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The Application of Time Series Analysis to Injury Epidemiology Data

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ABSTRACT

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Introduction: Injury fatality rates in the United States (US) decreased throughout the majority of the 20th century, mostly due to declining rates of occupational and motor vehicle injuries. However, near the beginning of the 21st century, fatal injury rates in the US began to increase. This is principally due to the nation's opioid epidemic, which has been characterized by different epidemic "waves", each driven by overdoses associated with specific substances. Given the temporally dynamic nature of US injury trends, this study aimed to explore the application of time series analysis to injury data in the US. First, rates of non-fatal occupational injuries treated in US emergency departments were assessed to determine if non-fatal occupational injury rates mirror the historic decline of fatal occupational injuries in the 20th and 21st centuries. Next, we explored the temporal shift from prescription to illicit opioid overdose deaths in West Virginia (WV) to elucidate the transition between the opioid epidemic's first and second waves in the state with the highest fatality rates in the nation. Finally, we compared the forecasting performance of three time series models when applied to national US opioid overdose data to explore what time series approaches best predict future rates of overdose.

Methods: Study one assessed temporal trends in non-fatal occupational injuries treated in US emergency departments (EDs) using data the National Electronic Injury Surveillance System – Occupational Supplement (NEISS-Work) dataset. Descriptive statistics were used to assess annual injury rate estimates and monthly seasonality. Autoregressive integrated moving average (ARIMA) modeling was used to quantify trends in ED-treated occupational injury rate estimates while controlling for serial data correlation. Analyses were conducted both overall and stratified by injury event type. Study two used data from the Drug Enforcement Agency's (DEA) Automation of Reports and Consolidated Orders System (ARCOS) database (accessed via *The Washington Post*) to determine when shipments of oxycodone and hydrocodone tablets to WV began decreasing; tablet shipments were measured both as dosage units and morphine milligram equivalents (MMEs). To identify the exact point when tablet shipments began decreasing, we used locally estimated scatterplot smoothing (LOESS). The point when total tablet shipments began decreasing was used as an intervention point in an interrupted time series analysis (ITSA) of prescription and illicit opioid overdose death rates calculated using data from the WV Forensic Drug Database (FDD), which collects drug death data from the WV Office of the Chief Medical Examiner. Prescription opioid deaths were defined as those involving oxycodone or hydrocodone, while illicit opioid overdoses were defined as those involving heroin or synthetic opioids other than methadone. The ITSA impact of the LOESS-identified points was compared via Akaike Information Criteria (AIC) to that of the 2010 release of an abuse deterrent formulation (ADF) of OxyContin, which is widely cited as a driving factor initiating the transition between the opioid epidemic's first and second waves. Study three examined the forecasting performance of ARIMA; Error, Trend, and Seasonality (ETS); and Facebook Prophet models when applied to national US opioid overdose death data, both overall and stratified by the type of opioid involved in overdoses. Overdose death counts were extracted from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. Overdose death rates were calculated using monthly all-cause

mortality as a denominator. Forecasts were validated used time series cross validation (TSCV), while forecast bias and predictive coverage probability were measured using mean average percent error (MAPE) and Winkler Scores, respectively.

Results: Study one found that US ED-treated non-fatal occupational injury rate estimates were highest in 2012 and lowest in 2019. Apart from falls, slips, and trips, all injuries occurred at the highest rate in a summer month. ARIMA modeling found that there was a significant decrease in monthly rate estimates for 2012-2019. Study two found that the point at which opioid tablet shipments (measured via dosage units) to WV began decreasing had a greater impact on changing rates of prescription and illicit opioid overdose rates than the 2010 ADF OxyContin release. Study three found that ETS models accurately forecasted monthly rates US opioid-involved overdoses while maintaining a high degree of precision relative to ARIMA or Facebook Prophet, particularly during the opioid epidemic's fentanyl-dominated third wave.

Discussion: The findings presented here indicate that although occupational injury rates have likely continued their decades-long decline in the US, the nation's opioid epidemic has contributed significantly to recent US injury rate increases and is temporally dynamic. Future research should explore trends in other injury data by expanding the methodology used here to other epidemiological contexts.

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Dedication

To the victims of preventable injuries in West Virginia, the state where I was born and raised.

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Chapter 1

Introduction

Injuries and Public Health

Injuries are among the most serious public health problems affecting the United States (US) and are consistently among the leading cause of death for all age groups in the nation (Centers for Disease Control and Prevention n.d.). Risk of mental health disorders (O'Donnell et al. 2013), substance use (Durand et al. 2019; Weil et al. 2018), and disability increase after incurring an injury. In addition to their psychosocial cost, injuries result in a large economic burden; in 2019 alone, US fatal and non-fatal injuries were associated with total economic costs of $2.2 trillion (Peterson et al. 2021a) and $4.3 trillion (Peterson et al. 2021b), respectively.

Defined by the World Health Organization (WHO) as "the physical damage that results when a human body is suddenly subjected to energy in amounts that exceed the threshold of physiological tolerance, or from a lack of one or more vital elements" (World Health Organization - Europe 2007), injuries comprise a diverse set of health-related events. Among other characteristics, injuries may be classified based on intent, mechanism, or body part in which they were incurred. Formal injury classification allows for the standardized the collection of injury data, including general schemes, such as the WHO International Classification of External Causes of Injury (World Health Organization 2003), as well as context-specific systems, such as the US Bureau of Labor of Labor Statistics' Occupational Injury and Illness Classification System (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021). These and other classification instruments allow for standardized injury data collection and surveillance, which occurs through death certificates (Rauscher et al. 2012), ED records (Weiss et al. 2021), and workers' compensation claims (Witt et al. 2018) among numerous other data sources. Injury surveillance is an integral step in the development of targeted injury prevention and control measures, which aim to reduce injury-associated morbidity and mortality (Azaroff et al. 2002; Hemenway et al. 2006; Horan 2003).

Despite their impact and relevance, injuries remain under-researched relative to other public health topics. In 1998, the National Academy of Sciences stated, "Injury is probably the most under recognized major public health problem facing the nation today," (Hemenway et al. 2006) while a 2015 analysis found that injuries are greatly underfunded relative to their burden (Richards 2015). This may be attributable to the common notion that injuries are unpreventable "accidents" and result from inevitable human behavior (Barss et al. 1998). The successful implementation of injury prevention measures, such as workplace safety interventions (Monforton and Windsor 2010), harm reduction practices (Clark et al. 2014; Wheeler et al. 2015), and suicide prevention measures (Kivisto and Phalen 2018; Yip et al. 2012) demonstrate this to be a misconception; injury risk factors, which are the result of one's built environment, can be addressed using a public health approach (Mitchell and Ryder 2020; Sleet and Moffett 2009).

