Effects of Washington's Opioid Prescribing Rules for Chronic, Non-Cancer Pain Management on Opioid Overdose Mortality and Pharmaceutical Opioid Distribution: 1999-2017

Soyeon I. Lippman

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Noel S. Weiss (Chair)

Crystal C. Hall

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Abstract

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Soyeon I. Lippman

Chair of the Supervisory Committee:

Noel S. Weiss
Department of Epidemiology

Background

Since the 1990s, the opioid crisis has affected individuals and communities across the United States. National and statewide comprehensive efforts to address the problem include policies to prevent opioid addiction, identify opioid-addicted individuals, and provide effective treatment. In Washington state, in response to rising prescription opioid-related overdose deaths, the legislature passed the Engrossed Substitute House Bill (ESHB) 2876 "Act Relating to Pain Management" in 2010 for the management of chronic non-cancer pain through prescription opioids.

Objective

To investigate the possible impacts of ESHB 2876 on opioid overdose deaths (OOD) and prescription opioid distribution at retail levels.

Methods

We conducted a single-sample interrupted time series analysis to examine impacts of ESHB 2876 on statewide OOD deaths and prescription opioids (hydrocodone and oxycodone) distributed at retail level in Washington State from 1999 to 2017. Segmented Poisson regression model was used for the analysis. Data for OOD of Washington State residents were obtained from the Wide-ranging OnLine Data for Epidemiologic Research (WONDER) system of the Centers for Disease Control and Prevention. Prescription hydrocodone and oxycodone distribution at retail levels were obtained from the

Automated Reports and Consolidated Ordering System (ARCOS) system of the Drug Enforcement Administration (DEA).

Results

Following ESHB 2876 implementation in 2011, opioid overdose mortality in Washington State decreased by 5% each year (95% CI: 4% to 7%), compared to the rates predicted from the mortality trend in the 12 years prior to ESHB 2876. The corresponding decline in the retail level hydrocodone and oxycodone distribution was 12% per year (95% CI: 10% to 15%). However, while the decrease in hydrocodone and oxycodone distribution occurred immediately following the legislation, the mortality trend began to attenuate three years prior to ESHB 2876 implementation.

Conclusion

Opioid overdose mortality and prescription opioid distribution trends decreased statewide after ESHB 2876 implementation. While our study suggests that ESHB 2876 is an effective intervention in reducing hydrocodone and oxycodone distribution at the retail level, it is not clear if the legislation had an influence in producing the decrease in opioid mortality.

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INTRODUCTION

Between 1999 and 2017, nearly 400,000 people died from an opioid overdose in the United States. In 2017 alone, 47,600 (14.9 per 100,000) deaths involved opioids. During the same time in Washington state, 11,320 individuals died from an opioid overdose, with 742 deaths (9.6 per 100,000) in 2017.[1,2] Until 2014, the rates of opioid overdose deaths (OOD) in Washington state had been consistently higher than the U.S. rates. The highest OOD rate among Washington residents occurred in 2009 (10.2 per 100,000), which was over 50% higher than the U.S. rate (6.6 per 100,000) in the same year. [2] (Figure 1).

Opioid Epidemic:

The ongoing opioid epidemic can be outlined as a triple wave epidemic. The first wave began in the 1990s with rapid rise in the rate of opioid prescriptions for chronic pain. This acceleration in prescription opioid sales was largely due to pharmaceutical companies and special interest groups aggressively marketing and lobbying state legislatures and medical boards to use opioid pain relievers for chronic non-cancer pain while asserting low risk of addiction and low risk of opioid-induced respiratory depression. For example, in 1995, a key product, OxyContin was introduced as a reformulation of oxycodone for extended release. The American Pain Society (in 1995), the Veterans' Health Administration (in 1999), and the Joint Commission that is responsible for certifying hospitals to receive Medicare payments (in 2001) all embraced and endorsed the Pain is the Fifth Vital Sign campaign. In Washington state, permissive opioid prescription was made into law in 2010, such that "no disciplinary action will be taken against a practitioner based solely on the quantity or frequency of opioids prescribed" (WAC 256-919-830).[1,3-8]

The second wave began in 2010, marked by rapid increase in overdose deaths involving heroin. Changes in regulations on the availability of prescription opioids, clinical guidelines, healthcare professionals' awareness of the opioid abuse and misuse, and concern for liability led to prescription opioids becoming harder to access. Coupled with availability of cheaper heroin and street demand for

prescription opioid pills, death from heroin overdose increased fivefold between 2010 and 2016. A national survey showed that 94% of heroin users shifted from prescription opioids to heroin because "prescription opioids were far more expensive and harder to obtain". [9,10]

The third and current wave began in 2013, with rapid rise in overdose deaths involving synthetic opioids, particularly death involving illicitly manufactured fentanyl. In some regions of the U.S., namely the eastern U.S., fentanyl and other synthetic opioids have become the dominant drug type. Rather than three distinct waves, the prescription opioid, heroin, and fentanyl waves are interrelated epidemics shaped by dynamic connections from individual and social behaviors, healthcare systems, industries, governments, and criminal justice systems, to international policies and economies. [1,3,5,8,11,12]

Policy Context:

In Washington, statewide laws, policies, executive orders, regulations, and guidance related to opioids have been established since 2006 to address the broad and interwoven aspects of the opioid epidemic, including opioid prescribing, monitoring of opioid use, and prevention efforts to reduce opioid misuse and overdose. [6,7,13-17] In 2006, Washington's Agency Medical Directors' Group (AMDG), composed of six Washington state agencies that purchase or regulate health care, developed an opioid prescribing guideline "WA Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain". The guideline focused on reducing high-dose prescribing, specifically dosing guidance for patients at or above 120 milligrams of morphine-equivalent dose per day. This was the first guideline in the U.S. to specify a dosing recommendation, and has since been updated in 2010 and 2015. [6]

In 2010, in response to rising prescription opioid-related overdose deaths, the Washington legislature passed the Engrossed Substitute House Bill (ESHB) 2876. The bill directed State health care boards and commissions* regulating health care professions with prescribing authority to repeal existing permissive pain management rules (WAC 256-919-830 from 1999), and adopt new rules for

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** Five boards and commissions include: Medical Quality Assurance Commission (MQAC), the Board of Osteopathic Medicine and Surgery (BOMS), the Podiatric Medical Board (PMB), Dental Quality Assurance Commission, and the Nursing Care Quality Assurance Commission.

the management of chronic, non-cancer pain. Specifically, the bill required that new rules include: "1) mandatory elements for dosing criteria, including a dosage amount that may not be exceeded without consultation with a pain management specialist; 2) guidance on when to seek specialty consultation and ways in which electronic specialty consultations may be sought; 3) guidance on tracking clinical progress by using assessment tools focusing on pain interference, physical function, and overall risk for poor outcome; and 4) guidance on tracking opioids use." The rules did not apply to: 1) palliative, hospice, or other end-of-life care; and 2) to the management of acute pain caused by injury or surgical procedures. The legislature mandated that these rules be adopted by June 30, 2011. [6,14,18] Unlike the AMDG's opioid prescribing guideline for pain, ESHB 2876 is an enforceable regulation.

ESHB 2876 is a key policy strategy as a primary intervention to prevent new cases of opioid addiction among patients with chronic, non-cancer pain who are prescribed opioid pain relievers for medical use, and indirectly affect individuals who may use or divert prescription opioids for nonmedical use. For example, among patients prescribed opioid pain relievers for chronic non-cancer pain, studies have shown that nearly 25% of those patients displayed opioid dependence and addiction. Between 1999 and 2017, both in the U.S. and Washington state, the greatest increase in opioid overdose death rates occurred among adults aged 55-64, persons with the most common medical use of opioid pain relievers. [8,19-21] Among individuals who use prescription opioids for nonmedical uses, adolescents and young adults aged 12-17 and 18-25, respectively, most commonly obtain prescription opioids from friends or family members with medical need for opioid pain relievers. A study based on nationwide survey on drug use and health found that over 50% of adolescents and young adults with opioid misuse reported obtaining or diverting opioids from friends or family members. Risk for future substance use disorder, including heroin and alcohol, is substantially higher for adolescents and young adults who have engaged with nonmedical prescription use. [8,22] Accordingly, policies aiming to reduce excess prescription opioids in order to prevent opioid dependence and addiction, and ultimately opioid-related deaths, have been implemented in multiple states, including Washington state. [4,8,21]

Also in 2010, Washington state law made the opioid-overdose reversal medication, naloxone

more accessible by enacting the Good Samaritan law in 2010 (RCW 69.50.315). The law provided legal immunity to drug-related overdose victims or bystanders seeking medical aid from drug possession changes, and provided legal provision to make naloxone more accessible through prescription and administration by bystanders at an overdose event. However, initial evaluation found low awareness and implementation of the law among law enforcement personnel and paramedics. [6,7,23]

In 2015, underscoring the complexities of the opioid epidemic, and the attendant need for cross-jurisdictional and interagency partnerships to address the opioid crisis, the Governor issued Executive Order 16-09, "Addressing the Opioid Use Public Health Crisis". The Order directed state agencies – including the Health Care Authority, Department of Social and Health Services, the Department of Health, and the Department of Labor and Industries – to work with partners across the state to implement a comprehensive opioid response plan (2016 Washington State Interagency Opioid Working Plan). Specifically, the Order included four priority goals: 1) prevent opioid misuse and abuse; 2) treat opioid use disorder and link with support services; 3) prevent deaths from overdose; and 4) use data to detect opioid uses, morbidity and mortality, and evaluate interventions. [7,17]

More recently, in 2017, the state legislature passed the ESHB 1427, providing language on new comprehensive opioid prescribing rules. The bill expanded previous pain rules to require the same five State health care boards and commissions to update and implement new comprehensive opioid prescribing rule. Specifically, ESHB 1427 directed the agencies to include rules for acute and perioperative pain, incorporate CDC 2016 Guideline for Prescribing Opioids for Chronic Pain, improve access to medication-assisted treatment, and expand access and required review of the Prescription Drug Monitoring Program (PDMP) data by prescribers. [7,24]

Most recently, in 2019, the Washington state health officer issued a statewide standing order to allow any person or organization to obtain naloxone from a pharmacy without a prescription, thereby facilitating the improved distribution of the opioid antagonist.[13] As of 2016, forty-two states have issued standing or protocol orders for naloxone, and five states provided pharmacists the authority to prescribe naloxone. However, evaluation of state naloxone dispensing policies found that despite standing

orders, multiple barriers to naloxone access still existed in pharmacies. The identified barriers included limited naloxone stocking in pharmacies, limited knowledge of the standing order by pharmacy staff, and out-of-pocket costs. [10,25-27]

Evaluation of state policies is crucial to determine their impact and value. Moreover, policy evaluation serves key purposes in documenting and informing implementation, providing information to ensure accountability of utilized resources, and informing future policies. To date, no studies have examined the impacts of ESHB 2876 on reducing opioid overdose deaths and distribution of prescription opioids. In this study, we investigated the impact of Washington State's new prescribing rules for chronic, non-cancer pain management rules on opioid overdose mortality and retail level distribution of opioids. Our study aimed to: 1) compare statewide opioid overdose mortality rates before and after ESHB 2876; and 2) compare statewide opioid distribution at the retail level before and after ESHB 2876.

