



Trends in the medical supply of fentanyl and fentanyl analogues: United States, 2006 to 2017

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ABSTRACT

Fentanyl is an important opioid for pain management, but also has exceptional potential for misuse. Seven states have implemented opioid prescribing laws. The objectives of this study were to: 1) characterize the temporal pattern of fentanyl, fentanyl analogue, and other opioid use over the past decade, and 2) determine whether opioid prescribing laws impacted fentanyl use in the US. Drug weights were obtained from the US Automated Reports of Consolidated Orders System (June 2018), a comprehensive publically available resource, from 2006 to 2017 for fentanyl, sufentanil, remifentanil, alfentanil, other prescription opioids, and analyzed by presence of a state opioid prescribing law. Fentanyl, corrected for population, was reduced from 2006 to 2017 (−17.9%) and these decreases significantly exceeded the changes in hydrocodone (−12.3%), oxycodone (−10.1%), morphine (−13.3%), or codeine (−8.8%). Fentanyl showed a particularly large decline in Maine, a state with a strong opioid prescribing law. There was a 3.5 fold difference in fentanyl (μg per capita) in Alaska (488.2) relative to Oregon (1718.4). Hospital use of remifentanil and sufentanil tripled from 2006 to 2017. Although all states experienced a 2006 to 2017 decline in fentanyl, and this reduction was larger than many other prescription opioids, the rate of decline varied over three-fold between states. Strong state laws may account for a portion of the variance in fentanyl and other opioid reductions. The population health risks of fentanyl and fentanyl analogues warrants ongoing vigilance.

It is difficult to overstate the role of fentanyl in both pain control (Stanley, 2014) and the U.S. opioid crisis (Armenian et al., 2018; Kuczyńska et al., 2018). This highly lipophilic opioid was synthesized in 1960 (Armenian et al., 2018) and is a strong mu ($\mu_{1/2}$) agonist with negligible affinity for delta or kappa receptors (Kuczyńska et al., 2018; Schumacher et al., 2018). Fentanyl is similar to other mu opioid receptor agonists in its pharmacologic effects, which include: analgesia, euphoria, sedation, nausea and respiratory depression. However, fentanyl has a rapid onset and short duration of action and, unlike most mu agonists, does not increase plasma histamine (Stanley, 2014). Estimates of the potency of fentanyl relative to morphine, e.g. ≥ 50 fold more potent, should be interpreted with caution because bioavailability varies depending on dosage and route of administration (Armenian et al., 2018). Fentanyl is available for use in a variety of formulations

including intravenous, buccal lozenge, tablet, and film, sublingual tablet and spray, intranasal spray, and transdermal (Kukanich and Clark, 2012; Stanley, 2014). The fentanyl analogues sufentanil, alfentanil, and remifentanil are United Nations Schedule I drugs, but are US Drug Enforcement Administration (DEA) Schedule II Controlled Substances (Armenian et al., 2018, Supplemental Table 1).

Medical professionals' diversion of fentanyl preceded more widespread misuse by the general public. A survey of anesthesia department chairs found that fentanyl exceeded all other operating room drugs, combined, for its involvement in resident drug abuse (Booth et al., 2002). Similar results were identified in anesthesiologist trainees who completed graduate education between 1975 and 2009, wherein fentanyl was the most common agent implicated in a Substance Use Disorder, even exceeding alcohol (Warner et al., 2013). Among the 46.2