Trends in US Injury Rates and the Nation's Opioid Epidemic

One of the major public health accomplishments of the 20th century was a massive decrease in injury death rates; all-cause injury fatality rates in the US decreased from 103.0 per 100,000 population in 1910 to 34.8 in 2000, respectively (National Safety Council). One major contributor to this trend were decreasing rates of fatal occupational injuries, largely the result of labor activists and other social reformers' efforts to see large-scale occupational safety and health policies enacted (Rosner and Markowitz 2020). Notable examples include the Walsh-Healey Act of 1936, which required federal contractors to abide by specific occupational safety standards, and the Occupational Safety and Health Act of 1970, which created the Occupational

Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) (Rosner and Markowitz 2020). Another factor contributing to declining injury fatality rates was improving motor vehicle safety, with motor vehicle-related fatalities decreasing by more than 50% between 1937 and 2000 (National Safety Council 2022). Improvements in this area are largely due to the implementation of US Federal Motor Vehicle Safety Standards, which ensure the safe design of motor vehicles (Kahane 2015), and targeted safety interventions, such as the implementation of state-level mandatory seat belt laws.

Despite nearly a century of decline, injury fatality rates began increasing in the 2000's (Figure 1). This trend is being driven primarily by increases in opioid-involved drug poisonings in what has been broadly called the US opioid epidemic. The opioid epidemic has been characterized waves of overdose deaths caused by different opioids (Figure 2) (Ciccarone 2019). The first wave of the opioid epidemic was characterized by overdoses involving prescription opioid medications, which were prescribed at increasing rates from the late 1990's to approximately 2010. This mass over prescription came as the medical community began emphasizing treating patient's pain, with the American Pain Society urging physicians to treat pain as the "fifth vital sign" in 1999 (Scher et al. 2018).

Evidence for the deliberate over-prescription of opioid medications during this time is abundant. One well-documented example is the targeted overprescribing of Purdue Pharma's Oxycontin, a brand name extended-release oxycodone formulation. Beginning in the late 1990's, the number sales representatives employed by Purdue doubled and lucrative bonuses incentivized Oxycontin sales (van Zee 2009). To increase sales, Purdue personnel distributed non-FDA approved marketing videos and quoted non-peer-reviewed studies, including a 1980 *New England Journal of Medicine* letter to the editor which downplayed the addictive potential of narcotic medications (Leung et al. 2017). As a result of the company's misrepresentation of Oxycontin's addictive properties, several Purdue executives pled guilty to criminal misbranding of Oxycontin in a 2007 federal case (van Zee 2009). While OxyContin has received much notoriety due to Purdue's illegal sales tactics, several other opioid medications were prescribed and abused at comparable rates throughout the first wave of the epidemic, including generic oxycodone and hydrocodone (Cicero et al. 2007; Cicero et al. 2005; Kenan et al. 2012).

Prescription opioid overdoses increased in tandem with opioid prescription rates (Ciccarone 2019). Thus, opinions within the medical community began to change regarding opioid prescribing practices. For example, the American Pain Society and the US Department of Veterans Affairs released updated prescribing guidelines in 2009 and 2011, respectively (Chou et al. 2009; US Department of Veterans Affairs 2017). Following these and other guideline revisions, opioid prescription rates began decreasing in 2011 and continued to decline following updated guidelines released by the Centers for Disease Control and Prevention in 2016 (Dowell et al. 2016). Other factors likely to have influenced decreasing prescription rates include changes in regulatory programs, such as the extension of Prescription Drug Monitoring Programs, class wide changes to FDA opioid labeling, and the 2014 rescheduling of hydrocodone to a more restrictive classification (Aitken and Kleinrock 2018; Seago et al. 2016).

The second wave of the US opioid epidemic was characterized by increasing rates of heroin overdoses and lasted from approximately 2010 to 2013 (Ciccarone 2019). The transition from prescription to illicit opioid use in the US was likely a result of decreasing prescription rates driving already-dependent prescription users to illicit and more dangerous opioids (Dart et al. 2015; Tuazon et al. 2019). Evidence for the pill-to-heroin pipeline is provided by examining age-stratified prescription and illicit opioid overdose rates: from 2012-2014, prescription opioid

overdoses decreased while heroin deaths increased in individuals aged 20-34 (Ciccarone 2019; Unick and Ciccarone 2017). Furthermore, Cicero et al. have estimated that in a sample of 2010-2013 heroin users, 75-79.5% abused prescription opioids prior to using heroin, suggesting a temporal link between the two; similar estimates were less than 20% in the 1960's, before over-prescription of opioid medications began (Cicero et al., 2014; Jones, 2013; Muhuri et al., 2013).

A "third wave" of opioid overdoses, beginning in 2013, was associated with the importation of the synthetic opioid fentanyl (Ciccarone, 2019b). Fentanyl has become a common additive in illicit heroin supplies within the United States due to its high potency, which decreases the amount of product needed to achieve a high; fentanyl is 50-100 times more potent than morphine (Centers for Disease Control and Prevention National Center for Injury Prevention and Control 2022). Although fentanyl/heroin combinations are preferable to heroin alone in certain demographic groups, such as younger people who inject drugs daily, fentanyl/heroin combinations are now practically unavoidable for people who inject drugs (Chandra et al. 2021; Latkin et al. 2019; McLean et al. 2019). In fact, heroin/fentanyl mixtures are so prevalent that ethnographic studies indicate users develop a heroin "connoisseurship" from their desire to discern the two (Ciccarone et al. 2017; Mars et al. 2016).

While fentanyl is currently responsible for most opioid overdose deaths in the US, the rate of synthetic opioid overdoses (other than methadone) began increasing only slowly from 2001 (Daniels 2018). This includes the "first fentanyl epidemic" of 2005-2007, when there was a brief spike in fentanyl overdoses. In response, the US Drug Enforcement Agency placed more stringent regulations on the pre-cursor chemicals necessary for its manufacturer, mainly N-phenethyl-4-piperidone (NPP) and 4-anilino-N-phenethyl-4-piperidine (ANPP) in 2007 and 2010, respectively. As a result of the DEA's crackdown, fentanyl overdose rates declined nationally (DEA Diversion Control Division 2016). Since the DEA's initial crackdown, illicit fentanyl has made a resurgence. From 2013-2014, the number of DEA fentanyl seizures nearly quintupled, coinciding with a near doubling of the number of US fentanyl overdoses (Gladden et al. 2016). Fentanyl prescriptions decreased during the same period, and from 2013 it is assumed that most fentanyl involved in overdoses is manufactured clandestinely then mixed with heroin.