METHODS

Study Design

We conducted a single-sample interrupted time series (ITS) analysis at the statewide level to assess the impact of ESHB 2876 using annual opioid overdose deaths and prescription opioid distribution in Washington from January 1, 1999 to December 31, 2017. [28-34] The mortality rates were calculated per 100,000 resident populations, and age-adjusted to the 2000 U.S. standard population. We assessed the appropriateness of our ITS design by addressing the standard risk of bias criteria for ITS studies suggested by the Cochrane Effective Practice and Organization of Care Review Group (EPOC). The criteria and our assessment of study against each criterion are provided in Appendix 1.

While the bill required that the rules be adopted by the five boards and commission by June 30, 2011, this study was conducted using annual death and pharmaceutical opioid distribution data, and the entirely of year 2011 was set as the time of intervention in the ITS analysis. Setting 2011 as the intervention touch-point, which includes all deaths in the calendar year, was determined to be

reasonable based on the legislative session timeline, stakeholder engagement and specific language in the bill. Specifically, the 2010 regular legislative session between January and March included the bill's first reading, and the House and the Senate passed the bill on February 10, 2010 and March 4, 2010, respectively. Also during 2010, public hearings and public workgroup meetings were held soliciting stakeholder input. Moreover, the bill's language stated that the existing permissive rules on the use of opioids as pharmacological interventions for management of long-term pain must be repealed by December 1, 2010.

Study Setting: Washington State, January 1, 1999 to December 31, 2017.

Study Subjects: Eligibility criteria to assess opioid overdose deaths included: decedent was a Washington state resident; death occurred between January 1, 2006 - December 31, 2016; and underlying and multiple cause-of-death met CDC's national opioid overdose mortality ICD-10 code standards (detailed under Study Design for main outcome). Eligibility criteria for assessing retail level oxycodone and hydrocodone distribution includes that the buyer (e.g. hospital, pharmacy) is located in Washington state.

Intervention: The study evaluated the impact of the policy intervention ESHB 2876, which directed State health care boards and commissions to update the existing pain management rules for chronic, non-cancer pain related to dosing criteria and minimum training.

Data Collection and Measures

Dependent Variables:

Opioid Overdose Deaths:

Annual opioid overdose deaths at from January 1, 1999 to December 31, 2017 were obtained from the publicly accessible Centers for Disease Control and Prevention's WONDER (Wide-ranging Online Data for Epidemiologic Research). Age distribution and age-adjustment weights based on the 2000 projected U.S. population were obtained from the CDC National Center for Health Statistics.[35,36]

Opioid overdose deaths were identified using International Classification of Diseases, Tenth Revision (ICD-10) following Center for Disease Control and Prevention's national opioid overdose

mortality ICD-10 code standards. Specifically, all drug overdose deaths were first identified using ICD-10 underlying cause-of-death codes X40–44 (unintentional), X60–X64 (suicide), X85 (homicide), or Y10–Y14 (undetermined intent).[1,12] Then among deaths with drug overdose as the underlying cause, the types of drugs or drug category were identified by the following ICD-10 multiple cause-of-death codes: Heroin (T40.1); Natural and semisynthetic opioids (T40.2), such as hydrocodone and oxycodone; Methadone (T40.3). Synthetic opioids other than methadone (T40.4), such as fentanyl and tramadol; Deaths involving any opioid (T40.0 (opium), T40.1, T40.2, T40.3, T40.4 and T40.6 (other and unspecified narcotics)); Cocaine (T40.5); and Psych stimulants with abuse potential (T43.6), which includes such drugs as methamphetamine, and 3,4-methylenedioxy-methamphetamine (MDMA)[1]

As drug overdose deaths may involve more than one type of drug, some deaths are included in more than one subcategory. That is, categories of drug overdose deaths are not mutually exclusive.

Retail Level Prescription Opioid Distribution:

Distribution of statewide pharmaceutical opioids was obtained from publicly accessible Drug Enforcement Administration (DEA)'s Automation of Reports and Consolidated Orders System (ARCOS). ARCOS is a data collection system in which manufacturers and distributors are mandated to report their controlled substance transactions to the DEA. It monitors controlled substances from the point of manufacture to the point of sale at the retail level, including hospitals and pharmacies. The raw data from 2006 to 2012 were made publicly accessible by the Washington Post as a result of a court order. [37,38] Distribution data at the zip code-level for 2013 to 2016 were extracted from the DEA's ARCOS Retail Drug Summary Report. [39]

Statewide distribution of pharmaceutical opioids includes only hydrocodone and oxycodone in this study, as they compose the majority of shipped prescription opioids. Opioid weights are converted to usual daily doses by dividing total reported grams by the usual grams per daily dose value, following World Health Organization Collaborating Centre for Drug Statistics Methodology. The converted daily dose is analyzed per 100 persons at the county-level. [40] Opioid distribution serves as a surrogate for

opioid use and mortality, as well as a more sensitive and immediate indicator for the impact of the legislation.

Annual county-level estimates of population size were obtained from the Washington State Office of Financial Management, Forecasting division. [41]

Demographic variables that are typically adjusted for in health outcome studies, such as age, sex, and race/ethnicity, and unemployment are not included as covariates in the analysis, as they remained relatively time-invariant during the study period 1999-2017. The study was determined to qualify for exempt status as publicly available data was used, per the University of Washington, Human Subjects Division, Human Subjects Research and Exempt Determination Worksheets. [42,43]

Statistical Analysis

Age-adjusted annual mortality rates were calculated for the pre- and post-intervention segments using the Washington State OFM population estimates as the denominator and age-specific weights from the CDC's National Center for Health Statistics based on the 2000 U.S. population.

As an initial step, we visually examined the statewide year-by-year rates of opioid overdose death and prescription opioid daily dose. We observed that the OOD rate began to level off in 2007, and that the association between OOD rate and time was nonlinear prior to the implementation of ESHB 2876. Accordingly, we fit a linear regression model to the OOD rate and time modeled as linear splines fit to the intervals 1999-2001, 2001-2004, 2004-2007, 2007-2010, 2010-2013, and 2013-2017. We tested for linearity of the association between OOD rate and time by performing a multiple partial chi square test that the hypothesis that the regression coefficients for the three linear spline terms were all equal to each other.

For interrupted time series analysis, segmented regression was conducted to estimate the impact of the ESHB 2876 on opioid overdose deaths and prescription opioids distributed at retail levels. Specifically, one-sample segmented Poisson regression was performed to estimate the difference in

annual opioid overdose mortality and pharmaceutical opioid distribution at the statewide-level before and after the intervention using the following model:

$$\ln(Y_t) = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 T_t X_t + \varepsilon_t$$

Visual interpretation of the ITS regression model is described in Appendix 2. The model specifications are as follows: Y_t is the outcome variable measured at each equally space time point t, measured as the number of opioid overdose death or number of prescription opioid daily dose; T_t is the time, in years, elapsed since the start of the study (January 1, 2006); X_t is a dummy variable indicating the intervention with 2011 set as the year when the intervention was implemented (0 for pre-intervention; 1 for post-intervention); $X_t T_t$ is an interaction term; β_0 estimates the baseline level of the outcome opioid overdose morality or prescription opioid dose at $T = 0$; β_1 estimates the pre-intervention trend (slope); β_2 estimates the change in the level of the outcomes immediately following the intervention. Significant p-values in β_2 demonstrate an immediate intervention effect; β_3 estimates the change in slope (trend) between the pre- and post-intervention, and is modeled as an interaction term between time, T, and intervention, X_t; and ε is residual (error); the sum of β_1 and β_3 is the post-intervention slope. β_3 is the key estimation of interest as it estimates the difference in the trend in the outcomes after the intervention, compared with the trend before the intervention.

Poisson regression coefficients and corresponding confidence intervals were exponentiated to compute the corresponding rate ratios. Because the outcome variable is in counts (number of deaths or number of daily doses), Poisson regression model was used, with population as an offset term.

The counterfactual is the expected trend in opioid overdose deaths in the absence of the ESHB 2876, which was modeled by extrapolating the pre-intervention trend in opioid overdose deaths or pharmaceutical opioid distribution into the post-intervention period. To measure the impact of the intervention, the projected counterfactual was compared to the observed deaths or distribution in the post-intervention period for any change in the trend.[32,44,45]

Autocorrelation: To check for autocorrelation, residuals were plotted against time and visually inspected. Moreover, residual autocorrelation and partial autocorrelation functions were examined using Durbin-Watson test statistic. No first-order autocorrelation was observed in our model assessing OOD, but was observed in assessing prescription opioid distribution. Accordingly, an autoregressive term was included for the lagged residuals in the regression model with prescription opioid distribution as the outcome. Initial analysis of pre-intervention trends (for both opioid overdose death and opioid prescription distribution outcomes) showed that both pre-intervention trends were stable over time, and thus no adjustment for seasonality was necessary for the model.

Sensitivity analysis: To assess potential lagged effects of the intervention on the outcomes (opioid overdose deaths or opioid prescription distribution), lagged effects of one year was examined by shifting the time of intervention by one year to 2012.

All analyses were performed using Stata 13.