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million in non-research payments made to US prescribers related to opioids, primarily for speaking fees, almost half were for fentanyl (Hadland et al., 2017). The manufacturer of a fentanyl spray was indicted for bribing doctors to prescribe fentanyl off-label and to lie to insurers and pharmacy benefit managers about patients' medical histories (Dyer, 2016). The DEA issued a nationwide public safety alert based upon an alarming increase in transdermal fentanyl related overdoses and thefts (Drug Enforcement Administration, 2016). Awareness of the risks of this agent among non-health care providers may have been increased by the autopsy reports of two celebrity musicians which noted the involvement of fentanyl in their deaths (Associated Press, 2018; Coscarelli, 2018). Synthetic opioids, primarily illicitly manufactured fentanyl, and prescription opioids were each implicated in over two-fifths of the forty-two thousand opioid related overdose deaths in the US in 2016 (Jones et al., 2018). However, these numbers should be interpreted cautiously because it is not always trivial for analytical chemists to differentiate between pharmaceutical grade and illicit fentanyl (Manchikanti et al., 2018). Fentanyl transdermal patches have been misused in a variety of methods including applying multiple patches simultaneously, applying “used” patches, whole patch ingestion, rectal insertion, or extracting the fentanyl for intravenous, insufflation, or inhalation (Kuczyńska et al., 2018).

Although the majority of fentanyl and fentanyl analogues are used for legitimate medical purposes, the opioid prescribing norms, patient expectations, and broader medical culture are changing rapidly. This includes reductions in opioid availability (Goodwin, 2018), the implementation of Prescription Drug Monitoring Programs in all states (Haffajee et al., 2018), prescribing guidelines (Dowell et al., 2016), changes in pharmacy (Wiener-Bronner, 2018) and pharmacy benefit managers policies (Joseph, 2017), and state laws (McGinty et al., 2018; Soh and Brantley, 2018). Opioid prescribing laws vary considerably in the patient groups covered, presence of morphine mg equivalent limits, and penalties for non-adherence. The Drug Enforcement Administration's (DEA) Automation of Reports and Consolidated Ordering System (ARCOS) is a comprehensive data source in which all manufacturers and distributors of select controlled substances report transactions. Fentanyl use decreased from 2011 until 2016 by 21.4% (Piper et al., 2018). The objective of this study was to obtain more recent (2017) data, other fentanyl analogues (alfentanil, remifentanil, sufentanil) and to better understand public policy factors, particularly state laws, which may contribute to further reductions.

1. Method

1.1. Procedures

The Drug Enforcement Administration monitors the production and distribution of controlled substances by weight (g). The total grams per year was accessed through ARCOS on their publically available Diversion Control Division website for fentanyl base, alfentanil, remifentanil, and sufentanil for each distributor: pharmacies, hospitals, practitioners, mid-level practitioners, and teaching institutions. Other typical (e.g. morphine) and atypical (e.g. tapentadol, Zajączkowska et al., 2018) opioids as well as a broad (2006 to 2017) interval was selected to provide a comparison with prior work (Cabrerá et al., 2019; Piper et al., 2018) although analyses also focused on more recent (2015–17 or 2016 to 2017) periods to determine any potential impact of recent state policies. Identification of the states which have implemented laws to limit opioid prescribing was determined previously (McGinty et al., 2018; Soh and Brantley, 2018) and by contacting the Prescription Drug Monitoring Programs in each state. Seven, primarily New England, states (CT, MA, ME, NY, PA, RI, VT) were selected for examination because they passed laws by late 2016 which went into effect between June 2016–July 2017 to limit opioid prescriptions (Supplementary Table 2). One state's (ME) law is inclusive of many patients, has clearly defined and limited exceptions, includes financial

penalties for non-adherence, and was classified as “broad”. The other six states were classified as “narrow” based on their coverage of fewer patients (e.g. only ER or new patients), more liberal exception policies, or absence of non-adherence penalties. The DEA lists opioid weight per 100 K of population in each state, or Washington DC, based on the most recent Census which was examined for each quarter. Procedures were approved by the IRB of the University of New England.

