Declining National Codeine Distribution in United States Hospitals and Pharmacies

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Abstract

Background: Past research has identified pronounced regional disparities in use of different opioids but less is known for codeine. The primary objective of this study was to analyze the trends of distribution of prescriptions containing codeine in the United States (U.S.) from 2010 to 2019 based on business type (i.e., hospitals, pharmacies, health care practitioners, teaching institutions). This investigation also analyzed the distribution of prescriptions containing codeine per Medicaid enrollees. In addition, this study aimed to identify regional disparities in prescribed milligrams (mg) of codeine per person across states and identify any extreme values during 2019.

Methods: The distribution of codeine via pharmacies, hospitals, and practitioners in kilograms was obtained from the Drug Enforcement Administration's Automated Reports and Consolidated Ordering System (ARCOS) from 2010 to 2019. In addition, the number of prescriptions of codeine per 1,000 Medicaid enrollees was obtained from the State Drug Utilization Database (SDUD) provided by Medicaid.

Results: There was a steady decrease (-25.0%) in total grams of codeine through all distributors from 2010 through 2019. There was an increase in total grams of codeine distributed in the U.S. from 2014 to 2015 of +28.9%; this was the largest increase between 2 consecutive years. The largest decrease from 2010 to 2019 for a given distributor type was hospitals, with an -89.6% decrease. Within the same time frame, there was a -20.8% decrease in grams of codeine distributed through pharmacies. Total grams of codeine distributed in Texas was significantly elevated relative to the national average.

Conclusion: The peak of prescription codeine in 2011 was consistent with the overall peak in prescription opioids, with a progressive decrease over the following decade. This could be explained by relatively recent recommendations regarding the therapeutic use of codeine and how other antitussive agents may be of better use. The precipitous rise of codeine in Texas that we observed has been recognized in prior studies. The national average prescription for codeine is 50 mg per person, while in Texas it is about 147 mg per person. Additionally, the peak in SDUD data in 2016 might be due to corresponding peak in Medicaid/CHIP enrollees for that year. In conclusion, more research investigating the variance of codeine prescription in Texas is needed.

Introduction

Since 1979, there have been over 600,000 deaths related to drug overdoses in the United States (U.S.) (1). Of those deaths, most have been attributed to opioids, varying from illegal narcotics such as heroin to prescriptions (2). When considering that the "first wave" of the opioid epidemic began in the late 1980s, this number offers an even bleaker picture (3). What began as a good-faith effort to be more proactive in managing pain has resulted in over 2 million Americans becoming addicted to opioids in some form (4). Recognizing this growing issue, various entities at the local, state, and federal levels implemented initiatives directed to combat the problem. One such initiative that began in 2016 was the U.S. surgeon general's "Turn the Tide Rx" campaign, which focused on providing educational resources as well as a voluntary pledge for clinicians to uphold (5). Despite numerous efforts to "turn the tide," the number of people addicted and dying from opioids continues to increase, so perhaps weaker opioids may provide an alternative.

Codeine is a prodrug converted to morphine by the cytochrome P450 enzyme CYP2D6 (6, 7). Morphine, the metabolite that provides analgesic effects, is further metabolized by glucuronidase enzymes to form the inactive metabolite morphine-3-glucoronide and the active metabolite morphine-6-glucoronide (6). Genetic polymorphisms of CYP2D6 leads to varied efficacies of codeine based on the phenotypic classifications of ultrarapid, normal, reduced, or poor metabolizer (6, 7). Despite this variation, codeine is the most prescribed opioid in pediatrics (8).

According to the 2016 Cochrane Review which examined the efficacy of codeine as a cough suppressant in children, there is a lack of sufficient evidence to support or oppose the use of cough and cold medications containing codeine (9). Various studies have recommended clinicians discover alternatives to codeine prescriptions in reaction to the continuous prescribing of codeine for children. This recommendation is due to the variety of effects and the danger of respiratory depression and mortality in children (10, 11, 12, 13). These suggestions are in accordance with the U.S. Food and Drug Administration's (FDA) 2012 "black box warning" and contraindications for codeine use in children (14, 15, 16).