RESULTS

Opioid Overdose Deaths

Table 1 and Figure 2 show the annual number and age-adjusted rates of deaths due to opioid overdose between 1999 and 2017. Appendices 3 and 4 show the annual opioid overdose death (OOD) numbers and rates by age group. Between 1999 and 2017, a total of 11,320 Washington residents died due to drug overdose involving any opioid. The annual count from OOD increased from 353 in 1999 to 742 in 2017. And the annual age-adjusted rate increased from 5.9 per 100,000 in 1999 to and 9.6 per 100,000 in 2017. The highest OOD count (708 persons) and age-adjusted rate (10.2 per 100,000) occurred in 2009. Prior to ESHB 2876 implementation, death rate due to opioids increased 6% per year (95% CI: 0.91 to 0.98, p=0.002). The 1% annual decrease in opioid overdose mortality rate after ESHB 2876 implementation was not statistically significant (95% CI: 0.98 to 1.01, p=0.884). However, relative to the modeled counterfactual without ESHB 2876 implementation, the 5% annual decrease in opioid overdose mortality was statistically significant (95% CI: 0.93 to 0.96, p<0.001) (Table 2, Figure 3).

Important to note, the increasing mortality trend began to level off in 2007, then appeared to increase again in 2016. Using regression spline analysis to test the association between OOD rate and time revealed that the association was nonlinear (χ^2 = 199.31, p<0.001) (Appendix 5). Appendix 6 shows the results of the regression spline analysis. For example, between 2001-2004, the OOD rate increased by 1.24 deaths per 100,000 each year (95% CI: 0.56 to 1.93, p=0.002), compared to the OOD rate slope predicted from the trend in rates during 1999-2001. However, between 2007-2010, the OOD rate decreased by 0.49 deaths per 100,000 each year, compared to the mortality slope from the trend observed during 2004-2007 (95% CI: -1.25 to 0.27, p=0.118).

Results of stratified analysis by age group are presented in Appendices 3 and 4. Among the age groups, the highest number of OOD occurred in the 18-44 age group, whereas the highest rate occurred in the 45-55 age group. With the exception of the 45-54 age group, all the age-groups experienced an increase in OOD between 1999 and 2017. Overall, the highest OOD rates were consistently observed among adults aged 45-54 years, and the greatest increase in OOD rate occurred among adults aged 55-64 years, followed by adults aged 65-74 years.

Sensitivity analysis on assessing OOD by shifting the intervention one year to 2012 did not alter our interpretation of results (Appendix 7).

Retail Level Prescription Opioid Distribution

Table 3 and Figure 4 show the number of daily doses of the opioids, hydrocodone and oxycodone, distributed to retail pharmacies per year between1999 and 2017. Between 1999 and 2017, over 945 million combined number of hydrocodone and oxycodone daily doses were distributed at the retail level. The number of hydrocodone daily doses increased from 279.6 per 100 in 1999 to its peak of 711.4 per 100 in 2011, then decreased to 476.3 in 2017. The number of oxycodone daily doses increased from 67.8 per 100 in 1999 to its peak of 279.6 per 100 in 2008, then decreased to 212.0 in 2017. During this study period, the total number of prescription opioids distributed is equivalent to every Washington resident receiving an average of 7.6 daily doses of hydrocodone or oxycodone per year.

Prior to ESHB 2876 implementation, prescription opioid distributed at retail pharmacies increased 9% per year (95% CI: 1.07 to 1.10, p<0.001). After ESHB 2876 implementation, prescription opioid distributed at retail pharmacies decreased 5% per year (95% CI: 0.93 to 0.97 p<0.001). Relative to the modeled counterfactual without ESHB 2876 implementation, the 12% annual decrease in retail level opioid distribution was statistically significant (95% CI: 0.85 to 0.90, p<0.001). (Table 4 and Figure 5).

Sensitivity analysis on assessing pharmaceutical opioid distribution at retail level by shifting the intervention one year to 2012 did not alter our interpretation of results (Appendix 8).

DISCUSSION

Between 1999 and 2017, a total of 11,320 Washington residents died due to opioid overdose. Using interrupted time series analysis with ESHB 2876 as the intervention, we observed a decrease of 5% (95% CI: 0.93 to 0.96, p<0.001) in OOD rate per year following ESHB 2876 implementation in Washington state, relative to the trend of OOD rate prior to ESHB 2876. Similarly, we observed a decrease in hydrocodone and oxycodone distribution at the retail level following ESHB 2876. Compared to hydrocodone and oxycodone distribution trends before ESHB 2876 implementation, our ITS analysis estimated a decrease of 12% per year (95% CI: 0.85 to 0.90, p<0.001).

We observed that while opioid overdose deaths increased from 1999 to 2017 for all age groups, the trajectories of OOD rates and proportional burden of overdose during the study period varied substantially across the age groups. For example, while both the number and rate of OOD among 45-55 year olds peaked between 2008 and 2010, then declined over time, both the number and rate of OOD increased across all the other age groups. Notably, during the recent years since 2004, opioid-related deaths increased most rapidly among adults 55 years and older. The observed changes in the pattern and burden of opioid overdose mortality over time across age groups are further described below.

Overall, the rate of death due to opioids rose throughout the study period. However, the increase in OOD rates began to slow down between 2007 and 2008. It is unclear what led to the attenuation in the OOD rate increase. A possible statewide effort that could have contributed to the observed slow down was the opioid dosing guideline released in 2007 by the WA Agency Medical Directors' Group (AMDG) discussed above. A study based on adults with opioid prescriptions among Medicaid fee-for-service population between 2006 and 2010 showed that high-dose opioid prescribing declined substantially after the dosing guideline. While adult Medicaid beneficiaries do not represent the overall Washington state population in terms of income, employment, disabilities, and other demographic characteristics, the guideline was disseminated widely throughout the medical communities. Accordingly, the effects of ESHB 2876 on reducing opioid prescription and the anticipated attendant effects on OOD could have occurred concurrently with the AMDG guideline.

However, why the attenuating effects of the guideline prior to the ESHB 2876 legislation are only observed in opioid overdose deaths, and not retail opioid distribution, is puzzling. A possibility is that around 2007, behaviors of prescription opioid users shifted from using prescription opioids to using heroine, and thus explaining the observed plateauing of deaths due to prescription opioids in 2007 followed by rapid rise in deaths due to heroine in 2010. The lag in the prescription opioid deaths to heroine deaths between 2007 and 2010 may represent substance using behavioral shift, changes in the availability and pricing of heroine, and statewide and national awareness of prescription opioid mortality across the medical and public health communities. Further studies conducted at the individual-level, and triangulating quantitative data based on surveillance, hospitalization, and vital records data with qualitative data of individual substance users during this period, would be needed for a clearer understanding of the observed OOD trends.

Whereas the effect of reducing opioid prescriptions on a decline in opioid-related deaths was expected to be gradual, we anticipated the bill's effects on opioid prescriptions to be immediate. In this study, opioid distribution at the retail level serves as a surrogate for opioid prescriptions, and represents an immediate economic outcome of ESHB 2876, which aims to reduce opioid prescribing statewide.

Indeed, we observed a rapid reversal of the increasing trend in pharmaceutical opioid distribution following ESHB 2876 implementation. This study's finding that opioid distribution declined 12% per year following ESHB 2876 compared to the trend prior to ESHB 2876 supports recent data on total prescription opioid prescribing rate, which showed a 25% decline in Washington opioid prescriptions between 2012 and 2017. [46]

During the study period, we observed the highest overall rate of OOD among adults between 45 and 54 years, and greatest increase in OOD among adults between over 55 years. It is unclear why the OOD rate among 45-54 leveled off then declined starting in 2005 in Washington state, where as the rate continued to increase in the U.S. (Appendix 9 and 10). However, in both Washington state and the U.S., OOD rates among adults older than 55 years continued to rise, which may be due to opioid misuse behaviors and age-related physiological and medical factors present in older adults. For example, older adults are more likely to experience health conditions requiring chronic pain treatment, such as diabetic neuropathy, osteoarthritis, knee and hip surgeries, and injuries due to falls. Adding concern to the higher likelihood of opioid treatment, initial opioid therapy to treat acute pain (for example for surgeries following injuries from falls) poses a higher risk for developing future chronic opioid use. Moreover, older adults may be less likely to recognize and seek treatment for their opioid dependency, and providers may be less likely to recognize opioid dependency and misuse among older adults due to assumptions regarding substance abuse being an issue in younger populations. Other factors that specifically affect older adults include Medicare policies on covered opioid formulations, reimbursements, and medication-assisted treatments.[21,47] Accordingly, policies that focus on opioid prescribing practices should be designed and implemented integrating differential implications on older adults.

Moreover, again similar to national trends, although the number and rate of deaths from prescription opioids have been declining, the number of deaths from heroin and illicitly manufactured fentanyl has rapidly escalated (Appendix 11). Prior misuse of prescription opioids is the strongest risk factor for starting heroin use. [9,48,49] Policies that lead to reduced opioid prescribing, such as ESHB 2876

examined in this study, may have the unintended consequences of driving prescription opioid users to transition to heroin use. Indeed, current heroin users report switching to heroin due to it being cheaper than prescription opioids and more accessible compared to pharmaceutical opioids, drugs that have become harder to obtain.[4,8,9,21,50]

While our study did not assess any differences in ESHB 2876 impact on OOD across racial groups, the bill may also have unintended consequences of imposing poorer healthcare delivery and resultant disparity in health outcomes among black patients compared to white patients. In the context of the opioid crisis, poorer health outcomes can be attributable to poorer treatment for opioid use disorders. Stigma is a key contributor to disparities in both treatment-seeking and treatment-providing behaviors for individuals with opioid use disorders. For example, as a result of black opioid users' internalized and anticipated stigma associated with opioid use, compounded by already existing racial biases in the healthcare system and racialization of drug use, they may be less likely to seek treatment and thus continue substance use, including switching from prescription opioids to illicit drugs. From the perspective of healthcare providers, as a result of public, structural, and their enacted stigma, studies have suggested that black patients experience higher rates of opioid discontinuation after positive urine drug-tests, higher rates of experiencing opioid tapering, and lower likelihood of receiving medication-assisted treatments including methadone and buprenorphine. Accordingly, preventative interventions such as ESHB 2876 should couple its implementation with treatment interventions that intentionally and thoughtfully account for disproportionate burden experienced by certain racial groups as a consequence of the preventative intervention.[51-54]

Our study is subject to several limitations: [31,32,45,55,56] Of particular importance is that other events that took place during the period of study may have influenced the outcomes. For example, other policies, additional funding resources, regulations, changes in data reporting, or other coincident events that target the same population and issue can possibly lead to over- or under-estimation of the intervention's impact. Indeed, the trend in increasing opioid overdose mortality began to slow down three years prior to the legislation. Therefore, with respect to opioid related mortality, it is uncertain

what influence ESHB 2876 had. Key statewide policies, such as Medicaid's opioid policies, Governor's executive order to address the opioid crisis, and state's interagency opioid response plan were introduced between 2015-2016, and thus would not have affected outcome during our study period. Similarly, while Washington's Prescription Monitoring Program was legislatively created in 2007, data collection did not start until 2011, and interests from healthcare providers and pharmacists in utilizing the database began to rise only in 2015. Nationally, the CDC released guidelines for prescribing opioids for chronic pain in 2016, coinciding with the end of this study period. As described above, the dosing recommendations released in 2007 by the Washington's Agency Medical Directors' Group (AMDG) could have prompted the decelerating increase in the observed deaths due to prescription opioids prior to ESHB 2876 implementation.