1.2. Data analysis

Statistical analysis was completed with Systat, version 13.1. ARCOS data is typically highly consistent across years (Piper et al., 2018). The percent change in opioids was analyzed as a repeated measure with the state population/US population * 51 as a weighting variable to account for the population differences between states. This state weighting was completed with IBM SPSS Statistics. Examination of the quarterly weights in Report 2 for each area (N = 9680) resulted in the identification of two state weights, which were extreme (30–50 fold higher than earlier and later scores). These outliers were replaced with the average of the prior and subsequent values. Similarly, alfentanil from hospitals in 2011 was unusually high (430.61 g) and this score was not shown in Fig. 3C. Fentanyl use per person was examined in each state relative (> 1 or 1.96 SDs) to the national average. Figures were prepared with GraphPad Prism, version 6.07. Heat maps were constructed using QGIS and Carto.

2. Results

Fig. 1 depicts the percent reduction in fentanyl use (–17.9%) from 2016 to 2017, weighted by state population, relative to other opioids. Use of fentanyl showed significantly greater reductions than use of oxycodone, hydrocodone, hydromorphone, and codeine, but not meperidine. Fentanyl decreases in use were significantly different than

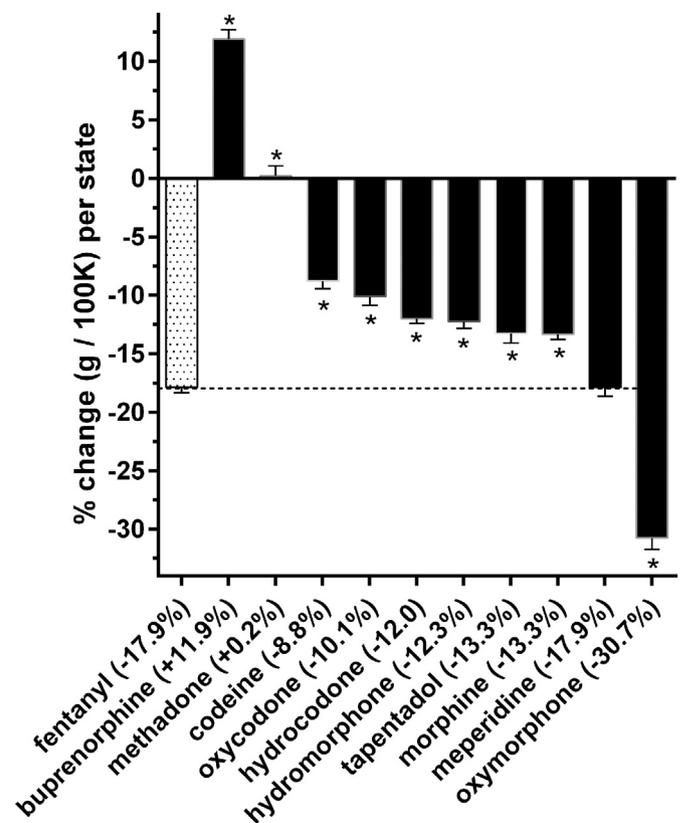


Fig. 1. Change in fentanyl (g/100K) from 2016 to 2017 relative to other opioids. *p < .05 versus fentanyl.

