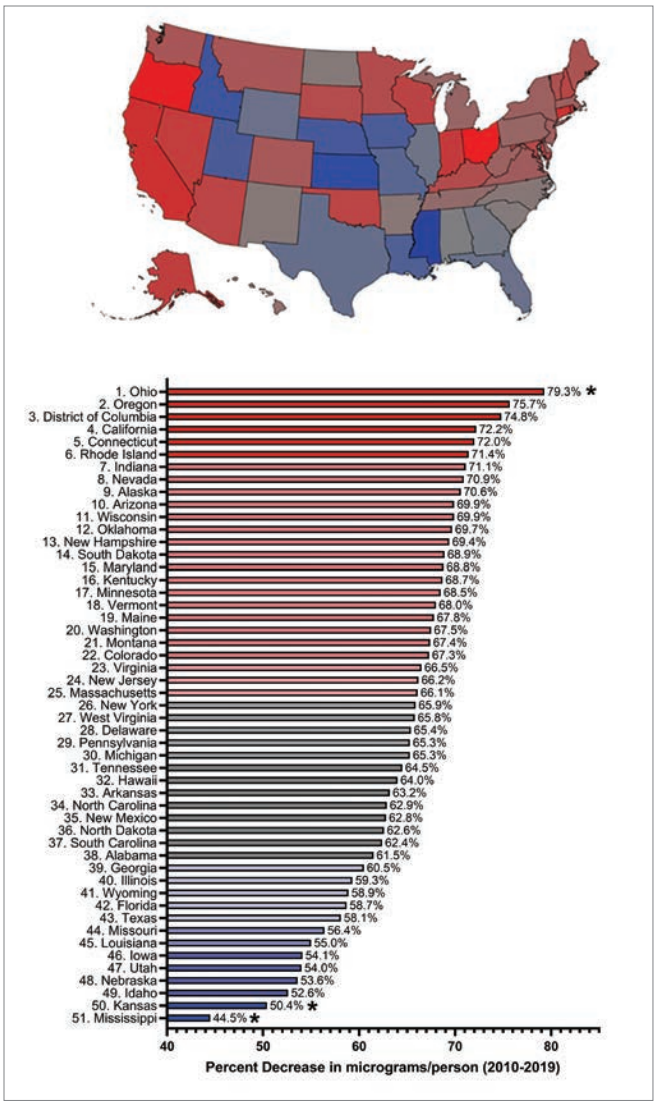


Figure 3. Percent decrease in distributed fentanyl base (µg/person) from 2010 to 2019 as reported by the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders System (blue: smallest reduction; red: largest reduction, * $p < 0.05$ versus state average).

Discussion

Fentanyl base experienced a pronounced and consistent year-over-year decline in distribution throughout the U.S. over the last decade (2010–2019) according to the DEA's ARCOS. This 65.5% decrease is congruent with and expands upon past research which found that the U.S. reduction in fentanyl was significantly greater than that of hydrocodone, morphine, or oxycodone (16). This decline was likely the result of efforts directed at one aspect of the opioid crisis. The over-prescribing of opioids including fentanyl by the medical community and in rare cases the criminal "pill-pushing" behaviors of certain prescribers, were deemed the primary culprits for the increased drug-related mortalities at this time (15). Similarly, alfentanil, a synthetic opioid with one-eighth the potency of fentanyl, also experienced a reduction. However, the extent of these recent