Implications for public health practice

When examining impacts of policies aimed at the population-level, it is important to holistically evaluate both the intended and untended consequences of the policy, as the goal of public health is to protect the health of all populations. While indeed the opioid epidemic is a public health crisis requiring comprehensive interdisciplinary response, individuals who truly suffer from chronic non-cancer pain (or chronic post-cancer pain) and judiciously use prescription opioids may be adversely affected by ESHB 2876. For example, heightened scrutiny, provider's liability concerns, and requirement for consultation with pain management specialist may add additional cost, delay or limited access to legitimately needed prescription opioids for their pain management. Primary care physicians prescribe the bulk of pharmaceutical opioids. And while healthcare providers acknowledge that the opioid crisis must be effectively addressed, and prescription opioids indeed have been the driving force for the opioid crisis, the added burden on providers' time to treat their patients with quality care while meeting regulatory requirements may incur unintended burden on patients suffering from chronic non-cancer pain who are not at risk for opioid misuse. In addition to affecting provider healthcare behavior, another behavioral influence on the patients may be to seek illicit opioids such as heroine as an unintended consequence

of higher medical cost for their pain management and limited access to medically treat their pain. Such switch to heroin is of particular concern among patients with previous history of using prescription opioid, as they are at higher risk for heroin use compared to those without prior prescription opioid use. [4,5,8,21] Moreover, the requirement of ESHB 2876 for consultation with pain management specialist may inequitably affect individuals living in rural areas with limited or lack of access to specialists.

Ultimately, the goal of public health policy is to improve population-level health and promote health equities. And improving population health requires a comprehensive approach including influencing individual and population-level behaviors within the context of structural and social environments. [57,58] ESHB 2876 works in conjunction with other state policies and programs that employ behavior strategies to prevent opioid misuse and provide overdose treatment. Strategies include reducing cognitive burden (overburdening mental resources that impair individual decision making), providing social proof (information about how peers behave in similar situation), and reducing hassle factors (barriers to performing tasks). [16,59,60] At the level of prescribers, the Washington state Department of Health has been working on integrating Prescription Drug Monitoring Program, a database containing patient-level records for dispensed controlled substances, into providers' electronic health record (EHR) systems. Previously, providers had to log into a web-based portal and manually search for individual patients and check their prescription of controlled medications. The integration at the point of care allows the providers with automated access to their patients' prescription drug usage data, thereby freeing up mental resources that would have been spent on querying outside of their EHR, and eliminating a barrier that may deter providers from identifying patients who may be doctor-shopping or are at higher risk for misuse.[61,62]

Another behavioral strategy applied at the prescriber-level is using social proof by providing facilities and practitioners with prescribing feedback reports.[63] Specifically, the legislature passed ESHB 1427 in 2017, which authorizes personnel of the Washington State Department of Health to provide "quality improvement feedback to providers, including comparison of their respective data to aggregate data for providers with the same type of license and same specialty." [63] The prescriber feedback report

is an informational tool designed for prescribers to be able to compare their prescribing practices with those of other prescribers within the same specialty. [64]

At the patient-level, state laws and policies have made naloxone more accessible by removing barriers to obtaining naloxone, particularly by individuals who may experience an overdose or witness an overdose. Naloxone is a competitive opioid antagonist, and requires timely administration to reverse opioid-induced respiratory depression. The statewide standing order signed by Washington state's health officer in August 2019 removes the barrier of needing a prescription for naloxone, thereby allowing any person to obtain naloxone from a pharmacy without a prescription.[13] Future evaluation of the effectiveness of the standing order will be needed, including naloxone stocking at pharmacies, pharmacists' perception of the standing order, naloxone dispensing practices, disparities in dispensing practices due to biased attitudes of dispensers towards patients or caregivers of those with opioid use disorder, and insurance coverage and third party billing practices for naloxone. [65,66]

While this study focuses on opioid overdose deaths, to comprehensively evaluate the public health impact of ESHB 2876, the full public health burden of opioid-related outcomes needs to be measured and assessed. Opioid overdose mortality represents the most downstream adverse public health outcome. The broader public health outcomes of the opioid crisis – beginning with the prescription opioid wave in the 1990s and now compounded with escalating heroin and fentanyl waves – include increases in: emergency room visits and hospitalizations for overdose on nonmedical prescription opioids and illicit drugs, individuals seeking treatments for addition; rate of neonatal abstinence syndrome; and concomitant transmission of HIV, hepatitis C and hepatitis B among injection drug users. These public health outcomes do not include the enormous economic and societal costs and other consequential burdens, including syringe uses, crime, incarceration, homelessness, unemployment, and public stigma against people with opioid use disorders who may already be experiencing wide spectrum of discrimination and health disparities. [4,5,8,21] Moreover, these impacts of the opioid crisis on public health, economies, and criminal justice do not include the devastating emotional and economic costs on individuals, families, and communities affected by the opioid crisis.

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TABLES AND FIGURES

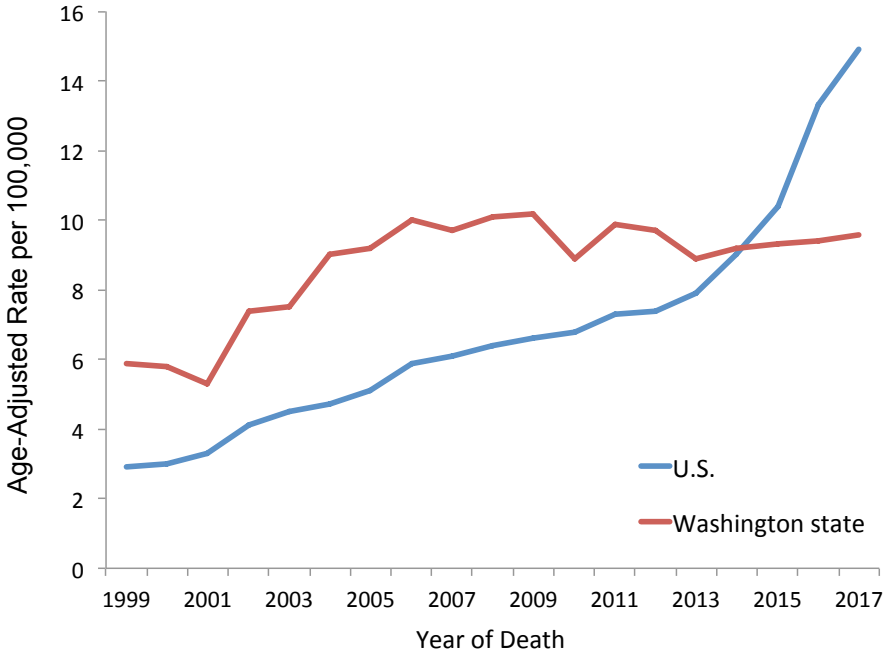


Figure 1. Age-adjusted Opioid Overdose Death Rates, U.S. and Washington State, 1999-2017.

Table 1. Number of Deaths and Age-Adjusted Rates per 100,000 for Opioid Overdose in Washington State, 1999-2017

Year	Count	Population	Adjusted Rate
1999	353	5,842,564	5.9
2000	353	5,894,121	5.8
2001	324	5,985,722	5.3
2002	455	6,052,349	7.4
2003	471	6,104,115	7.5
2004	575	6,178,645	9
2005	603	6,257,305	9.2
2006	661	6,370,753	10
2007	651	6,461,587	9.7
2008	690	6,562,231	10.1
2009	708	6,667,426	10.2
2010	628	6,724,540	8.9
2011	697	6,830,038	9.9
2012	695	6,897,012	9.7
2013	640	6,971,406	8.9
2014	673	7,061,530	9.2
2015	692	7,170,351	9.3
2016	709	7,288,000	9.4
2017	742	7,405,743	9.6

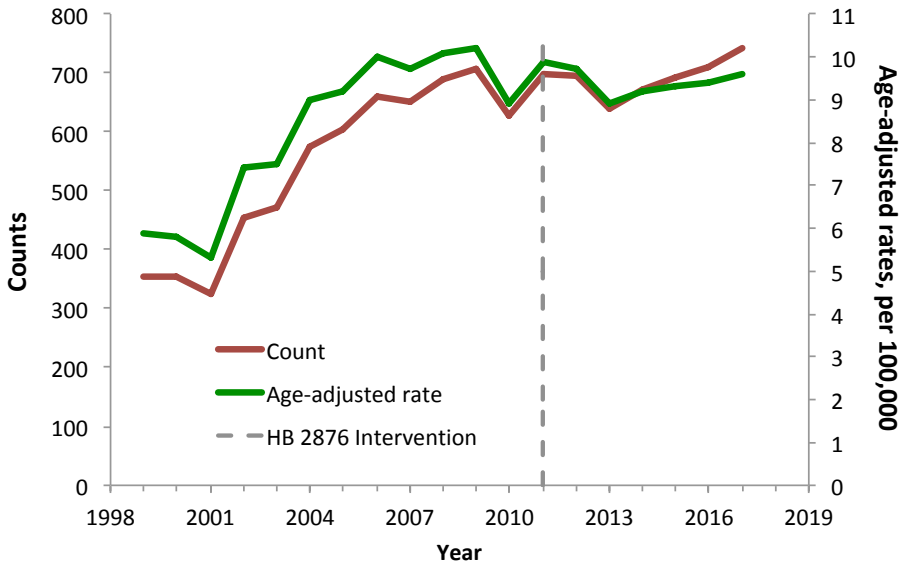


Figure 2. Number of Deaths and Age-Adjusted Rates per 100,000 for Opioid Overdose in Washington State, 1999-2017

Table 2. Interrupted Time Series Regression Analysis of Opioid Overdose Mortality in Washington State Before and After ESHB 2876 Implementation.