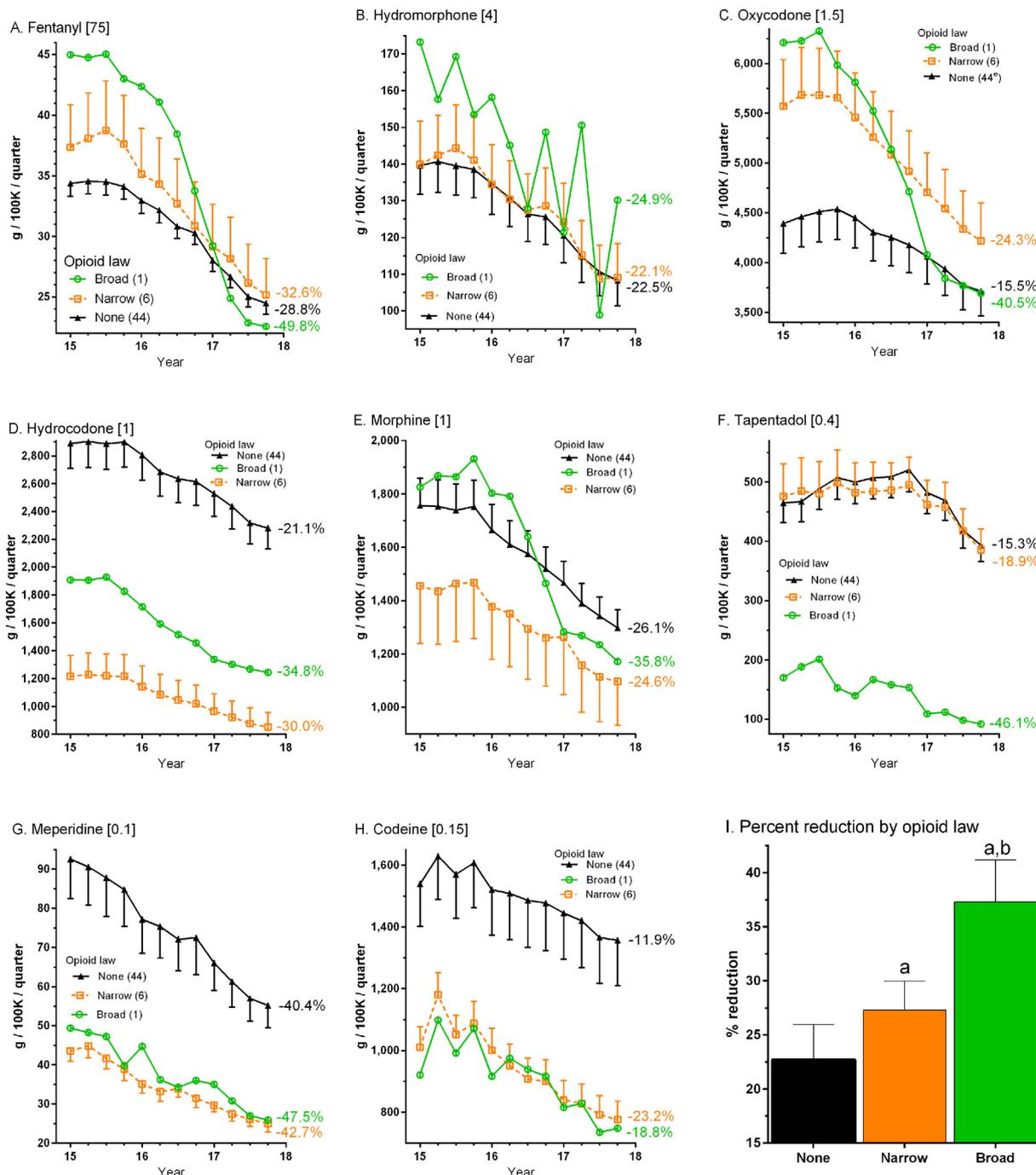


Fig. 2. Opioids (g) per quarter (± SEM) per 100,000 persons according to the decennial Census by opioid prescribing law (A to H). The oral morphine mg equivalent is in brackets and number of states are in parentheses. ^aExclusion of an outlier (Idaho = 35,329.4 during the first quarter of 2017). Mean (± SEM) percent change from the first quarter of 2015 until the fourth quarter of 2017 (I). ^a*p* < 0.05 versus none. ^b*p* < 0.05 versus narrow.

buprenorphine and methadone use which increased. However, the decline in use of oxycodone (see also Supplemental Fig. 1) was significantly greater than the decline in use of fentanyl.