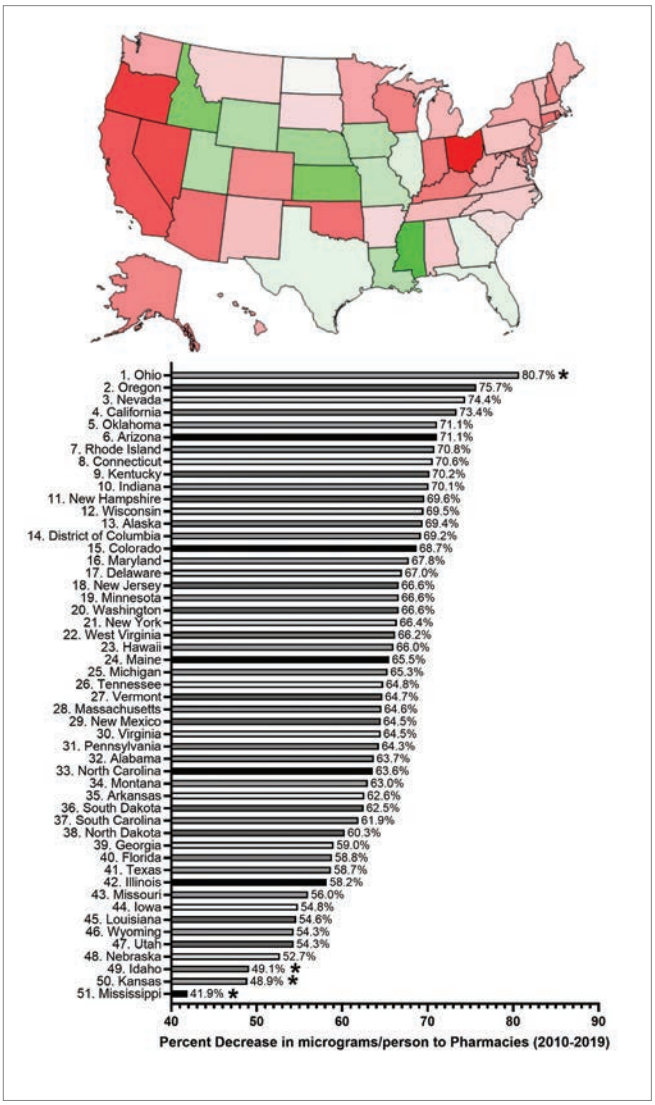


Figure 4. Percent decrease (-40%, green, to -80%, red) in fentanyl base (µg/person) distributed to pharmacies in the U.S. from 2010 to 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System.

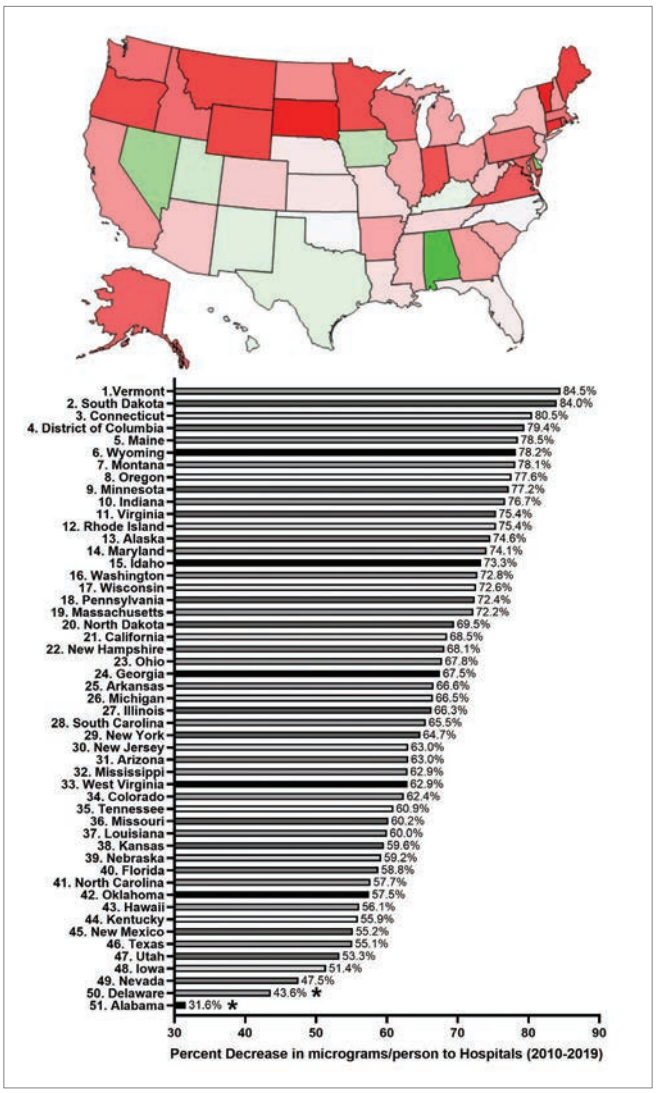


Figure 5. Percent decrease (-30, green, to -85%, red) in fentanyl base (µg/person) distributed to hospitals in the United States from 2010 to 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System.

reductions cannot be fully appreciated, because the DEA stopped reporting analog distribution in 2017 (23). In contrast to these fentanyl analogues, the amount of remifentanil and sufentanil increased during this period but were very modest relative to fentanyl. The rise in these derivatives — especially sufentanil, which is 10-fold more potent than fentanyl — is concerning and if diverted in appreciable quantities, could contribute to the death toll of the crisis (24).