Currently, fentanyl is responsible for most drug overdose deaths in the US and fentanyl overdose rates have skyrocketed since 2013; the 2021 opioid overdose rates were more than double their rate in 2014, when fentanyl began entering supplies in significant quantities (National Center for Health Statistics 2022). Adding to this concern is evidence that illegal opioid potency is being pushed beyond that of fentanyl/heroin mixtures. For example, there were reports that carfentanil, a synthetic opioid 10,000 stronger than morphine and 100 times stronger than fentanyl, began entering illicit opioid supplies in 2014 (Delcher et al. 2020). Furthermore, while the first two waves of the epidemic effected primarily rural and Caucasian populations, rates of opioid overdose in non-white and urban populations have also increased drastically since fentanyl entered illicit supplies (Shiels et al. 2018).

A fourth wave of the opioid epidemic began around 2016, characterized by increasing psychostimulant/opioid polysubstance use and overdose. The primary psychostimulant used in polysubstance combination with opioids is methamphetamine, although cocaine involvement is also common in some areas (Jenkins 2021). Opioid use has been reported to be stable throughout the fourth wave, indicating the wave is being driven by increased use of psychostimulants (Jenkins 2021). In the context of the opioid epidemic, increasing methamphetamine use rates may be a result of challenges within the substance use disorder treatment infrastructure. For example, methamphetamine/opioid polysubstance users report less interest in entering substance

use treatment and have poorer retention rates compared to opioid-only users. There is evidence that increasing methamphetamine overdose deaths are being driven primarily by co-use with synthetic opioids. For example, a 2022 study of West Virginia medical examiner's data showed that although methamphetamine/fentanyl overdose deaths increased drastically in the state, the proportion that involved only methamphetamine have remained stable (Dai et al. 2022).

Time Series Analysis and Injury Epidemiology

Recent increases in overdose rates demonstrate that US fatal injury rates are not perpetually declining. Thus, injury epidemiologists need the capability to investigate, quantify, and anticipate changes in temporally collected injury data. One set of approaches, known as "time series analysis", provide this ability. Widely used in the fields of economics (Nerlove et al. 2014) and climatology (Privalsky 2020) (among others), time series analysis has gained acceptance within public health for its ability to model temporal trends in disease and forecast future rates of health-related events.

The primary feature delineating time series analysis from more general methods, such as simple linear regression, is its ability to adjust for serially correlated data structures. Serial correlation, formally known as autoregression, can be thought of as a time series having correlation with a delayed, or "lagged", copy of itself (Figure 3) (U.S. Department of Commerce National Institute of Standards and Technology (NIST) 2012a). Autocorrelation patterns are often detected using autocorrelation function (ACF) plots, which display the correlation between a time series and its lagged values. After inspection of ACF plots, significant lags may be modeled through a moving average (MA) function. Let *Yt* represent a outcome variable *Y*, in our case an injury count or rate, measured at time points $t = 1, 2, \ldots T,$ where T is the length of the time series. An MA model may be applied to a time series through the model

$$Y_t = c + e_t - (\theta_1 e_{t-1} + \theta_2 e_{t-2} + \cdots + \theta_q e_{t-q})_t$$

where c is a constant or y-intercept; θ_q is parameter of the model for the MA component at lag q; and e is random noise at time t.

Time series also often display patterns of partial autocorrelation, which is the correlation between a time series and a lagged copy of itself controlled for correlation at all other lags (U.S. Department of Commerce National Institute of Standards and Technology (NIST) 2012b). Similar to the process for determining the autocorrelation terms to include in a model, determining which partial autocorrelation lags to include is determined via inspection of partial autocorrelation function (PACF) plots. The functions used to model lags detected in PACF are autocorrelation functions. As previous, let *Yt* represent a dependent variable *Y* measured at time points *t*. An AR model may be applied to a time series through the model

$$Y_t = c + (\phi_1 Y_t + \phi_2 Y_t + \cdots + \phi_p Y_t) + e_t$$

where c is a constant; ϕ_p is the parameter of the AR component at lag p; e is random noise at time t.

In injury data, autoregression and partial autoregression often takes the form of seasonality (Pierce 2013), where correlation patterns occur at a sub-annual interval. However, injury data can, and often do, display several serial correlation patterns (Hu et al. 2022; Lin et al. 2015). Additionally, it must be mentioned that although ACF and PACF plots are usually

inspected to determine AR and MA lags, respectively, this is a rule of thumb and either type of autocorrelation may sometimes be addressed by either type of function. Moreover, both functions are often included in the same model, called an autoregressive moving average (ARMA) model. As previous, let *Yt* represent a dependent variable *Y* measured at time points *t*. Using the same notation as previously for AR and MA components, an ARMA model may be applied to a time series through the model

$$Y_t = c + (\phi_1 Y_{t-1} + \phi_2 Y_{t-2} + \cdots + \phi_p Y_{t-p}) + e_t - (\theta_1 e_{t-1} + \theta_2 e_{t-2} + \cdots + \theta_q e_{t-q})$$

Another structure common in time series data is non-stationarity. A time series is said to be stationary if its mean and covariance are constant throughout time (Hyndman and Athanasopoulos 2021a). For a time, series to be modeled using an ARMA approach, the time series must be stationary or non-stationarity must be controlled. To control for non-stationarity, time series may be "differenced" by taking the difference between a value at time *t* and its lagged value. Y_{dt} represents a time series differenced through the equation

$$Y_{dt} = Y_t - Y_{t-d}$$

where *d* is the lag of the difference.

In 1970, Box and Jenkins introduced the autoregressive integrated moving average (ARIMA) model, which simultaneously models a time series' autocorrelation, partial autocorrelation, and non-stationarity (Box et al. 2016). The is done by incorporating a differencing step (called "integration" by Box et al.) within the above mentioned ARMA process. As previously, let *Yt* represent a dependent variable *Y* measured at time points *t*. An ARIMA model may be applied to a time series through the model

$$Y_t = c + (\phi_1 Y_{dt-1} + \phi_2 Y_{dt-2} + \cdots + \phi_p Y_{dt-p}) + e_t - (\theta_1 e_{t-1} + \theta_2 e_{t-2} + \cdots + \theta_q e_{t-q})$$

where c is a constant; ϕ_p and θ_q are parameters of the model for the AR and MA components, respectively; *e* is random noise at time *t*; and *p*, *d*, and *q* denote the lag terms for the AR, differencing, and MA components, respectively.