Fig. 2A shows the quarterly distribution of fentanyl from 2015 to 2017. The forty-four states without a prescribing opioid law saw an appreciable (Mean = 10.8 g/100K) reduction in fentanyl use from the first quarter of 2015 until the fourth quarter of 2017. States with relatively narrow opioid laws showed a slightly larger decrease during this period (Mean = 13.0, RI = 8.2, MA: 8.7, NY: 11.9, PA: 13.2, CT: 16.6, VT: 19.4, Supplemental Fig. 2). The state (ME) with the most broad legislation showed a decline in fentanyl use that was over twice as great (22.4) as states that had not implemented an opioid law.

Although all opioids showed substantial reductions, the percent change from 2015 to 2017 was especially pronounced in Maine for use of oxycodone, morphine, and tapentadol (Fig. 2C, E, F). States with a narrow law had a larger change from 2015 to 2017 than states without a law (*t*(7) = 2.81, *p* < .05). Further, the state with a broad law had a larger reduction than states with a narrow law (*t*(7) = 2.82, *p* < .05, Fig. 2I).

Fig. 3A depicts the almost four-fold regional variation in the percent decrease in fentanyl use between states (Min = -10.3% in Mississippi, Max = -36.0% in Maine). There was a cluster of states in the Northeast (ME, NY, VT), but also others scattered across the US (AL, AZ, ND, MD, NM, OR, WI) with the largest reductions.