From a regional perspective, Ohio generated the greatest decline in fentanyl (-79%) while Mississippi had the smallest decrease (-44.4%). Macroscopically, these two states have many similarities including the breakdown of their insured population and the demographics of the population impacted by opioid overdoses. However, other state socioeconomic differences may influence the percentages of decrease between the two states. The median annual household income for Ohio in 2019 was $58,642 while it was $45,692 in Mississippi. Healthcare expenditures per capita in 2014 (the most recent reported data) was $8,712 in Ohio and $7,646 in Mississippi (25). Other notable differences include the states' total Medicaid and Medicare spending. In 2019, Ohio's total spending for Medicaid and Medicare respectively was roughly $24 million and $14 million, whereas Mississippi's was approximately $6 million and $5 million. Furthermore, Mississippi's percentage of uninsured patients is almost double that of Ohio's at 6.7% compared to 12.9% (25). The ability to address a state's opioid crisis is impacted by the risk factors affecting their patients and the vulnerability of their socioeconomic infrastructure; nevertheless, how the specific socioeconomic factors influence the opioid crisis is an area of ongoing research. Microscopically, there are key distinctions between the states that may explain the differences in their abilities to mitigate the opioid epidemic.

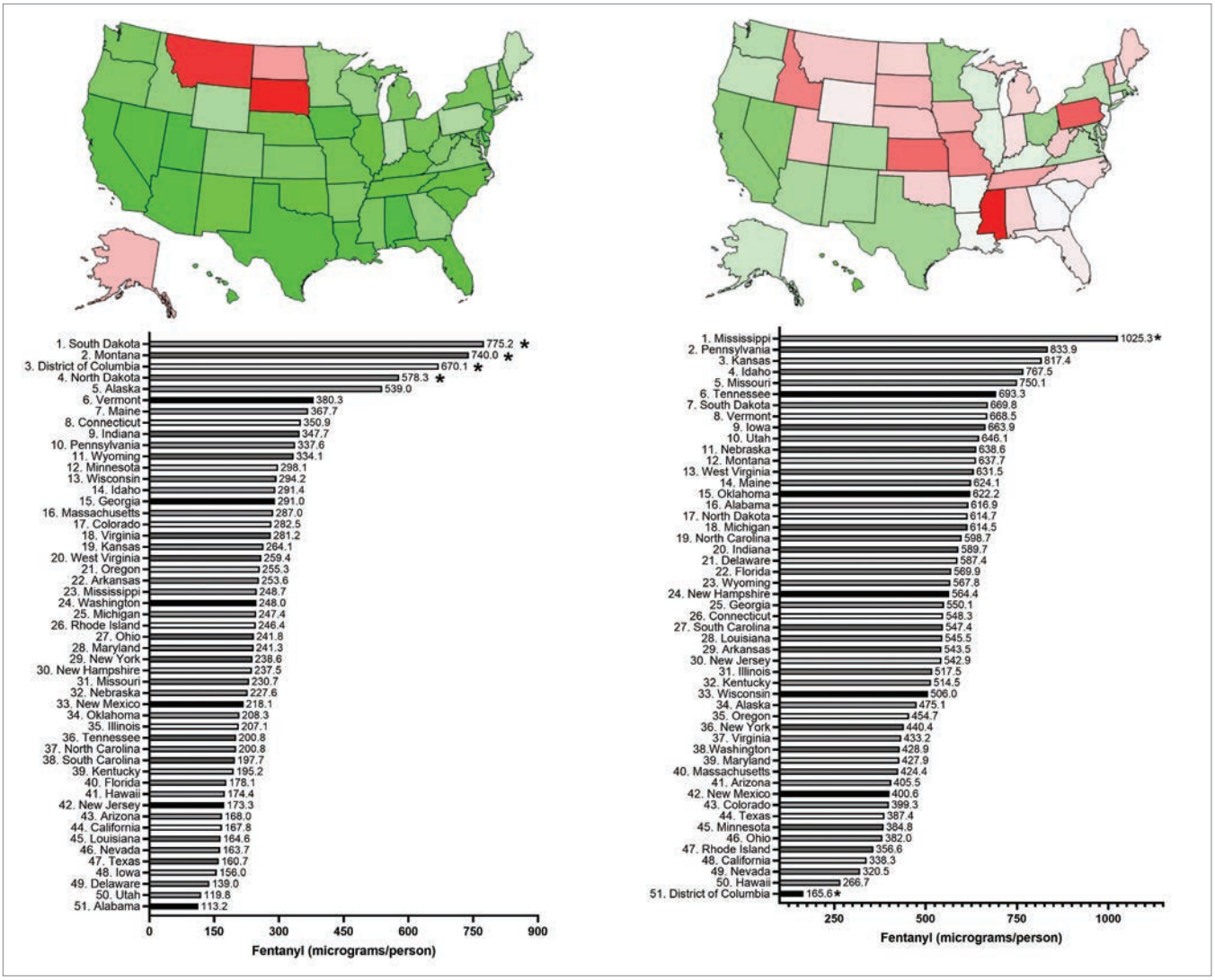


Figure 6. (A) Fentanyl (µg/person) distributed to pharmacies in 2010 as reported by the DEA's Automated Reports and Consolidated Orders System (green: lowest; red: highest). (B) Fentanyl (µg/person) distributed to pharmacies in 2019 as reported by the DEA's Automated Reports and Consolidated Orders System. Note that the range is lower relative to that in Figure 4A (green: lowest; red: highest).