The final step to fitting an ARIMA model to a time series is determining if residual serial correlation is statistically random and non-stationarity is adequately controlled. This is accomplished by 1.) inspecting the ACF and PACF plots of the fitted model's residuals to see if any single lagged residual is statistically significant and 2.) determining if the model's overall residual serial correlation is random by applying a portmanteau test to the model, such as the Ljung-Box (Box et al. 2016), Breusch-Godfrey (Breusch 1978; Godfrey 1978), or Durbin-Watson (Durbin and Watson 1971) test. The purpose of the portmanteau test is to determine if the model's fitted residuals are significantly different from a "white noise", or statistically random, process.

ARIMA models are useful in situations where it is necessary to model time series data that displays autocorrelation, such as seasonality in occupational injuries. However, these and other time series models have numerous other practical applications, including interrupted time series analysis (ITSA). ITSA quantifies the impact of an intervention with a known start date by segmenting time series data into two distinct periods: one before the intervention and one after

(Lopez Bernal et al. 2016). These segmented portions may then be compared statistically to determine if they are significantly different. While ITSA can be performed using simple linear regression, it is often necessary to use ARIMA modeling to control for serial data correlation and non-stationarity (Hudson et al. 2019). Within the field of injury epidemiology, ITSA has been used to assess the impact of occupational health interventions (Monforton and Windsor 2010), harm reduction programs (Walley et al. 2013), and the COVID-19 pandemic (Matthay et al. 2021) on rates of injuries.

An ITSA model takes the form

$$Y_t = N_t + I_t$$

where Y_t is an outcome variable of interest, N_t is model "noise" (i.e., serial data correlation), and I_t is an impact of interest (McDowall et al. 2019). N_t, in the case where serial data correlation is present, takes the form of an ARIMA model. I_t, the impact of an intervention of interest, takes the form of a dummy variable in which the variable is zero before the intervention start date. The dummy variable can be one after the intervention start date and/or a variable of increasing slope after the intervention; these impacts are known as "step-change" and "ramp" impacts, respectively (Nyugen 2022). Additionally, a linear time variable may be included to measure pre-intervention slope. The determination of which impact variables to include is often made based on expert consultation and previous literature. However, when the impact of an intervention is unknown or unclear, parameter significance, model parsimony, and minimization of Akaike Information Criteria (AIC) are used to determine which impact variables to include (Gilmour et al. 2006; Lopez Bernal et al. 2018; Schaffer et al. 2021).

A noted methodological limitation of ITSA is its application to events occurring on an unidentified date or within a vaguely defined period (Cruz et al. 2017; Gilmour et al. 2006). This pitfall results from the chronologically deductive nature of ITSA: the start date of an intervention must be inferred from known temporal information regarding the intervention itself (Lopez Bernal et al. 2016). When natural events are not externally controlled, or a precise intervention start date cannot be inferred, ITSA is generally considered impractical (Habib et al. 2021). Attempts to remedy this issue, while scare, have been made. One notable example is a method developed by Gilmour et al., who consulted relevant literature and law enforcement officers to infer a start date of the 2000-2001 Australian heroin shortage (Gilmour et al. 2006). While innovative, Gilmour et al.'s technique infers intervention start dates using principally subjective sources, likely introducing bias. Another method was introduced by Cruz et al., who identified intervention start dates of a nursing care delivery intervention by including a moving changepoint variable within a standard ITSA model (Cruz et al. 2017). Although Cruz et al.'s approach is objective, it's emphasis on statistical changes in outcome data may infer epidemiological spurious intervention start dates.

Another useful extension of time series analysis within injury epidemiology is forecasting. Time series forecasting is a statistical method for predicting future response based on historical data and relevant predictors (Hyndman and Athanasopoulos 2021b). These approaches have demonstrated efficacy in predicting changes in healthcare and economic burdens associated with public health events (Cascante-Vega et al. 2022; Khan et al. 2020). Additionally, they have been used to forecast drug overdose (Lo-Ciganic et al. 2022; Saloner et al. 2020a; Saloner et al. 2020b), occupational injuries (Małysa 2022), and road traffic injuries (Khasawneh et al. 2022).

To ensure forecasts represent a plausible future scenario, time series forecasts are "validated" by generating a forecast for which data already exist. This test forecast can then be compared to the extant data to determine its accuracy. Forecasting studies within injury epidemiology often use the fixed origin method for forecast validation (Cartus et al. 2022; Sumner et al. 2022), which uses a small, unmodeled section of data at the end of a time series (the test set) to assess the forecasting ability of the preceding segment (the training set) (Hyndman and Athanasopoulos 2021d). Despite wide use, the fixed origin method is easily biased by trends occurring near the forecast origin (i.e., the transition from training to test set), limiting its generalizability to a single temporal scenario (Tashman 2000). More robust forecast evaluation procedures, such as time series cross validation (TSCV), have seen recent use in public health research, primarily within infectious disease epidemiology (Atchadé and Sokadjo 2022; Zhang et al. 2014) and, more rarely, within injury epidemiology (Schleimer et al. 2021). TSCV uses several training sets, each of which increases in length on a rolling basis, producing forecasts to be compared against each successive test set (Hyndman and Athanasopoulos 2021c). As the majority of data is used both as a training and test set throughout the TSCV process, it is highly generalizable and less easily biased by isolated, non-representative trends (Bergmeir and Benítez 2012).

As forecasts represent a statistically likely outcome were historical trends to continue, they may be inaccurate if an unexpected event occurs within the forecast window (Naess et al. 2015). A notable example of this phenomenon is seen in overdose (Cartus et al. 2022) and motor vehicle injury (Inada et al. 2021) forecasts of the year 2020, which were lower and higher, respectively, than observed rates due to the initiation of the COVID-19 pandemic. However, forecasts may still be of use in these circumstances as they can serve as a counterfactual scenario in which an unexpected event did not occur (Rizzi and Vaupel 2021; Wang et al. 2022).

Purpose Statement

Currently, time series analysis is underutilized within the field of injury epidemiology. Of over 1.02 million articles listed on PubMed containing terms related to injury or overdose, only 3,282 include common time series phrases in their title or abstract.[1] Given this underutilization, the studies presented here aim to explore and demonstrate the applicability of time series analysis to injury data. While the development of novel time series techniques has intrinsic value of its own, this is not the purpose of this study. Instead, it aims to implement time series approaches that, to the author's knowledge, have yet to be used in specific epidemiologic contexts.
The results of this study will provide three specific contributions to the field of injury epidemiology:

- The quantification of temporal trends in occupational injuries treated in US emergency departments from 2012 to 2019.
- The use of interrupted time series analysis to examine the transition from prescription to illicit opioid overdose in West Virginia.
- The comparison of three time series models in their ability to forecast US opioid-involved overdose death rates.