Depending on the formulation, codeine is classified as a Schedule II, III or V drug in the U.S. (17, 18, 19). The Drug Enforcement Administration's (DEA) Automation of Reports and Consolidated Orders System (ARCOS) monitors the manufacturing and distribution of all Schedule I and II drugs as well as Schedule III narcotic and gamma-hydroxybutyric acid (GHB) substances (20). After rescheduling codeine products in Australia to be prescription-only in 2018, researchers examined the drug sales trends and noted a modest increase in sales (21). Interestingly, another study compared international postoperative opioid prescriptions and found codeine and tramadol accounted for approximately 58% and 45% in Canada and Sweden, and only 7% in the U.S. However, the U.S. prescribed higher doses of opioids overall following surgery more often than in Canada or Sweden (22). Though the U.S. prescribed comparatively lower postoperative codeine, the number of weaker opioid prescriptions at discharge from the emergency room in the U.S. grew from 2012 to 2017, according to the CDC's National Health Statistics Report. The formulation acetaminophen-codeine was 12.5% of all opioids prescribed in 2016–2017 (23). To date, there has been no comprehensive study analyzing national codeine prescription trends.

This study's principal objective was to analyze the distribution trends of codeine-containing prescriptions within the U.S. from 2010 to 2019 based on business type (i.e., hospitals, pharmacies, and health care practitioners). Additionally, an analysis of the distribution of prescriptions containing codeine per Medicaid enrollees from 2014 to 2019 was conducted to further elucidate any trends. Finally, this study aimed to identify regional disparities in prescribed codeine across states and identify any extreme values within the 10-year time frame.

Methods

The ARCOS database, expressly the Retail Drug Summary Reports, was the source of data regarding the national distribution of codeine within the U.S. from 2010 to 2019. The requirement for reporting certain controlled substances transactions from the point of manufacture to distributors — hospitals, retail pharmacies, practitioners, mid-level practitioners, and teaching institutions — to the Attorney General was made possible due to the Controlled Substances Act of 1970. However, since only certain controlled substances are monitored and recorded, it was not possible to consider all the formulations of codeine available nationally. Notably, the Schedule IV and V codeine formulations were not included in the analysis. Report 1 of the ARCOS Retail Drug Summary Reports provided data for grams of codeine distributed by zip code, while the total amount of codeine distributed nationally and by state per quarter (in grams) was collected from Report 4. Additionally, Report 5 was the source for grams of codeine purchased by healthcare business types (i.e., hospitals, pharmacies, and health care practitioners). While Report 5 did contain data on other healthcare business types (e.g., mid-level practitioners and narcotic treatment programs), the amount used by those businesses was deemed to be negligible. Data on the populations of interest were collected from American Community Survey and U.S. Census Bureau to normalize other findings for a given state or year.

The number of codeine prescriptions covered by state Medicaid agencies reported through Medicaid's State Drug Utilization Data (SDUD) database from 2014 to 2019 for all 50 states and Washington D.C. was also collected and corrected for the number of Medicaid enrollees. In addition, the number of prescriptions ordered nationally from 2014 to 2019 was collected. Finally, data analysis, figures, and heat maps were completed using GraphPad Prism, Version 9.1.0., JMP, and Microsoft Excel. This study was deemed exempt from review by the Geisinger Institutional Review Board.

Results

From 2010 to 2019, the total amount of codeine distributed across all the major business types of distributors in the U.S. declined by 25% (Figure 1). Further analysis determined that hospitals experienced the largest decrease in codeine distribution with a decline of 89.6%, while pharmacies had a 20.8% decrease in codeine distribution. Practitioners experienced the smallest decrease in codeine distribution of the three business types, with a decrease of 0.15%. Though all business types experienced a decline in codeine distribution in the given period, there was an increase in codeine administration between 2014–2015. More specifically, there was an increase of 28.9% in total codeine distribution across the U.S. (Figure 1). The peak year for codeine distribution was in 2011, with an average of 53.7 mg per state. Comparing the peak year to the lowest and most recent data year in 2019, most states demonstrated a decline in distribution with an average 40.1% decrease nationwide (Figure 2). Figure 2 gives a quantitative illustration of Washington D.C. and the 46 states which experienced a reduction in codeine distribution over the 10-year focus. In contrast, four states showed an increase in codeine administration: Texas (240%), Oklahoma (28.7%), West Virginia (35.4%), and Arkansas (28.7%), which were all considered statistically significant with an alpha value of 0.05