Ohio had one of the highest numbers of opioid-related deaths compared to any state at a rate of 32.9 deaths/100K with fentanyl resulting in a death rate of 21.7 deaths/100K (26). To combat these alarming numbers, Ohio's Opiate Action Team doubled their spending from $10/person in 2017 to $19/person in 2018 (27). This increased funding created more treatment and recovery programs, established preventative measures, and improved prescribing practices for opioids and pain management (27, 28). These expansions also addressed the illegal street opioids to an extent which could have augmented the decrease (28).

Unlike Ohio, Mississippi had the smallest decrease of fentanyl (-44.4%). In 2018, fentanyl accounted for 2.9 deaths/100K and the rate of prescription opioid-related deaths was 1.4 deaths/100K. However, the more alarming number in 2018 was the 76.8 opioid prescriptions for every 100 persons (29). This represents an approximately 40% greater use compared to the national average in 2018, but also represents one of the lower annual prescribing rates in the state's recent history (29). To date, it appears that Mississippi is one of a handful of states still attempting to pass or just recently passed any type of legislation to combat fentanyl and other opioid misuse. The Opioid Crisis Response Act of 2018 attempts to reduce the trafficking of fentanyl and other opioids, improve prescribing practices, and increase programs for prevention, treatment, and recovery for those struggling with addiction (30). Parker's Law is still under review by the full House, but it would impose stricter criminal penalties on individuals trafficking fentanyl, heroin, and other substances, including life in prison if an illegally distributed substance leads to an overdose death (31). The delayed approach to mitigating the crisis may explain the limited decrease in fentanyl distribution and stagnant death rate figures. Opioid-prescribing laws generally showed only modest benefits unless the legislation included fiscal penalties for non-adherence (16). The substantial region inhomogeneity in fentanyl (6.2-fold in pharmacies, 6.8-fold in hospitals) may warrant continued attention to characterize the epidemiological