[1] As of April 10, 2023. PubMed search for ***("Wounds and Injuries"[Mesh] OR "Drug Overdose"[Mesh])*** compared to ***("Wounds and Injuries"[Mesh] OR "Drug Overdose"[Mesh]) AND ("time series"[All Fields] OR "Interrupted Time Series Analysis"[Mesh] OR "interrupted time series" OR "ARIMA" OR "forecast*" OR "autoregress*" OR "stationarity" OR "non-stationary").***

These three investigations, while diverse in their injury-related subject matter, are connected by their use of time series methodology. Each provides a unique application of time series analysis to a specific injury dataset. The first study seeks to determine if a well-established injury trend (decreasing rates of non-fatal US occupational injuries) have continued into recent years and is statistically significant. The second two studies aim to explore the application of time series techniques to the US opioid epidemic, a more recent area of investigation within injury epidemiology relative to its history. It is anticipated that the demonstrative value of these studies promotes the application of their methods within other injury-related epidemiological contexts.

Specific Aims

- *Specific Aim 1:* Describe temporal trends in occupational injuries treated in US emergency departments (EDs) from 2012 to 2019, both overall and by injury event type.
    - *Aim 1a:* Report annual national injury rate estimates.
    - *Aim 1b:* Report seasonality of monthly national injury rate estimates.
    - *Aim 1c:* Report inferential statistics on trends in national monthly injury rate estimates.
- *Specific Aim 2:* To elucidate the temporal transition from prescription to illicit opioid overdoses in West Virginia (WV).
    - *Aim 2a:* Identify a plausible point at which prescription opioid shipments to WV began decreasing.
    - *Aim 2b:* Compare the temporal impact of decreasing opioid shipments to the 2010 release of an abuse deterrent formulation of Oxycontin.
- *Specific Aim 3:* Compare ARIMA, ETS, and Facebook Prophet models in their ability to forecast US opioid-involved overdose death rates.
    - *Aim 3a:* Assess model performance both overall and stratified by individual opioid involvement.
    - *Aim 3b:* Assess model performance stratified by state-level drug overdose death reporting specificity.

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Figures and Tables

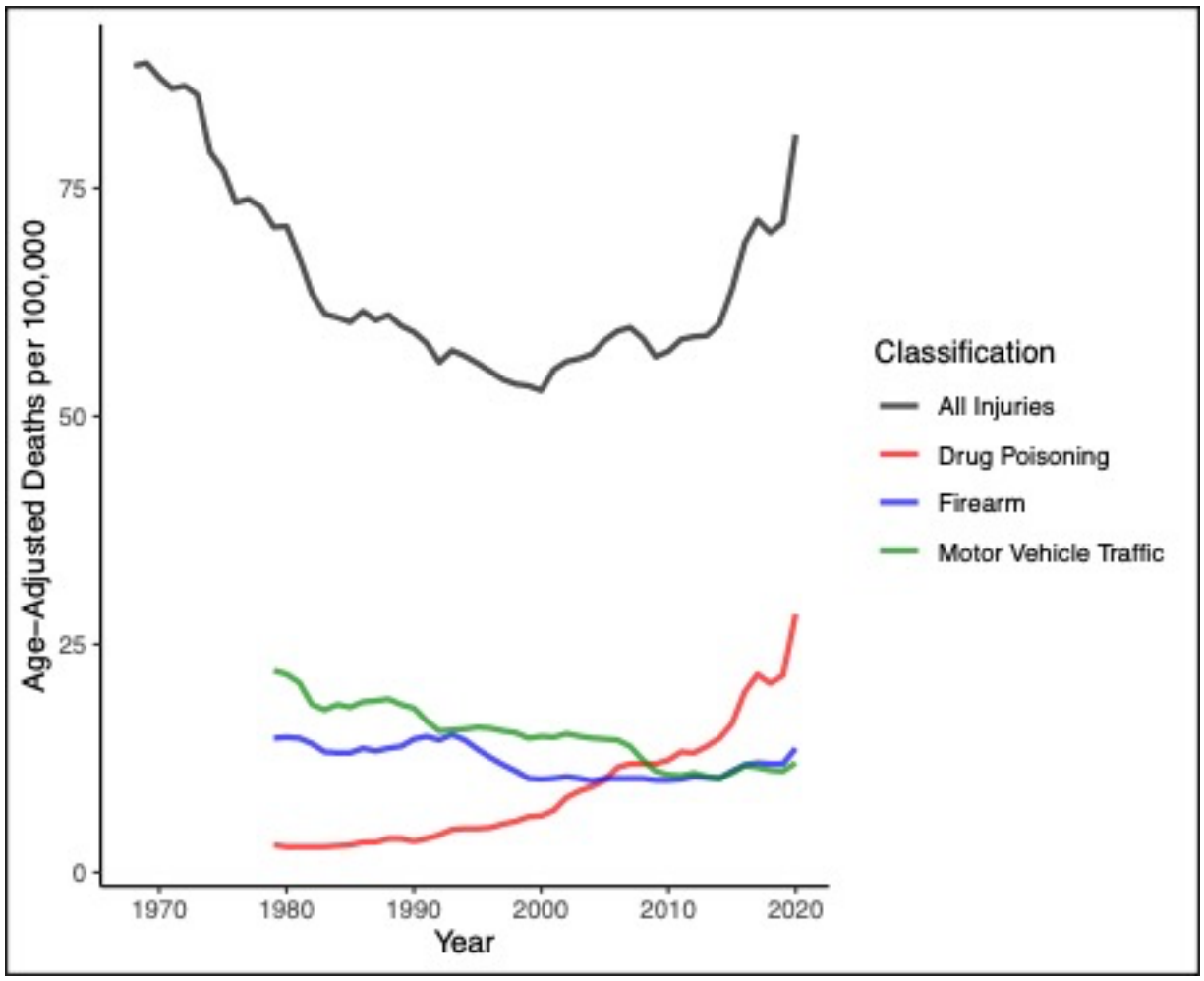

Figure 1. Annual injury rates in the United States, both total and by select causes (1968-2020).[a]

[a]Data from CDC WONDER. Series breaks associated with the transition to ICD-8 to ICD-9 coding and ICD-9 to ICD-10 occurring at 1978-1979 and 1998-1999, respectively.