Time Period*	Rate Ratio (RR)	95% Confidence Interval	P-value
Before HB 2876	1.06	0.91 to 0.98	0.002
After HB 2876	0.99	0.98 to 1.01	0.884
After HB 2876 relative to without HB 2876	0.95	0.93 to 0.96	<.0001

*Before HB 2876 RR reflects the annual change in OOD trend prior to HB 2876, and computed from the model coefficient B1. After HB 2876 RR reflects the annual change in OOD trend after HB 2876, and computed from the model coefficients B1 + B3. After HB 2876 relative to without HB 2876 RR reflects the annual change in OOD trend after HB 2876 relative to the preintervention trend, and computed from the model coefficient B3.

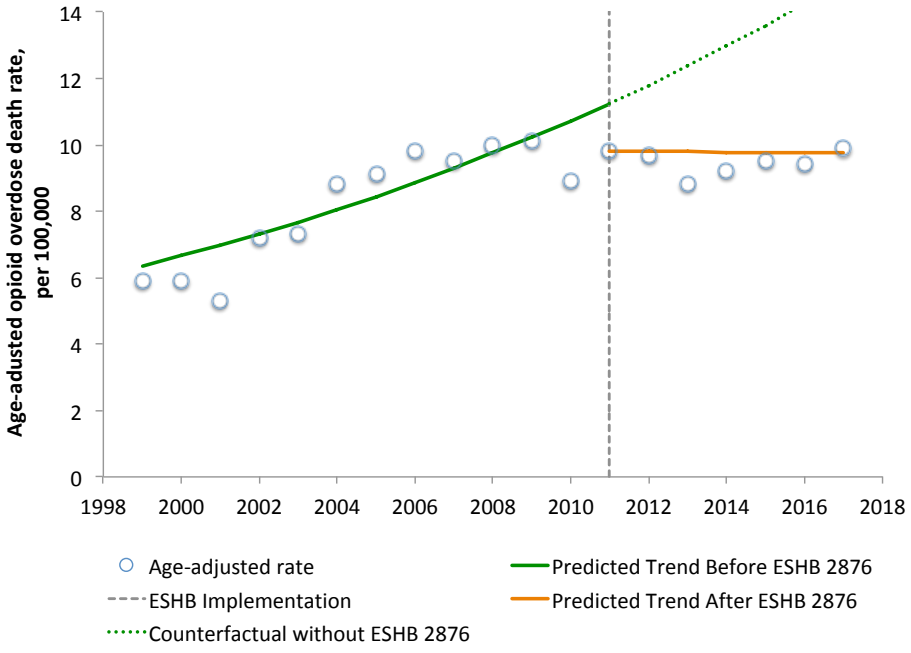


Figure 3. Trends in Opioid Overdose Deaths in Washington State Before and After ESHB 2876 Implementation.

Table 3. Number of Daily Doses Distributed to Retail Pharmacies per 100 for Hydrocodone and Oxycodone in Washington State, 1999-2017

Year	Hydrocodone	Oxycodone	Hydrocodone and Oxycodone
1999	279.6	67.8	347.4
2000	313.7	96.1	409.8
2001	350.2	135.1	485.3
2002	413.6	150.8	564.4
2003	457.8	178.8	636.6
2004	486.9	181.0	667.9
2005	506.1	185.0	691.1
2006	561.2	227.0	788.2
2007	600.2	254.2	854.4
2008	614.2	279.6	893.8
2009	643.1	276.5	919.6
2010	676.5	277.6	954.1
2011	711.4	270.8	982.2
2012	672.3	262.0	934.3
2013	651.1	257.1	908.2
2014	637.8	256.6	894.4
2015	601.3	258.2	859.5
2016	547.4	242.9	790.3
2017	476.3	212.0	688.3

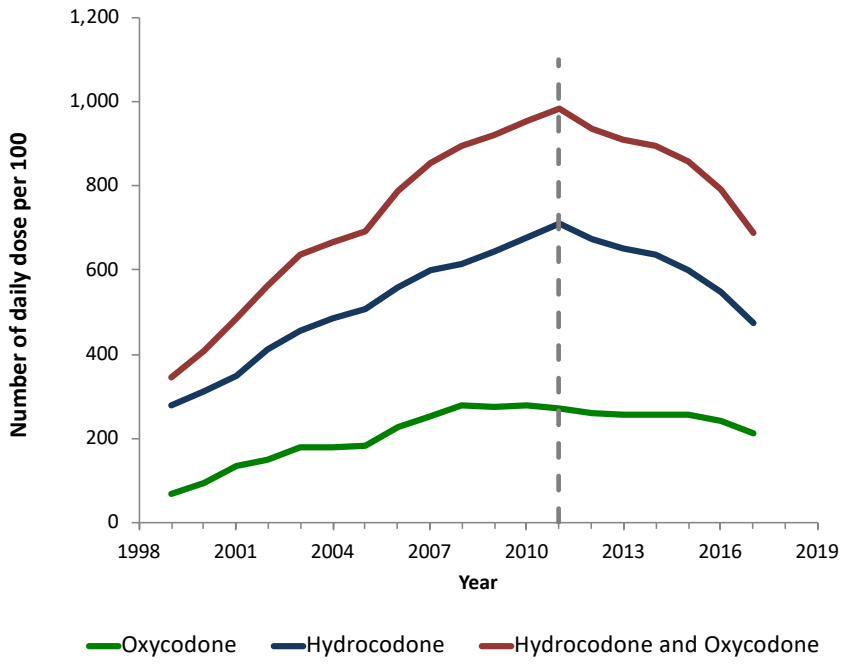


Figure 4. Number of Daily Doses Distributed to Retail Pharmacies per 100 for Hydrocodone and Oxycodone in Washington State, 1999-2017

Table 4. Interrupted Time Series Regression Analysis of Retail Level Opioid Distribution in Washington State Before and After ESHB 2876 Implementation.

Time Period*	Rate Ratio (RR)	95% Confidence Interval	P-value
Before HB 2876	1.09	1.07 to 1.10	<.0001
After HB 2876	0.95	0.93 to 0.97	<.0001
After HB 2876 relative to without HB 2876	0.88	0.85 to 0.90	<.0001

*Before HB 2876 RR reflects the annual change in opioid distribution trend prior to HB 2876, and computed from the model coefficient B1. After HB 2876 RR reflects the annual change in opioid distribution trend prior to HB 2876, and computed from the model coefficients B1 + B3. After HB 2876 relative to without HB 2876 RR reflects the annual change in opioid distribution trend after HB 2876 relative to the preintervention trend, and computed from the model coefficient B3.