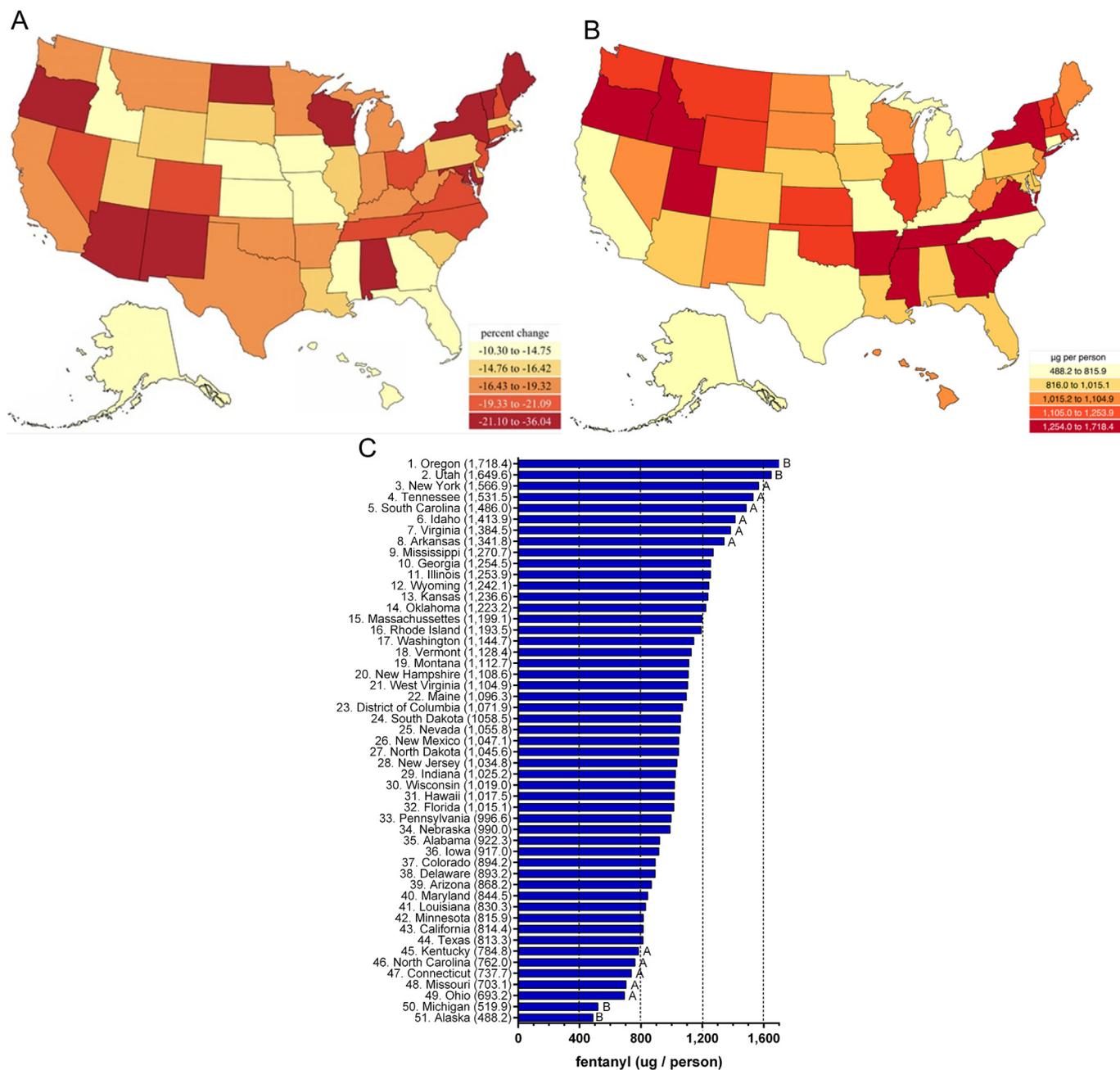


Fig. 3. Heat maps of the percent change in fentanyl (g/100 K) from 2016 to 2017 (A) or the µg of fentanyl per person per state in 2017 (B & C) as reported by the Drug Enforcement Administration's Automated Reports and Consolidated Orders (ARCOS) system.

A. Percent change in fentanyl from 2016 to 2017.

B. Fentanyl per person.

C. Fentanyl (µg per person, per state, in 2017) ranked. Score $\geq \pm 1.0^A$ or $\pm 1.96^B$ SDs versus the United States national average (1065.5, SD = 268.2).

Fig. 3B shows a 3.52 fold difference in fentanyl use (µg per person) in 2017 in Alaska (488.2) relative to Oregon (1718.4). Oregon and Utah (1649.6) were elevated (≥ 1.96 SDs) compared to the average (1066, SD = 268) state. Fig. 3C depicts that Alaska and Michigan (519.9) were the lowest (< 1.96 SDs). The southeast was heterogenous with Kentucky and North Carolina > 1 SD below and Virginia and South Carolina > 1 SD above the national average.

Relative to 2006, the total volume in 2017 for all business activities was decreased by -24.3% for use of fentanyl (Fig. 4) and -8.1% for use of alfentanil but increased $+186.9\%$ for use of sufentanil and $+189.6\%$ for use of remifentanil (Supplementary Fig. 2). US pharmacies were the predominant source for fentanyl and sufentanil, particularly in the last six-years, while hospitals distributed the preponderance

of remifentanil and alfentanil from 2006 to 2017. Use of fentanyl from pharmacies peaked in 2010 at 455.5 kg and decreased by -37.2% to 286.0 kg in 2017. Use of fentanyl was reduced -18.4% from pharmacies and -12.2% from hospitals from 2016 to 2017. Remifentanil use approximately tripled from hospitals (0.55 to 1.61 kg) and doubled for practitioners (17.3 to 40.9 g) between 2006 and 2017. Alfentanil use has been dynamic but decreased 13.5% (0.35 to 0.30 kg) from hospitals. Sufentanil use grew 148.2% (50.7 to 125.7 g) from pharmacies and tripled (16.6 to 49.9 g) from hospitals.