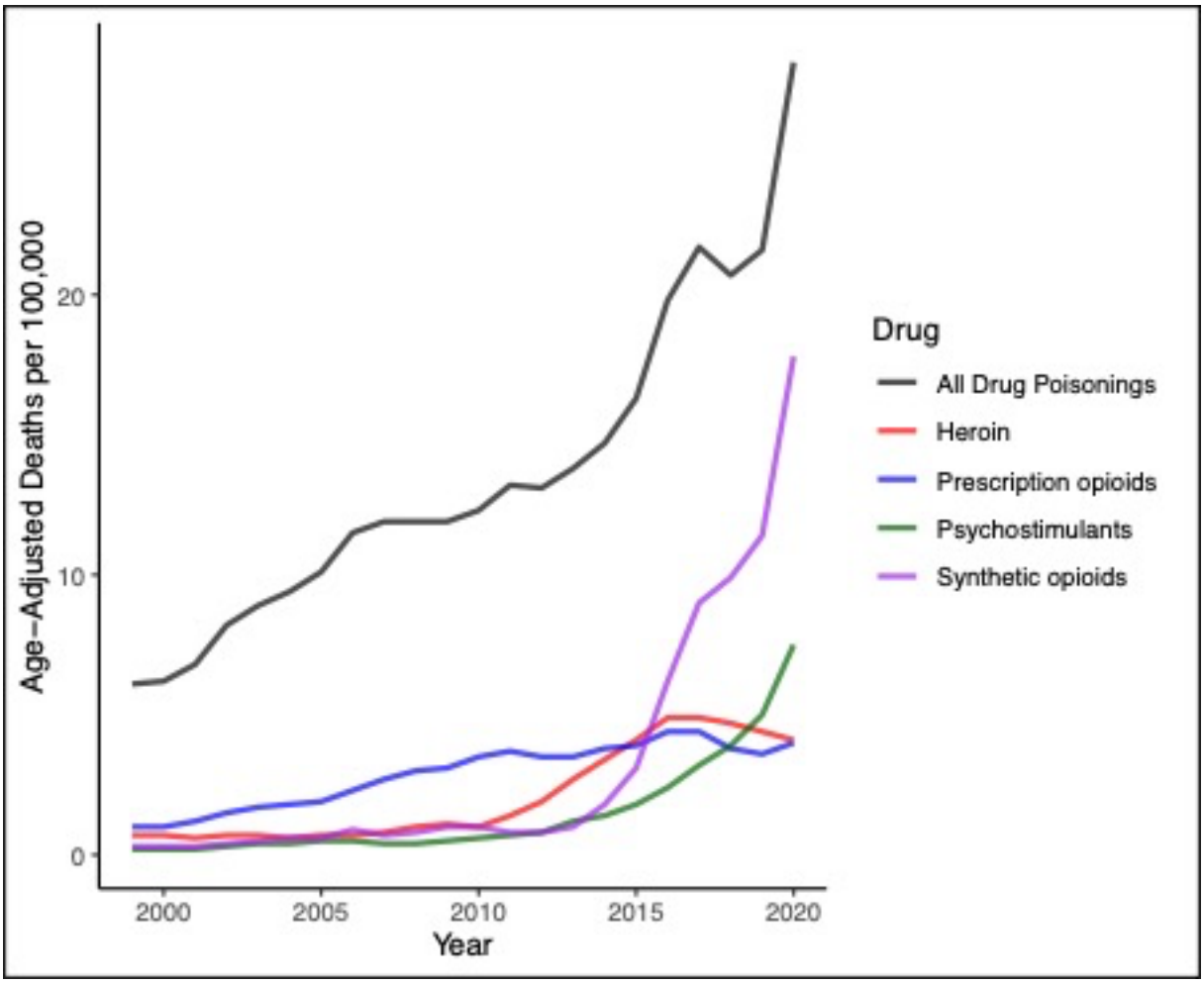

Figure 2. Annual drug poisonings in the United States (US), both overall and stratified by multiple cause of death codes pertinent to the US opioid epidemic (1999-2020).[a]

[a]Data from CDC WONDER. Drug poisonings defined as any death with ICD-10 underlying cause of death codes for poisoning (X40–X44, X60–X64, X85, or Y10–Y14). Individual drug involvement defined using ICD-10 multiple cause of death codes for heroin (T40.1), other opioids (T40.2; labeled "Prescription opioids"), other synthetic narcotics (T40.4; labeled "Synthetic opioids"), and psychostimulants with potential for abuse (T43.6; labeled "Psychostimulants"). ICD-10 multiple cause of death codes are not mutually exclusive.

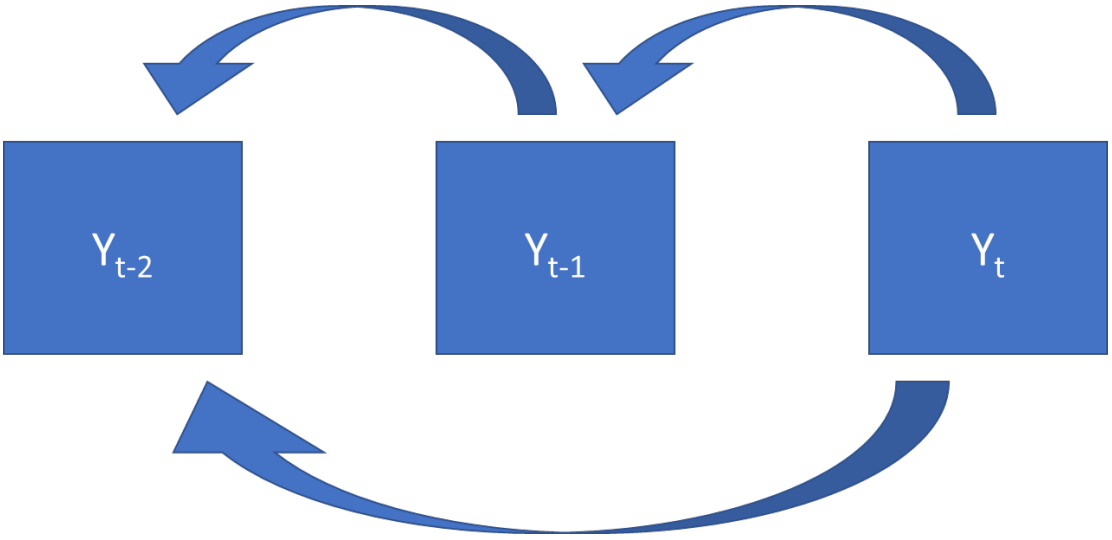

Figure 3. A time series Y_t correlated with delayed copies of itself at lags of one and two. Autocorrelation is the overall correlation of Y_t with both Y_{t-1} and Y_{t-2} (top two arrows); this specific example shows an autocorrelation lag of one. Partial autocorrelation of Y_t with Y_{t-2} would be their correlation adjusted the correlation between Y_t and Y_{t-1} (shown by the bottom arrow); this specific example shows partial autocorrelation with a lag of two.