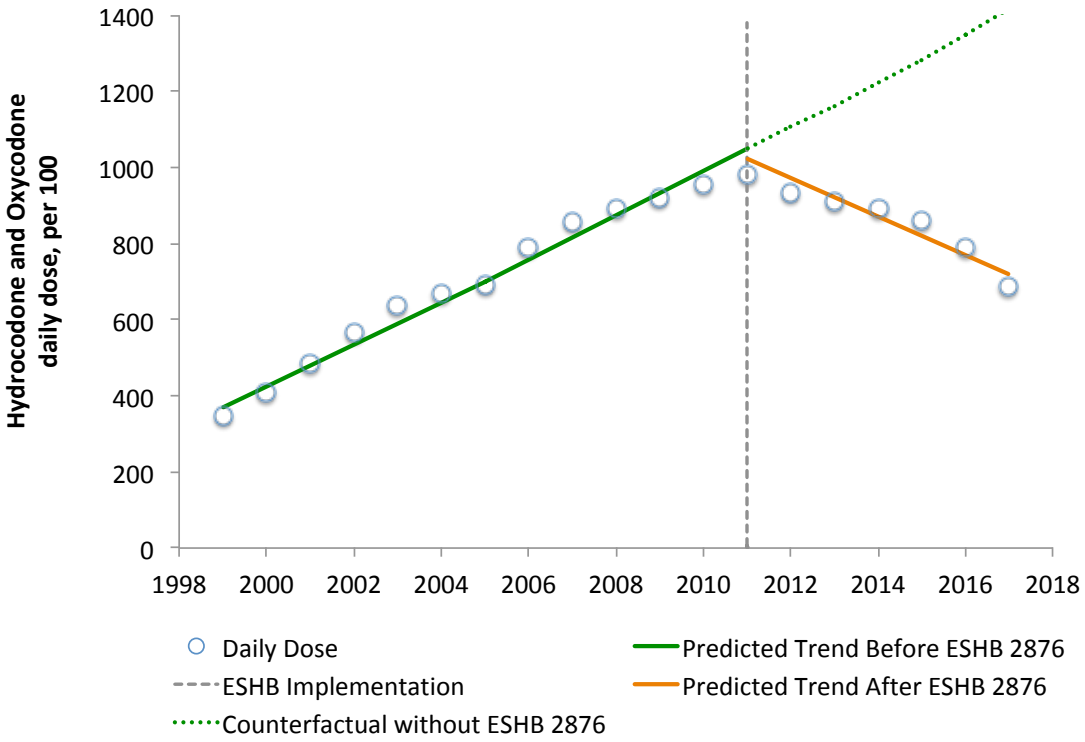


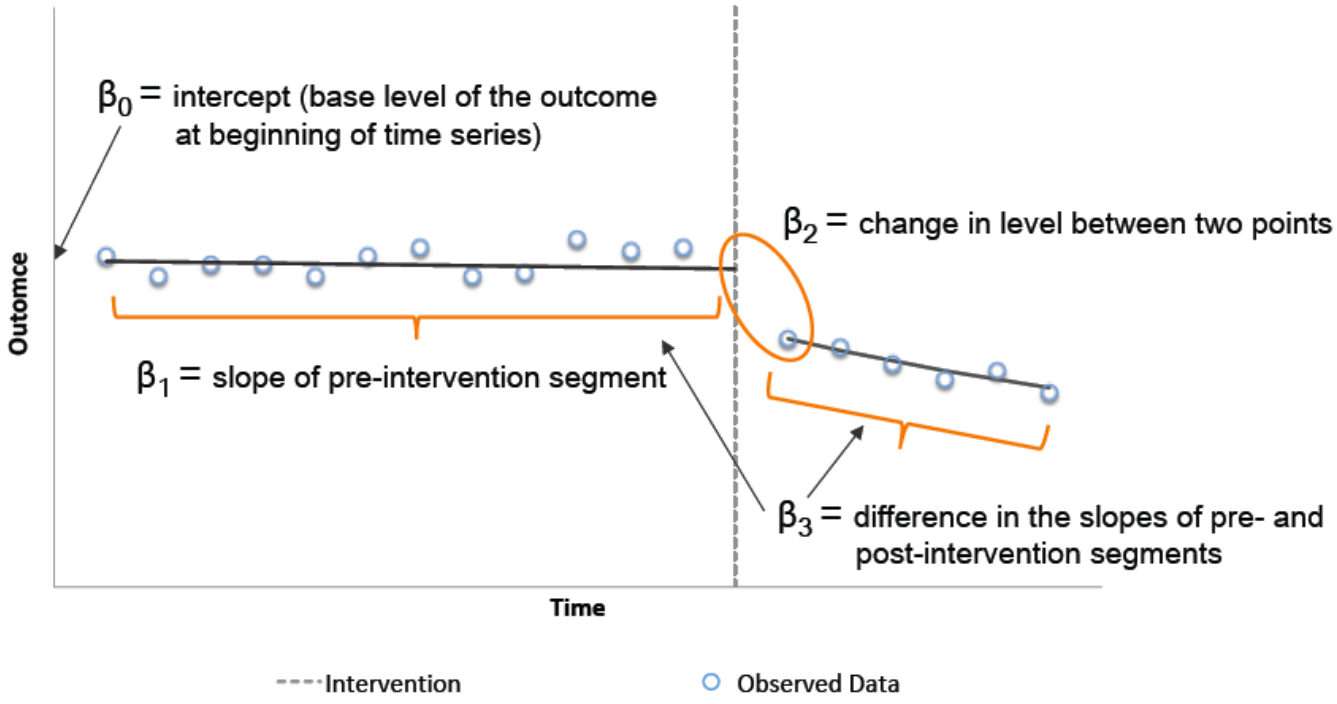
Figure 5. Trends in Hydrocodone and Oxycodone Distribution at Retail Level in Washington State Before and After ESHB 2876 Implementation.

APPENDIX

Appendix 1: Standard Criteria for Assessing Risk of Bias in Interrupted Time Series (ITS) Studies by Cochrane Effective Practice and Organization of Care Review Group (EPOC).

Criteria	Scoring Guide	Current Study Assessment
1. Intervention was independent of other changes	Score “Low risk”if there are compelling arguments that the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables/historic events during study period. If Events/variables identified, note what they are. Score “High risk”if reported that intervention was not independent of other changes in time.	Low risk. No other policies, regulations, or guidelines are known to have been implemented or established concurrently with HB 2876.
2. Shape of the intervention effect was pre-specified	Score “Low risk" if point of analysis is the point of intervention OR a rational explanation for the shape of intervention effect was given by the author(s). Where appropriate, this should include an explanation if the point of analysis is NOT the point of intervention. Score “High risk" if it is clear that the condition above is not met.	Low risk. The shape of the opioid overdose death and prescription opioid distribution measures before and after HB 2876 was pre-specified prior to analysis. Analysis with the intervention set at 2011 is discussed in the study design.
3. Intervention was unlikely to affect data collection	Score “Low risk" if reported that intervention itself was unlikely to affect data collection (for example, sources and methods of data collection were the same before and after the intervention); Score “High risk" if the intervention itself was likely to affect data collection (for example, any change in source or method of data collection reported).	Low risk. Routine administrative and surveillance data are utilized for mortality data, and controlled substances distribution data are required by law to be submitted to the DEA.
4. Knowledge of the allocated intervention was adequately prevented during the study	Score “Low risk" if the authors state explicitly that the primary outcome variables were assessed blindly, or the outcomes are objective, e.g. length of hospital stay. Primary outcomes are those variables that correspond to the primary hypothesis or question as defined by the authors. Score “High risk" if the outcomes were not assessed blindly. Score “Unclear risk" if not specified in the paper.	Low risk. Same explanation as Criteria 3.

5. Incomplete outcome data was adequately addressed	Score “Low risk" if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre-and post-intervention periods or the proportion of missing data was less than the effect size i.e. unlikely to overturn the study result). Score “High risk" if missing outcome data was likely to bias the results. Score “Unclear risk" if not specified in the paper (Do not assume 100% follow up unless stated explicitly).	Low risk. Over 99% of mortality data of Washington residents are estimated to be reported to the state health department, and distribution of controlled substances are required by law for retailers to report to the DEA.
6. Study was free from elective outcome reporting	Score “Low risk" if there is no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section are reported in the results section). Score “High risk" if some important outcomes are subsequently omitted from the results. Score “Unclear risk" if not specified in the paper.	Low risk. All mortality data identified to be related to opioid overdose were utilized. Hydrocodone and Oxycodone data represent the majority of prescription opioid distributed at the retail level, and thus serve as appropriate proxy for all prescription opioids distributed at retail level.
7. Study was free from other risks of bias	Score “Low risk" if there is no evidence of other risk of biases. (e.g. should consider if seasonality is an issue (i.e. if January to June comprises the pre-intervention period and July to December the post, could the “seasons’ have caused a spurious effect).	Some risk. The exact temporal and horizontal mechanisms from initial opioid exposure (whether medically necessitated or non-medical) to opioid overdose death is unknown and likely to be widely variable among individuals. Variations in opioid overdose mortality among age groups over time have been shown. HB 2876 is intended only for prescription of opioid for chronic, non-cancer pain management. The target patient population for this bill is likely older population who are more likely to have received opioids for chronic, non-cancer pain. As such, the mechanism of the bill's impact on this age-group population is likely different from the mechanism of impact on other age-group populations who would have obtained their non-medical opioids from friends or family members in the target age-group population.



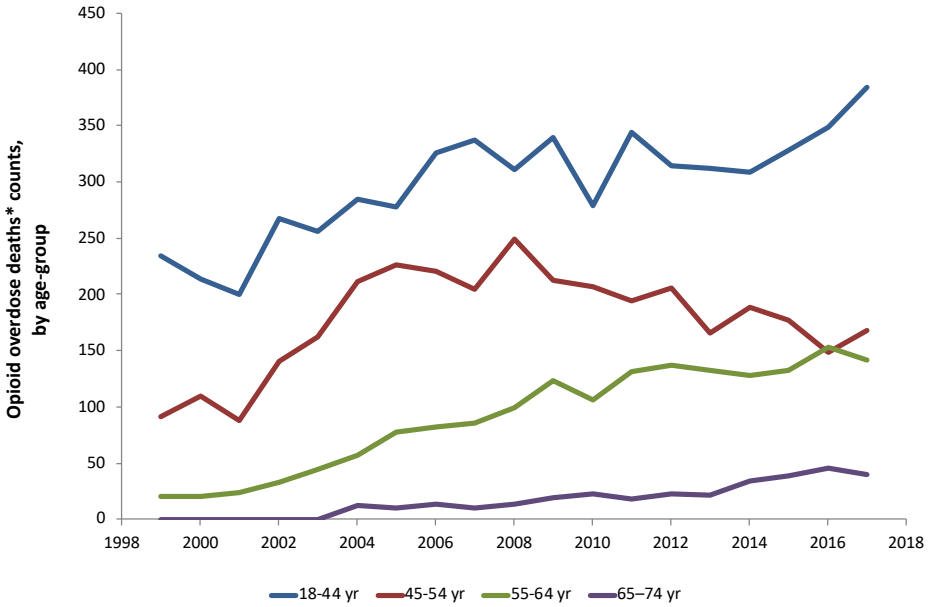
Appendix 2. Visual Representation and Interpretation of ITS Regression Analysis Parameter Coefficients.

Appendix 3. Opioid Overdose Deaths, Crude Rate per 100,000, by Age Group, Washington State, 1999-2017.*