3. Discussion

There are two key findings from this report about the use of

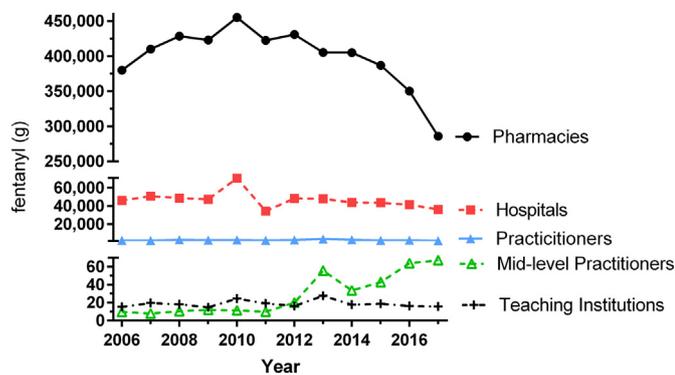


Fig. 4. Weight of fentanyl as reported to the US Drug Enforcement Administration's Automated Reports and Consolidated Orders (ARCOS) system from 2006 to 2017. Practitioners include physicians, dentists, and veterinarians. Mid-level practitioners include physician assistants and nurse practitioners.

fentanyl, fentanyl analogues, and other opioids. First, although all nine of the agents used for pain management showed recent reductions, use of fentanyl showed a larger decrease than use of hydrocodone, oxycodone, hydromorphone, morphine, and the relatively weak opioids codeine and tapentadol. One formulation of oxymorphone, Opana ER, was removed from the market in June 2017 (Department of Justice, 2018) due to an HIV and hepatitis B outbreak in Scott County, Indiana involving injection use (Conrad et al., 2015) although there were also earlier concerns about Thrombocytopenic Purpura (Marder et al., 2013). Not surprisingly, the oxymorphone decline was almost twice as large as that of fentanyl. The licit supply of prescription opioids are monitored by the US Drug Enforcement Administration. The production quota of oxymorphone decreased by almost one-third (31.4%) between 2017 and 2019. In contrast, buprenorphine use showed an appreciable increase nationally. Buprenorphine treatment for opioid use disorders continues to expand although there are concerns about limited availability in rural areas (Andrilla et al., 2019). Collectively, these results indicate continued divergence between the reductions in prescription opioids for pain and increasing use of opioid use disorder treatments (Piper et al., 2018).

There are multiple factors which contributed to these national fentanyl reductions. Corrective measures in the opioid prescribing culture (Dowell et al., 2016; Joseph, 2017; Haffajee et al., 2018; Manchikanti et al., 2018; Ornstein and Jones, 2018) may be having a greater, or more rapid, impact on use of fentanyl than on other opioids used for pain. Patients that read about illicit fentanyl (e.g. Shanon, 2018) may be apprehensive about receiving fentanyl prescriptions. An appreciation for the lethal potential of this opioid (Associated Press, 2018) may have been further increased when Nebraska selected fentanyl to be employed as part of a four substance cocktail with diazepam, cisatracurium besylate, and potassium chloride for capital punishment (Smith, 2018). Negative connotations with this agent were further increased when the former CEO of an Arizona company that produces the fentanyl spray, plead guilty to providing kickbacks to doctors to increase prescriptions (Wiles, 2018). Heightened scrutiny of legal, but ethically dubious, practices like US physicians receiving \$46.2 million in non-research payments for opioids, \$21.2 million related to fentanyl (Hadland et al., 2017), may contribute to further de-escalation in licit use. Arguably (Albert, 2018), the decline in the DEAs fentanyl manufacturing quotas (1750 kg in 2017, 1342 kg in 2018, and 1185 kg in 2019) may be the most central policy factor. A one-third reduction from 2017 to 2019 may continue to result in drug shortages that further decrease misuse and legitimate use.