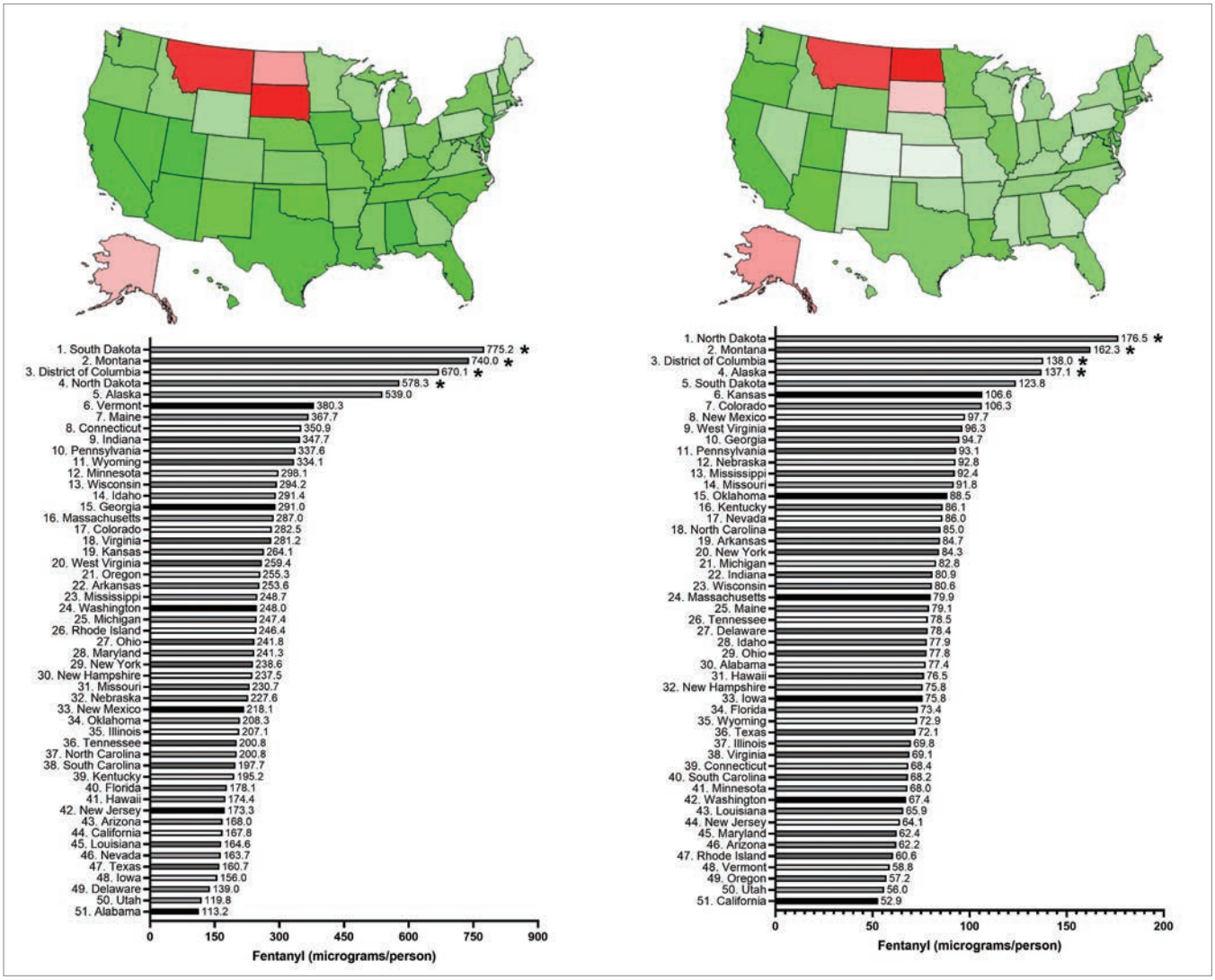


Figure 7. (A) Fentanyl (µg/person) distributed to hospitals in 2010 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders System (green: lowest; red: highest). (B) Fentanyl (µg/person) distributed to hospitals in 2019 as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders Systems (green: lowest; red: highest).

differences in nociceptive and non-nociceptive factors responsible for these differences. Ohio's reduction in fentanyl to pharmacies over the last decade (-80.7%) was almost twice as large as that of Mississippi's (-41.9%).

The effects of evolving policies and legislation attempting to subdue the impact of the opioid crisis may have penetrated further than just the amounts of fentanyl produced and distributed to also impact prescribing preferences. Using Medicaid, the 10 most prescribed fentanyl formulations showed pronounced changes. There was an 44.9% decrease in transdermal patch prescriptions and a 45.2% increase in injectable prescriptions from 2010 until 2019. This apparent change in prescribing preferences is potentially linked to the improved prescribing guidelines encouraged by state and federal laws. The impact in the change of prescribing preferences is further highlighted by the change in reimbursement from 2010 to 2019 which saw a transition away from transdermal and toward injectable formulations.

Transdermal patches, compared to other legally produced formulations, are uniquely susceptible to use and misuse. Even after administration, some patches contain 28–84% of the initial dose, which can be drawn out of the reservoir and misused. This type of diversion was documented in nursing homes and assisted living facilities (32, 33). Patches can also come in contact with non-patients accidentally, leading to absorption through the skin resulting in toxicity and death (2, 33–35). For these reasons, there are FDA and manufacturer warnings for health care professionals, FDA public health advisories, product labeling changes, and increased monitoring and disposal practices of patches have been adopted by many facilities to protect their patients, employees, and others in the environment (36–38). Additionally, the IV/IM formulations, relative to the sizable declines observed in their use in Medicaid, may be more preferred.