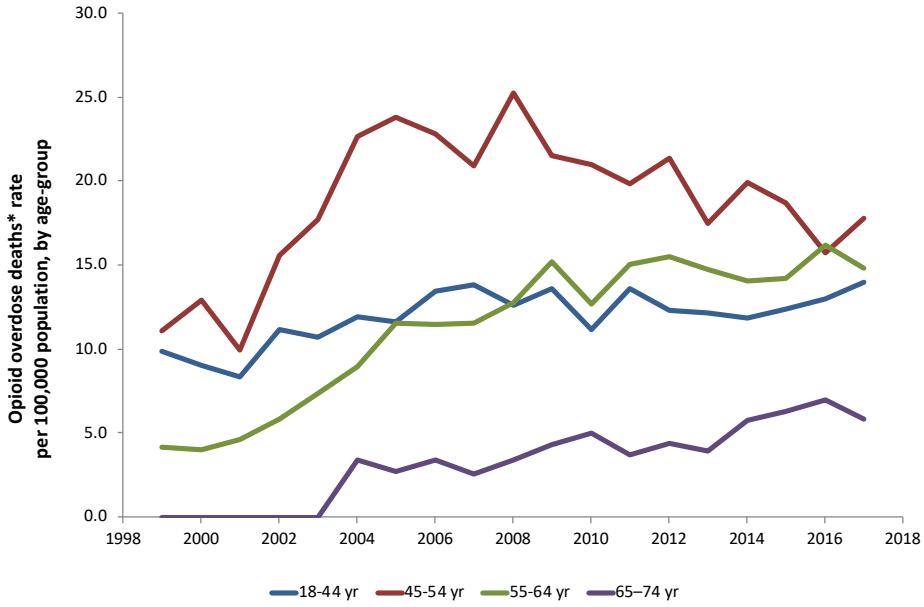
	0-17 yr			18-44 yr			45-54 yr			55–64 yr			65–74 yr			≥75 yr		
	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate
1999	suppressed	1,507,824	suppressed	234	2,371,455	9.9	91	823,218	11.1	20	482,712	4.1	suppressed	336,570	suppressed	suppressed	320,786	suppressed
2000	suppressed	1,513,843	suppressed	214	2,375,578	9.0	109	845,972	12.9	20	496,580	4.0	suppressed	337,166	suppressed	suppressed	324,982	suppressed
2001	suppressed	1,517,527	suppressed	200	2,392,062	8.4	88	884,847	9.9	24	521,330	4.6	suppressed	338,233	suppressed	suppressed	331,723	suppressed
2002	suppressed	1,517,655	suppressed	268	2,395,120	11.2	140	897,507	15.6	33	564,617	5.8	suppressed	341,459	suppressed	suppressed	335,991	suppressed
2003	suppressed	1,514,877	suppressed	256	2,387,923	10.7	162	914,898	17.7	44	599,307	7.3	suppressed	347,452	suppressed	suppressed	339,658	suppressed
2004	suppressed	1,520,751	suppressed	285	2,389,580	11.9	211	932,340	22.6	57	636,967	8.9	12	355,111	3.4	suppressed	343,896	suppressed
2005	suppressed	1,523,890	suppressed	278	2,396,252	11.6	226	948,345	23.8	78	675,247	11.6	10	365,134	2.7	10	348,437	2.9
2006	14	1,536,926	0.9	326	2,420,996	13.5	220	965,611	22.8	82	713,269	11.5	13	378,827	3.4	suppressed	355,124	suppressed
2007	suppressed	1,549,582	suppressed	337	2,432,422	13.9	205	979,052	20.9	86	747,598	11.5	10	394,125	2.5	suppressed	358,808	suppressed
2008	11	1,560,302	0.7	311	2,461,817	12.6	249	985,424	25.3	99	777,195	12.7	14	416,478	3.4	suppressed	361,015	suppressed
2009	suppressed	1,574,403	suppressed	339	2,487,819	13.6	213	989,369	21.5	123	809,219	15.2	19	440,366	4.3	suppressed	366,250	suppressed
2010	suppressed	1,581,354	suppressed	279	2,492,139	11.2	207	988,205	20.9	106	835,165	12.7	23	457,220	5.0	suppressed	370,457	suppressed
2011	suppressed	1,581,757	suppressed	344	2,534,655	13.6	194	976,313	19.9	131	872,440	15.0	18	484,392	3.7	suppressed	380,481	suppressed
2012	suppressed	1,584,967	suppressed	314	2,554,748	12.3	206	964,294	21.4	137	884,586	15.5	23	522,719	4.4	11	385,698	2.9
2013	suppressed	1,595,795	suppressed	312	2,575,835	12.1	166	951,348	17.4	132	897,344	14.7	22	557,905	3.9	suppressed	393,179	suppressed
2014	suppressed	1,602,721	suppressed	309	2,608,438	11.8	188	945,765	19.9	128	911,851	14.0	34	590,319	5.8	10	402,436	2.5
2015	suppressed	1,611,842	suppressed	328	2,647,199	12.4	177	946,393	18.7	132	928,871	14.2	39	623,304	6.3	11	412,742	2.7
2016	suppressed	1,629,498	suppressed	349	2,683,759	13.0	149	947,910	15.7	153	945,770	16.2	46	656,507	7.0	suppressed	424,556	suppressed
2017	suppressed	1,645,816	suppressed	384	2,743,297	14.0	168	944,695	17.8	142	956,893	14.8	40	681,763	5.9	suppressed	433,279	suppressed
TOTAL	95	29,671,330	0.3	5,667	47,351,094	12.0	3,369	17,831,506	18.9	1,727	14,256,961	12.1	345	8,625,050	4.0	117	6,989,498	1.7

* Following the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) Small Number Standards, non-zero category counts less than ten and rates derived from corresponding categories are suppressed to prevent disclosure of an individual's information.

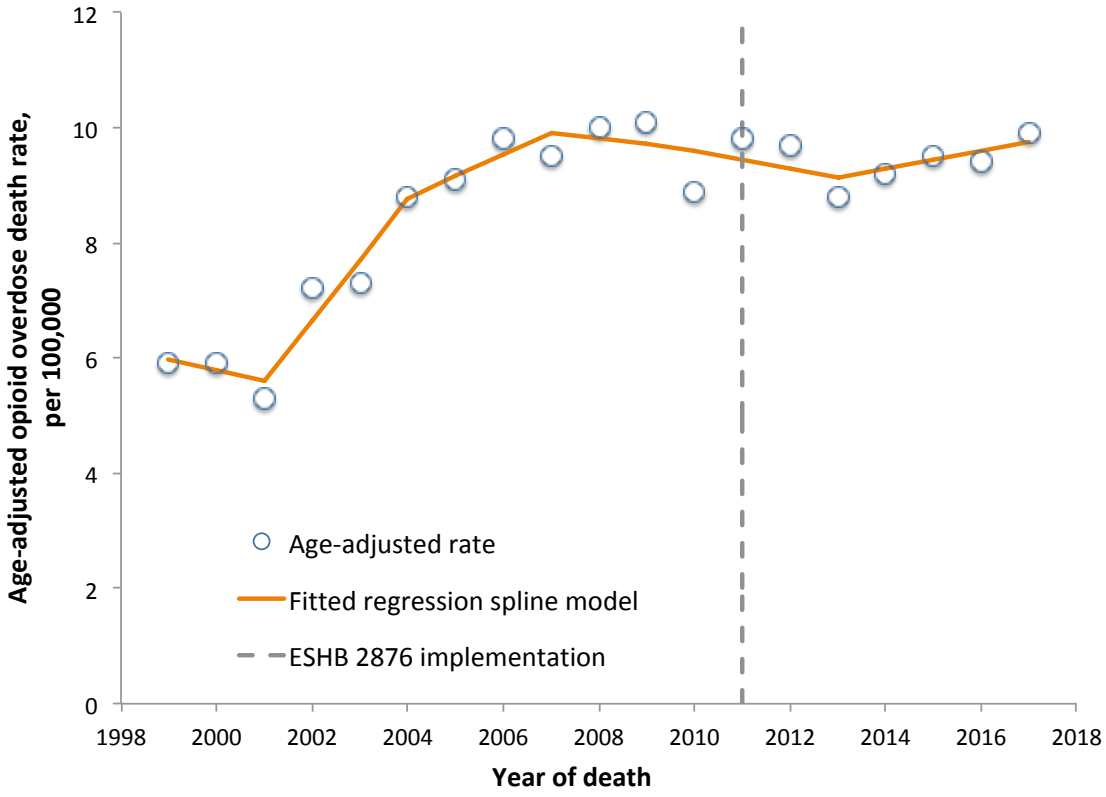
A.



B.



Appendix 4. Opioid Overdose Death Counts (A) and Rates per 100,000 (B), by Age-Group, Washington State, 1999-2017.



Appendix 5. Linear Spline Regression Analysis of Opioid Overdose Death Rates over Time, 1999-2017. Spline Intervals: 1999-2001, 2001-2004, 2004-2007, 2007-2010, 2010-2013, and 2013-2017.

Appendix 6. Parameter Estimates from Linear Spline Regression Analysis of Opioid Overdose Death Rates over Time, 1999-2017

Spline Interval	Corresponding Interval (Years)	Coefficient*	95% Confidence Interval	p-value
Spline 1	1999-2001	-0.18	-0.63 to 0.26	0.388
Spline 2	2001-2004	1.24	0.56 to 1.93	0.002
Spline 3	2004-2007	-0.67	-1.15 to -0.20	0.009
Spline 4	2007-2010	-0.49	-1.25 to 0.27	0.188
Spline 5	2010-2013	-0.06	-1.00 to 0.88	0.898
Spline 6	2013-2017	0.32	-0.30 to 0.94	0.282

*Interpretation: Change in slope from the preceding interval.

Appendix 7. Interrupted Time Series Regression Sensitivity Analysis of Opioid Overdose Mortality in Washington State Before and After ESHB 2876 Implementation Occurring in 2012.

Time Period*	Rate Ratio (RR)	95% Confidence Interval	P-value
Before HB 2876	1.05	1.04 to 1.06	<.0001
After HB 2876	1.01	0.99 to 1.02	0.576
After HB 2876 relative to without HB 2876	0.96	0.94 to 0.98	<.0001

*Before HB 2876 RR reflects the annual change in OOD trend prior to HB 2876, and computed from the model coefficient B1. After HB 2876 RR reflects the annual change in OOD trend after HB 2876, and computed from the model coefficients B1 + B3. After HB 2876 relative to without HB 2876 RR reflects the annual change in OOD trend after HB 2876 relative to the preintervention trend, and computed from the model coefficient B3.

Appendix 8. Interrupted Time Series Regression Sensitivity Analysis of Retail Level Opioid Distribution in Washington State Before and After ESHB 2876 Implementation Occurring in 2012.

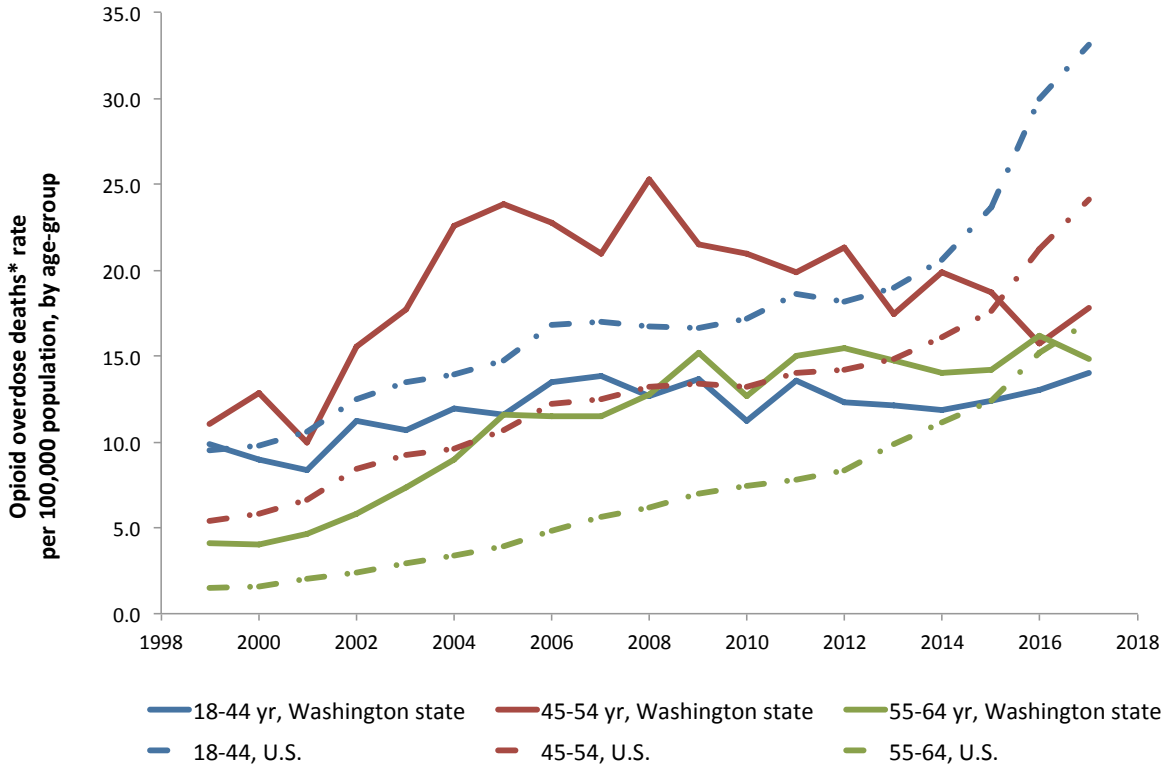
Time Period*	Rate Ratio (RR)	95% Confidence Interval	P-value
Before HB 2876	1.08	1.08 to 1.08	<.0001
After HB 2876	0.95	0.95 to 0.95	<.0001
After HB 2876 relative to without HB 2876	0.88	0.88 to 0.88	<.0001