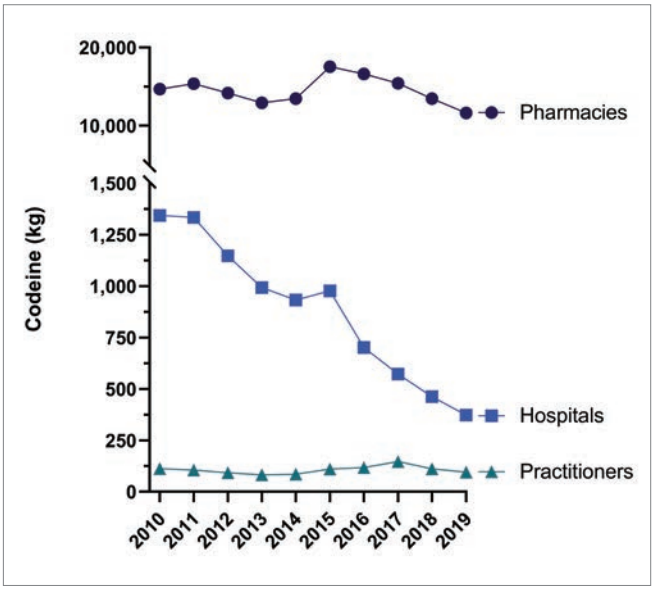

Figure 1. Codeine (kg) by business activity as reported by the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS) from 2010 to 2019.

(Figures 2 and 3). The heat map also illustrates that Nevada is the state with the most notable decline in codeine distribution between 2011 and 2019 with a decrease of 68%, which was considered statistically significant via paired t-test with an alpha value of 0.05 (Figure 3). Lastly, Figure 4 displays the distribution of codeine (mg/person) in the most recent year, 2019, per state.

Medicaid prescriptions per 1,000 enrollees were examined between the years of 2014 to 2019. Figure 5 shows the prescriptions per 1,000 enrollees increased to a peak in the third quarter of 2016 with a subsequent drop in 2017 and stabilization to the most recent year of 2019. The prescriptions per 1,000 enrollees increased from 21,517 prescriptions in the first quarter of 2014 to 391,214 prescriptions in the third quarter of 2016, reflecting a 1,718.16% increase. Progressing from this peak in the third quarter of 2016 (391,214 prescriptions) to the first quarter in 2017 (166,848 prescriptions) resulted in a 57.35% decrease in prescriptions per 1,000 enrollees.

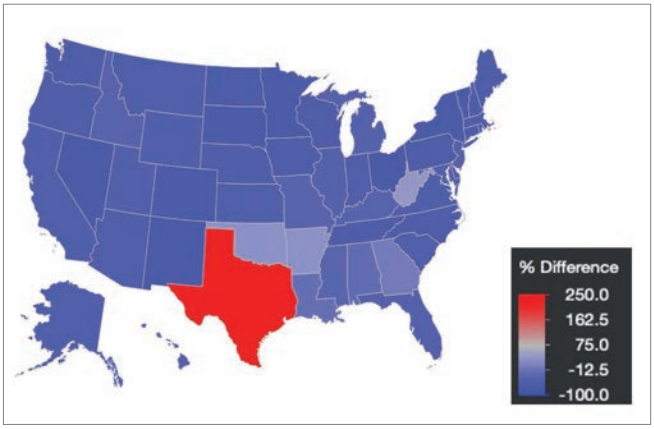

Figure 2. Percent change in distribution of codeine (mg/person) from 2011 to 2019 as reported by the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS), where blue indicates a decrease in distribution and red indicates an increase.

Discussion

This study investigated trends in codeine distribution and use in the U.S. between 2011 and 2019, with 2011 corresponding to the peak year for codeine administration. Our data suggest declining distribution of codeine by 25% across all major distributors in the U.S. (hospitals, pharmacies, practitioners) from 2011 to 2019. In addition, our data was indicative of regional disparities in codeine utilization when comparing 2011 to 2019. Forty-six out of 50 states experienced a decline in codeine distribution, while four states increased: Texas, Oklahoma, West Virginia, and Arkansas. When comparing the amount of codeine distributed in Texas in 2011 compared to 2019, there was a 240% increase in the amount of codeine utilized. Furthermore, an analysis of Medicaid prescriptions per 1,000 enrollees was examined from 2014 to 2019. The data indicated a peak in Medicaid prescriptions during the third quarter of 2016 (391,214 prescriptions per 1,000 enrollees) followed by a subsequent drop in prescriptions during the first quarter of 2017 (166,848 prescriptions per 1,000 enrollees), reflecting a 57.35% decline before stabilizing in 2019.