In 2019, 47,511 prescribers from 80 different specialties and industries reported prescribing both generic and brand name

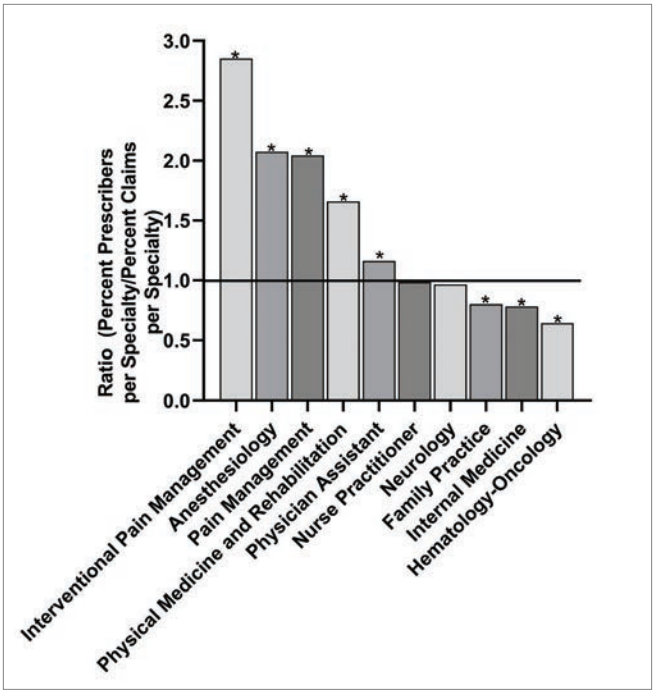


Figure 8. Ratio of prescribers per specialty to fentanyl prescription claims per specialty for 2018 as reported by Medicare (*chi-square p < 0.00001).

fentanyl to Medicaid. A large percentage of claims (41.6%) were submitted by general practitioners in family practice (FP) and internal medicine. Although these specialties comprised the greatest percentages of prescribers and claims, they were both deemed to be underrepresented in the overall analysis of fentanyl prescribers. In contrast to the general specialties, anesthesiology, pain management (i.e., interventional pain management and general pain management), and physical and rehabilitative medicine were overrepresented. These results were congruent with previous studies that concluded that specific specialties are not solely responsible for the opioid crisis (22, 39). Neurology, a specialty underrepresented in fentanyl prescriptions, had a claim to prescriber ratio of 38:1 while FP had a ratio of 31:1. This is interesting because neurology only comprised 1.3% of prescribers and 1.2% of claims compared to 29.3% and 23.5% for FP. A previous study found that 8 neurologists prescribed more controlled medications than 141 emergency medicine and urgent care prescribers combined, which suggests an interesting pattern within the specialty and a potential area for future investigation (40). The employment of Prescription Drug Monitoring Programs has improved the surveillance and communication among physicians and specialties, but a broad effort addressing the prescribing practices of each discipline might improve the variations seen in opioid prescribing practices (39, 40).

While this manuscript employed three complementary databases, no study is without limitations. A concern with ARCOS is reporting by drug weight instead of more standard units like prescriptions as Medicaid does. However, there was an excellent concordance (r = 0.985) between ARCOS and a state prescription drug monitoring program for another opioid (41). Examination of fentanyl use among the Medicaid and Medicare programs provides some insights into patient populations, but further research with the rich information provided by electronic medical records to characterize which pharmacological, or non-pharmacological, agents are substituting for fentanyl in the U.S. is needed.

Despite the progress, the opioid crisis remains untamed and continues to amass an escalating death count (41). The majority of these deaths are attributed to the illegal drug trades ravaging the streets. Persons with substance abuse disorder want to avoid fentanyl, but the illegal industry utilizes fentanyl in so many ways that it is hidden even to the most seasoned user (42). Most of the successful efforts to mitigate the crisis have targeted the legal production of fentanyl. This may contribute to the shortage of anesthetic drugs across the country during the COVID-19 pandemic. This shortage led the DEA to increase production and imports to treat those patients on ventilators (43, 44). Unethical and illegal practices by one company manufacturing fentanyl, InSys, have resulted in clear consequences including prison sentences, fines, and bankruptcy (45). Future attempts at addressing the opioid crisis must regulate the legal entities of the problem but cannot ignore the uncontrollable nature of the illegal street market. Social programs increasing routes to treatment and recovery, educating users and misusers about the dangers of fentanyl, and providing fentanyl detection methods to street users are all approaches currently under investigation (10, 14).

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