Secondly, there was tremendous variability between states in fentanyl prescribing. There was a four-fold difference in per capita fentanyl between the Northwestern states of Oregon and Alaska. Five-fold state

differences in the per person morphine mg equivalent of ten opioids was noted earlier (Piper et al., 2018). Pain is a biopsychosocial process, but these pronounced pharmacoepidemiological differences may be driven by economic and social factors (e.g. Ornstein and Jones, 2018). There was an almost four-fold difference between states with the smallest (−10.3%) and largest (−36.0%) one-year reduction in fentanyl. In two-years, Maine went from using eight grams more, to four grams less of fentanyl per one-hundred thousand persons relative to most other states. Although this change is pronounced and corresponds with implementation of the strongest opioid prescribing law in the nation (Supplementary Table 2), this striking finding should be viewed as preliminary until other states implement similarly thorough policies. The evidence quality of state-level opioid initiatives and their impact on health outcomes is low (Haegerich et al., 2014). One challenge in this field is that states often institute multiple changes at the same time and there are other confounding, but important, contributors to opioid prescribing (Hadland et al., 2017). Importantly, recent legislation in Maine included, not only an opioid prescribing cap, but also mandatory Prescription Drug Monitoring Program (PDMP) enrollment for health care providers and mandatory PDMP query of patients, which were all operational for 2017. Twenty states had mandatory PDMP enrollment, twenty states had PDMP query, and eleven states had pill mill laws in place by January of 2017 (McGinty et al., 2018). Although clear differences were identified based on law specificity (Fig. 2H), further study will be necessary to identify which aspect(s) of these types of laws, including the presence of clear penalties for non-adherence, is most impactful on these changing opioid use patterns. This is particularly important for fentanyl given its potency and appreciable misuse potential (Armenian et al., 2018).

In the context of pronounced declines in the use of fentanyl and decreased availability (Goodwin, 2018), sufentanil use in pharmacies doubled and remifentanil use in hospitals tripled. This pattern of results may reflect substitution of fentanyl with fentanyl analogues, particularly for inpatient procedures. Relative to fentanyl, fentanyl analogues are much less prevalent and currently appear to be infrequently used for nonmedical purposes. However, given the history of fentanyl being misused by health care providers (Booth et al., 2002; Warner et al., 2013) prior to expanding to others, continued vigilance is warranted. There may be particular concern for a recently approved sublingual formulation of sufentanil (Dsuvia).

ARCOS tracks information from manufacturer to the point of dispensing or the retail level. Although ARCOS may be the most comprehensive data source in the US for pharmacoepidemiology research of controlled substances, some other strengths and limitations should be noted. Mail order or Internet pharmacies or dark-web suppliers can send controlled substances across state lines so Fig. 3 should be interpreted accordingly. These findings reflect the data submitted to the DEA by distributors whose veracity has been questioned (Bernstein et al., 2016). Fentanyl, the fentanyl analogues, and other opioids have some, albeit modest, veterinary use and ARCOS does not provide a mechanism to distinguish between human and non-human recipients. However, we view this inclusiveness as a partial strength, as some opioids intended for non-humans may end up being misused by humans (Mason et al., 2018). Additional updates and monitoring for any unintended consequences may be needed to further examine the potential contribution of state laws as only two (New York, Vermont) to six (Rhode Island) quarters of opioid use post-implementation were available for this investigation. Drug shortages in smaller states could result in volatility (Fig. 2B) and adversely impact pain management. The substantial potency of fentanyl and fentanyl analogues may increase susceptibility to pharmacy or hospital theft. The quantity of fentanyl diverted is, understandably, not publically available but could have resulted in more variable data than observed with other opioids (Piper et al., 2018).

4. Conclusion

The escalation of opioid prescribing in the 1990s resulted from a confluence of factors, including liberalization of laws governing opioid prescribing, new pain management standards including by the Joint Commission, and misleading marketing (Manchikanti et al., 2010). Following an opioid peak in 2011 (Piper et al., 2018), the de-escalation of prescribing may similarly be driven by multiple factors (Dowell et al., 2016; Ornstein and Jones, 2018) of which state laws (McGinty et al., 2018) may be an element. The substantial fentanyl reductions identified here may provide an early indication of further strategies which could aid in a return to more cautious and restrained prescription opioid use which may reverse adverse population health outcomes.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpmed.2019.02.017>.

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