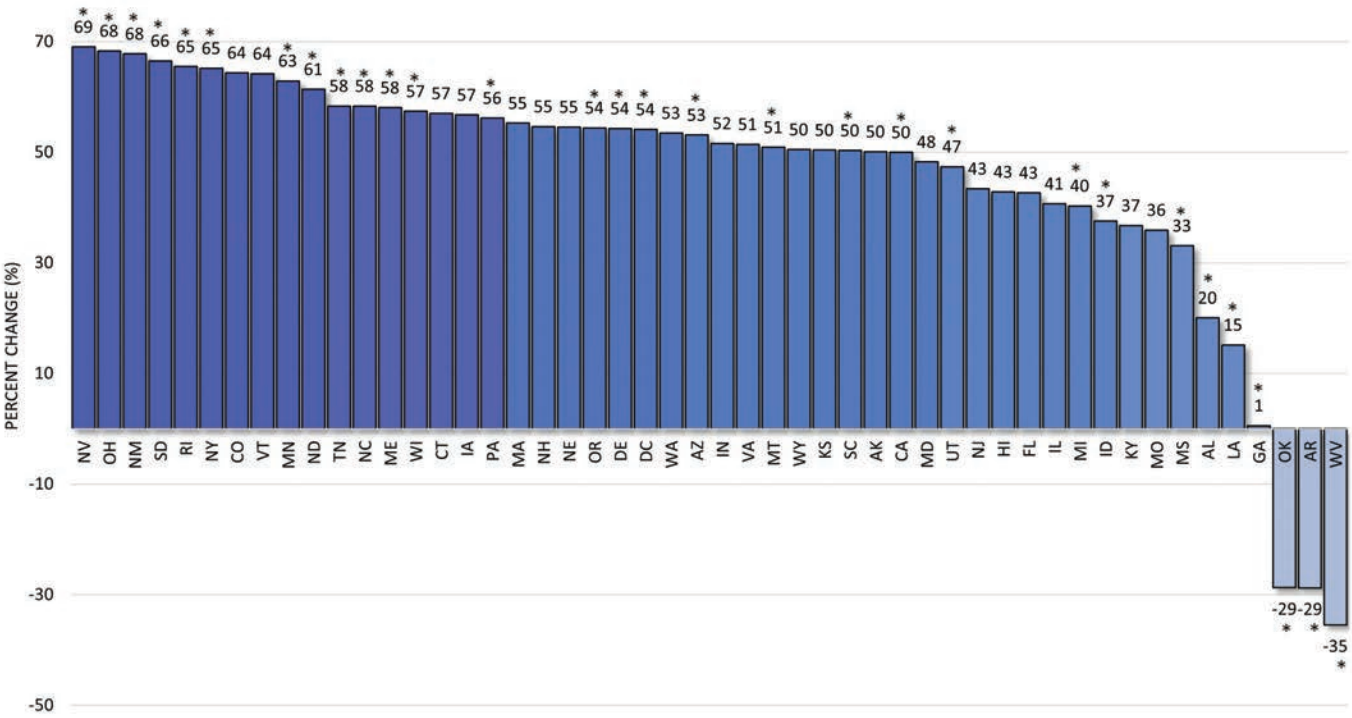

Figure 3. Percent change in codeine distribution (mg/person) between 2011 and 2019 as reported by the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS) for 49 states and Washington D.C. (excluding Texas for clarity), (paired t-test, *$p < 0.05$).

This pattern of change in the declining distribution of codeine from the peak year of 2011 can be explained with a further examination into other prescription opioids. The peak codeine prescription rate in 2011 was consistent with the overall peak in prescription opioid rates during the same year (20). Comparing the codeine prescription rate between the peak year of 2011 and 2019, the average percent decrease of milligrams of codeine per person was 40.1%. This decrease could be explained by policies that were implemented across the U.S. As of 2015, 50 states and the District of Columbia put in place an Electronic Prescribing of Controlled Substances (EPCS) system; moreover, as of April 2021, 24 states have mandatory EPCS protocols in place (24). Given the ongoing trend towards more instituted policies directed towards prescribed substances, such as codeine, this may play an integral role in accounting for opioid prescription reduction. The system's ubiquitous nature and goal for monitoring the opioid crisis implemented impactful guidelines to control opioid mismanagement.