*Before HB 2876 RR reflects the annual change in opioid distribution trend prior to HB 2876, and computed from the model coefficient B1. After HB 2876 RR reflects the annual change in opioid distribution trend prior to HB 2876, and computed from the model coefficients B1 + B3. After HB 2876 relative to without HB 2876 RR reflects the annual change in opioid distribution trend after HB 2876 relative to the preintervention trend, and computed from the model coefficient B3.

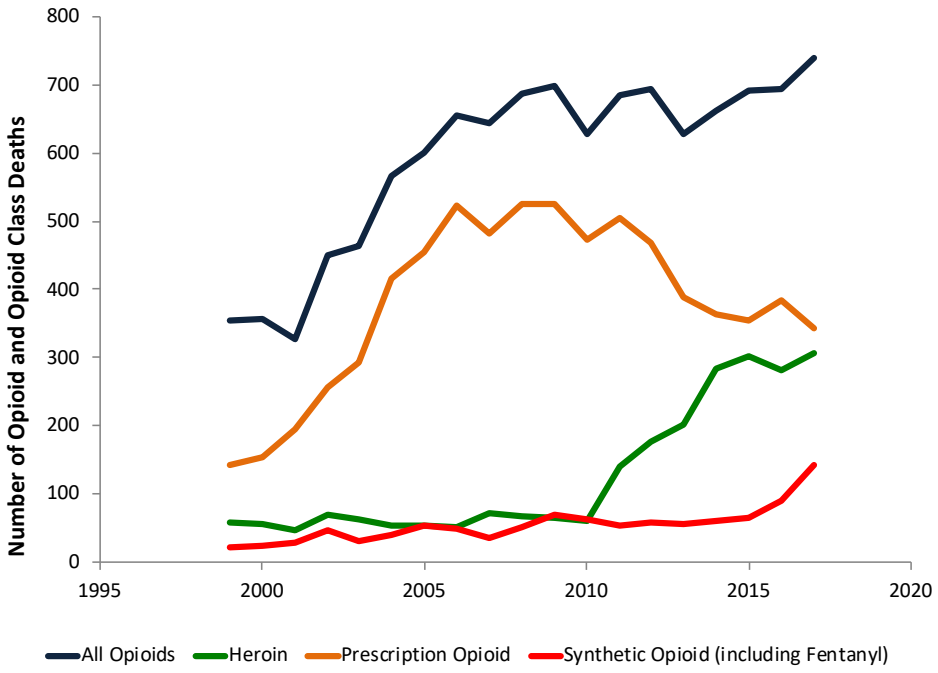
Appendix 9: Table: Opioid Overdose Deaths, Crude Rate per 100,000, by Age Group, Washington State and U.S.,1999-2017.

	18-44 yr						45-54 yr						55–64 yr					
	Washington state			U.S.			Washington state			U.S.			Washington state			U.S.		
	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate	Count	Population	Rate
1999	234	2,371,455	9.9	10,660	111,940,433	9.5	91	823,218	11.1	1,985	36,577,819	5.4	20	482,712	4.1	354	23,778,026	1.5
2000	214	2,375,578	9.0	10,940	112,183,705	9.8	109	845,972	12.9	2,183	37,677,952	5.8	20	496,580	4.0	395	24,274,684	1.6
2001	200	2,392,062	8.4	11,900	112,515,926	10.6	88	884,847	9.9	2,580	39,386,268	6.6	24	521,330	4.6	493	25,105,295	2.0
2002	268	2,395,120	11.2	14,104	112,471,003	12.5	140	897,507	15.6	3,359	39,992,194	8.4	33	564,617	5.8	646	26,703,332	2.4
2003	256	2,387,923	10.7	15,129	112,314,747	13.5	162	914,898	17.7	3,757	40,819,954	9.2	44	599,307	7.3	822	28,008,945	2.9
2004	285	2,389,580	11.9	15,627	112,369,010	13.9	211	932,340	22.6	4,001	41,629,930	9.6	57	636,967	8.9	1,005	29,305,304	3.4
2005	278	2,396,252	11.6	16,524	112,205,731	14.7	226	948,345	23.8	4,537	42,495,904	10.7	78	675,247	11.6	1,194	30,641,497	3.9
2006	326	2,420,996	13.5	18,907	112,241,819	16.8	220	965,611	22.8	5,294	43,286,159	12.2	82	713,269	11.5	1,522	31,930,113	4.8
2007	337	2,432,422	13.9	19,078	112,317,718	17.0	205	979,052	20.9	5,475	43,939,939	12.5	86	747,598	11.5	1,847	33,128,434	5.6
2008	311	2,461,817	12.6	18,843	112,594,233	16.7	249	985,424	25.3	5,874	44,460,447	13.2	99	777,195	12.7	2,114	34,157,063	6.2
2009	339	2,487,819	13.6	18,664	112,741,499	16.6	213	989,369	21.5	6,022	44,867,088	13.4	123	809,219	15.2	2,482	35,405,600	7.0
2010	279	2,492,139	11.2	19,442	112,806,642	17.2	207	988,205	20.9	5,941	45,006,716	13.2	106	835,165	12.7	2,700	36,482,729	7.4
2011	344	2,534,655	13.6	21,104	113,483,161	18.6	194	976,313	19.9	6,258	44,718,203	14.0	131	872,440	15.0	2,952	38,062,140	7.8
2012	314	2,554,748	12.3	20,793	114,185,656	18.2	206	964,294	21.4	6,299	44,268,738	14.2	137	884,586	15.5	3,221	38,586,202	8.3
2013	312	2,575,835	12.1	21,748	114,754,930	19.0	166	951,348	17.4	6,469	43,767,532	14.8	132	897,344	14.7	3,873	39,316,431	9.9
2014	309	2,608,438	11.8	23,811	115,493,795	20.6	188	945,765	19.9	6,987	43,458,851	16.1	128	911,851	14.0	4,452	40,077,581	11.1
2015	328	2,647,199	12.4	27,426	115,946,877	23.7	177	946,393	18.7	7,595	43,188,161	17.6	132	928,871	14.2	5,089	40,877,819	12.4
2016	349	2,683,759	13.0	34,784	115,991,210	30.0	149	947,910	15.7	9,074	42,786,679	21.2	153	945,770	16.2	6,321	41,463,144	15.2
2017	384	2,743,297	14.0	38,617	116,834,511	33.1	168	944,695	17.8	10,207	42,374,952	24.1	142	956,893	14.8	7,153	41,995,658	17.0
TOTAL	5,667	47,351,094	12.0	378,101	2,155,392,606	17.5	3,369	17,831,506	18.9	103,897	804,703,486	12.9	1,727	14,256,961	12.1	48,635	639,299,997	7.6

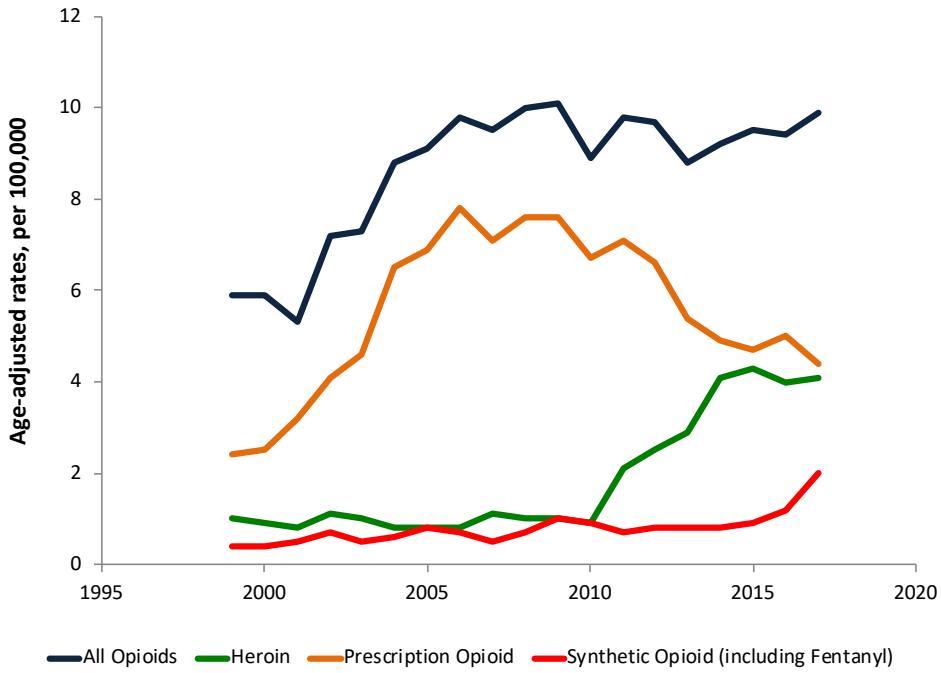
Appendix 10: Figure: Opioid Overdose Rates per 100,000, by Age Group, Washington State and U.S.,1999-2017.



A.



B



Appendix 11. Number (A) and Age-Adjusted Rate per 100,000 (B) of Opioid and Opioid Class Mortality in Washington State, 1999–2017