Chapter 2

Temporal trends in occupational injuries treated in US emergency departments, 2012-2019

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Abstract

Background: Evidence suggests that rates of occupational injuries in the United States (US) are decreasing. As several different occupational injury surveillance systems are used in the US, more detailed investigation of this trend is merited. Furthermore, studies of this decrease remain descriptive and do not use inferential statistics. The aim of this study was to provide both descriptive and inferential statistics of temporal trends of occupational injuries treated in US emergency departments (EDs) for 2012 to 2019.

Methods: Monthly nonfatal occupational injury rates from 2012 to 2019 were estimated using the National Electronic Injury Surveillance System - Occupational Supplement (NEISS-Work) dataset, a nationally representative sample of ED-treated occupational injuries. Rates were generated for all injuries and by injury event type using monthly full-time worker-equivalents (FTE) data from the US Current Population Survey as a denominator. Seasonality indices were used to detect seasonal variation in monthly injury rates. Trend analysis using linear regression adjusted for seasonality was conducted to quantify changes in injury rates from 2012 to 2019.

Results: Occupational injuries occurred at an average rate of 176.2 (95% CI = ±30.9) per 10,000 FTE during the study period. Rates were highest in 2012 and declined to their lowest level in 2019.All injury event types occurred at their highest rate in summer months (July or August) apart from falls, slips and trips, which occurred at their highest rate in January. Trend analyses indicated that total injury rates decreased significantly throughout the study period (-18.5%; 95% CI = ±14.5%). Significant decreases were also detected for injuries associated with contact with foreign object and equipment (-26.9%; 95% CI = ±10.5%), transportation incidents (-23.2%; 95% CI = ±14.7%), and falls, slips, and trips (-18.1%; 95% CI = ±8.9%).

Conclusions: This study supports evidence that occupational injuries treated in US EDs have decreased since 2012. Potential contributors to this decrease include increased workplace mechanization and automation, as well as changing patterns in US employment and health insurance access.

Introduction

Non-fatal occupational injuries represent a significant source of morbidity for workers in the United States (US), with an estimated 1,108,300 non-fatal occupational injuries requiring time away from work in 2019 (U.S. Bureau of Labor Statistics 2020a). Furthermore, occupational injuries cost the US economy an estimated $171 billion in 2019 alone (National Safety Council n.d.). In addition to a large national economic burden, occupational injuries result in significant psychosocial harm to workers (Kim and Choi 2016; Lax and Klein 2008), their families (e.g., through lost earnings and an increased time spent caring for an injured family member; Boden 2005; Dembe 2001), and their communities (Boden et al. 2001).

A crucial step in preventing occupational injuries is epidemiologic surveillance (Azaroff et al. 2002). As the US has no centralized occupational injury reporting system, non-fatal injury surveillance occurs through multiple sources, including emergency department (ED) records, employer-based surveys, and workers compensation claims (National Academy of Science 2018; Bush et al. 2021). Each source has relative strengths and weaknesses. For instance, ED treated injuries, collected via the National Electronic Injury Surveillance System – Occupational Supplement (NEISS-Work), represent workers of any employment type (e.g., public, private, self-employed, volunteers, etc.) but are limited to workers who seek ED treatment (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2019a). Conversely, employer-reported injury data, collected through the Bureau of Labor Statistics' (BLS) Survey of Occupational Injuries and Illnesses (SOII), are collected through a large survey with high response rates but are limited to injuries incurred by privately employed workers (Williams 2022; Council of State and Territorial Epidemiologists 2021) ; while some state and local government employees are included in SOII, injuries incurred by federal and self-employed workers are not captured (Wiatrowski 2014). Finally, workers compensation data include many variables and allow for individual-level longitudinal analysis, but require an injury to be billed to, or have a claim associated with, a worker's compensation system (Seabury et al. 2014; Witt et al. 2018). Previous literature estimates that over 40% of ED-treated occupational injuries nationally are not billed to workers' compensation (Groenewold and Baron 2013) and that workers' compensation is the expected payer in less than 5% of ED-treated occupational injuries at the state-level (Bush et al. 2021). Furthermore, workers' compensation datasets are typically available only at the state level or for small proportions of the national working population (Murphy et al. 2021).

Despite their differences, several independent data sources report decreases in US non-fatal occupational injury rates, continuing a decades-long trend of declines (Bhushan and Leigh 2011). For instance, Guerin et al. reported that annual occupational injury rates treated in US EDs declined from 2012 to 2018 for workers aged 18-44 (Guerin et al. 2020). Similarly, employer-reported data from the BLS SOII indicate that non-fatal occupational injuries and illnesses decreased from 3.7 per 100 full-time worker-equivalents (FTE) in 2012 to 3.0 in 2019 (U.S. Bureau of Labor Statistics 2013; U.S. Bureau of Labor Statistics 2020b). Previous studies have suggested that several factors may potentially be contributing to these declines, including the outsourcing of dangerous jobs to lower-income countries (Abdalla et al. 2017), increased mechanization (Issa et al. 2019), and the implementation of targeted safety regulations (Monforton and Windsor 2010). Additionally, several factors may affect occupational injury surveillance without changing the rate at which workers incur injuries, such as decreased injury reporting as a result of changing rates of unionization (Morse et al. 2003) or changes to health insurance access (Berdahl and Zodet 2010).

Although data suggests US occupational injury rates are declining, current literature describing trends in US all-industry occupational injuries is limited to annual descriptive statistics; inferential times series analyses of national injury trends have largely been used only to assess the impact of safety interventions within single industries (Monforton and Windsor 2010) or trends in specific types of occupational injuries (e.g., non-fatal traumatic brain injuries; Konda et al., 2015). Likewise, studies using US occupational injury surveillance data regularly exclude the assessment of seasonality, a temporal pattern common in injury data. Thus, we aimed to use NEISS-Work, a nationally representative database of occupational injuries treated in US EDs, to assess temporal trends in ED-treated occupational injuries in the US from 2012 to 2019. The specific aims of this study were: 1.) to report yearly national injury rate estimates, both overall and by injury event type, 2.) to report seasonality of monthly injury rate estimates, both overall and by injury event type, and 3.) to report inferential statistics on trends in occupational injury rates during the study period.

Methods

Data source

Non-fatal occupational injury data for the years 2012 through 2019 were obtained from NEISS-Work, a nationally representative database of non-fatal occupational injuries treated in US EDs. The National Institute for Occupational Safety and Health (NIOSH) obtains the data for NEISS-Work through an inter-agency agreement with the Consumer Product Safety Commission (CPSC), the agency responsible for collecting the NEISS-Work data. For the purposes of NEISS-Work, an occupational injury is defined as an injury for which an ED chart or other hospital record indicates that the injury involved a non-institutionalized civilian who was injured while working for pay or compensation of any kind, working on a farm, or volunteering for an organization (Marsh et al. 2016; Reichard and Marsh 2021).