The U.S. Food and Drug Administration (FDA) guidelines and policies may also be a decisive contributing factor to the progressive decline in codeine distribution. During the period of interest between 2011 and 2019, the FDA instituted policies requiring labeling changes for prescription opioid cough and cold medicine to limit their use to adults 18 years and older (15). Included in these labeling changes is the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing in prescription cough and cold medicines containing codeine (16). These mandated FDA policies are likely another contributing factor to the declining distribution of codeine among different healthcare distributors.

According to our regional analysis, 46 of 50 states demonstrated a precipitous decline in codeine utilization when comparing the peak year of 2011 to 2019. However, the four states with an increase in codeine administration were Texas, Oklahoma, West Virginia, and Arkansas. This indicates the presence of a regional disparity in codeine utilizations primarily centered around the southern region of the U.S. in close proximity to Texas, excluding West Virginia. Texas presented with the most notable increase in codeine administration — a 240% increase when comparing 2011 to 2019. According to ARCOS, the spike in codeine distribution for Texas began increasing largely in 2015 and continued to climb with each successive year. The precipitous rise in Texas has been recognized in another study as well (25). A possible explanation for the pronounced regional disparity in Texas, Oklahoma, and Arkansas could be a result

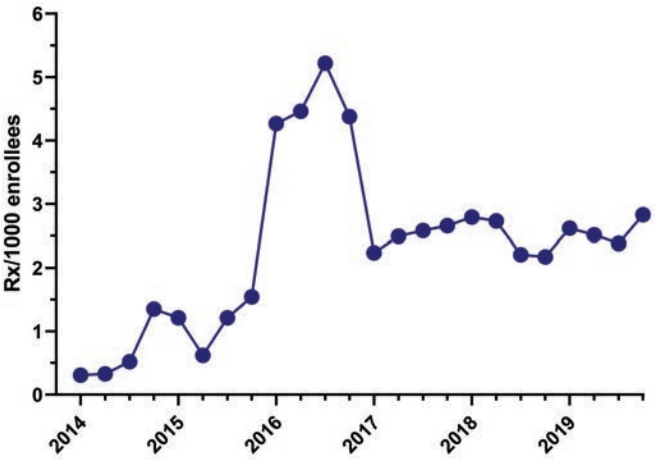

Figure 5. Number of codeine prescriptions per 1,000 Medicaid enrollees as reported by the State Drug Utilization Database (SDUD) from 2014 to 2019.

Figure 4. Distribution of codeine (mg/person) in 2019 as reported by the United States Drug Enforcement Administration's Automated Reports and Consolidated Orders System (ARCOS). The light blue bars include data within one standard deviation of the mean with "a" denoting point outside one standard deviation and "b" denoting points within one standard deviation but outside the 95% confidence interval.

from the cultural roots of codeine consumption. On the other hand, the regional disparity could be a result of the complex interplay between variations in health status, attitudes and cultural responses to health care, and access to health care in Texas and its neighboring states. Future research should focus on sociocultural/economic factors that may mediate the pronounced regional disparity.

Looking to the future, it would be beneficial to further investigate the decreasing trend in codeine in the principal distributors, such as hospitals and pharmacies. Perhaps this decrease resulted from a negative connotation regarding codeine, fear of the drug being misused, or the presence of safer alternatives less likely to cause addiction or abuse such as NSAIDS. Alternatively, it could have been caused by the implementation of stricter guidelines monitoring the control, spread, and prescription of codeine nationally or the adoption of systems designed to distribute codeine more efficiently with the concern about people's health, safety, and well-being.

Finally, examining the Medicaid codeine prescriptions per 1,000 enrollees, it is clear that further research is necessary to investigate the 1,718.16% increase in prescriptions between the first quarter of 2014 and the third quarter of 2016. According to Medicaid data, the number of national Medicaid enrollees peaked around 2016 and mirrors the rise and fall of prescriptions per 1,000 enrollees between 2014 and 2019. This could be a contributing reason for the increase of codeine prescriptions observed in 2016, but further research should be conducted to discover other possible factors. Overall, gaining insight to combat the opioid epidemic will be aided by further analysis of codeine prescription trends in the U.S.

Acknowledgments

The authors extend their gratitude to Colleen Jordan for her assistance with citations and Iris Johnston for providing access to articles.

Disclosures

BJP is part of an osteoarthritis research team supported by Pfizer and Eli Lilly. The other authors have no disclosures.

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