The NEISS-Work data are collected through a probability sample of approximately 67 hospitals that report non-fatal data on occupational injuries seen in their EDs to the CPSC via coders trained to identify the work relatedness of occupational injury data based on extensive manual review of hospital admission information and ED chart inspection. NEISS-Work does not rely on International Statistical Classification of Diseases (ICD) codes or workers compensation billing status (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021a) to identify cases, although the latter may be used as part of the overall manual chart review case identification process. Participating hospitals are stratified based on annual number of ED visits. Hospitals must have a minimum of 6 beds and a 24-hour ED for inclusion. Individual cases reported to NEISS-Work are weighted based on the inverse probability of the reporting hospital being included in the sample so that the estimates represent population total injuries for the US (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021a).

Data for 2012-2019 were chosen as this was the longest period for which data for injury event were all comparably coded to the same version (v 2.01) of the BLS Occupational Injury and Illness Classification System (OIICS). BLS OIICS codes are used to assign injury event and diagnosis codes in NEISS-Work using a narrative comment field developed by coders through review of ED chart and hospital admission data. Data for years prior to 2012 were coded based on the BLS OIICS v 1.01 (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021b). The shift from the BLS OIICS v 1.01 to v 2.01 in 2012 was considered a break in series. Furthermore, the 2019 data were the most recent data available at

the time of analysis (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021a). Due to a series break that resulted in the exclusion of most illness cases starting with data from 2015, data for 2012-2014 were re-reviewed to ensure compatibility throughout the study period (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021a).

Statistical analysis

All data were stored on a secure drive accessible only to the study team. Statistical analyses were performed in Rstudio version 4.0.1 (Rstudio Team 2022). Using the NEISS-Work dataset, national ED-treated occupational injury count estimates were produced using the R packages "survey" and "srvyr" (Ellis et al. 2021; Lumley 2021) using the aforementioned NEISS-Work survey weights. ED-treated occupational injury count estimates were generated for all injuries and by injury event type, a categorical variable denoting the way an injury was incurred and is based on the aforementioned BLS OIICS v 2.01 classification system (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021b); all analyses were conducted both for total injury rate estimates and stratified by injury event type. ED-treated occupational injury rates were calculated per 10,000 FTE using Current Population Survey (CPS) estimates which were generated using NIOSH's Employed Labor Force (ELF) query system; as NEISS-Work includes all work-related ED-treated injuries, FTE estimates were generated for all jobs (as opposed to "primary" or "secondary" jobs only) (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021c). Standard errors (SE) for FTE estimates were generated using generalized variance functions provided by BLS; standard errors were used to calculate monthly FTE variances by multiplying the square of the SE by corresponding ELF-generated monthly FTE estimates (i.e., the corresponding monthly sample size) (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021c). Variances of both numerator (injury count estimates) and denominator (FTE) data were used to calculate 95% confidence intervals (CI) for ED-treated occupational injury rate estimates based on Taylor Series expansion (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021d) and were reported as injury rate estimates ± margin of error.

Seasonality of injury rate estimates was assessed by calculating seasonality indices per month. Seasonality indices were calculated by dividing the mean rate for each month by the mean monthly occupational injury rate for the entire dataset; seasonality indices of greater and less than one indicate higher than and lower than expected injury rates for a given month, respectively (Zhang et al. 2014).

To assess linear trends in injury rates over time, we fit a linear regression model to monthly injury rate estimates and adjusted for autocorrelation and serially correlated error terms using autoregressive integrated moving average (ARIMA) modeling. This analysis was conducted using both monthly total injury rate estimates and monthly estimates stratified by injury event type. In data violating the linear regression assumption of no autocorrelation, ARIMA models are used to control for serial correlation (e.g., seasonality)by including lagged dependent variable values and errors, including in studies of injury data (Box et al. 2016; Zhu et al. 2015). An ARIMA model takes the form ARIMA(p,d,q)$(P,D,Q)_m$, where p is the order of autocorrelation, d is the number of differences applied to the data, q is the order of moving average terms, $P,D,$ and Q are the seasonal versions of these terms, and m is the order of seasonality (e.g., 12 for annually seasonality in monthly data) (Hyndman and Athanasopoulos

2018a). ARIMA models were fit to monthly injury rates by examining autocorrelation and partial autocorrelation plots. A lagged regression estimate was included if it showed statistical significance ($p < 0.05$) and was necessary to control for serial correlation. Finally, significance of each model's Ljung-Box *Q* statistic was observed to ensure proper model fit, with a non-significant value considered a properly fit model (Ljung and Box 1978). The conditional sum of squares method was used to estimate all models. To assess temporal trends, a trend regressor with slope of one was included in each ARIMA model as a covariate and reported with 95% CIs (Hyndman and Athanasopoulos 2018b). A total percent decrease in injury rates throughout the study period was estimated by multiplying this term by 96 (i.e., the total number of months in the study period) and calculating the percent difference from the model's intercept; an analogous calculation using each trend parameter's 95% CI was performed to determine each percent decrease's 95% CI.

Results

Monthly estimates of occupational injuries treated in the US EDs with 95% confidence intervals are presented graphically in Figure 1 (graphical representation of monthly estimates of injury rates by injury event type are available in the Supplementary Material, Supplemental Figures 1-6). Injuries were incurred at an average rate of 176.2 (95% CI = ±30.9) per 10,000 FTE during the study period (Table 1). Annual injuries were estimated at their highest rate in 2012 (188.4 ±38.9 per 10,000 FTE) and their lowest in 2019 (156.8 ±34.5 per 10,000 FTE). Injuries caused by contact with objects and equipment had the highest cause specific rate during the study period (58.6 ±0.4 per 10,000 FTE); followed by overexertion and other bodily reactions (48.5; ±10.6 per 10,000 FTE); falls, slips, and trips (27.7 ±4.8 per 10,000 FTE); exposure to harmful substances or environments (17.9 ±3.9 per 10,000 FTE); and violence and other injuries by persons or animals (15.5 ±3.5 per 10,000 FTE). Analyses of rates of monthly injuries caused by fires and explosions, as well as nonclassifiable sources, were not reported due to NEISS-Work sample size reporting standards (unreliably small numbers).

Rates varied widely by month and seasonality indices for total injury rates were greatest in July (1.15) and lowest in February (0.87) (Table 2). With the exception of falls, slips, and trips, all other injury event types showed similar seasonality (lowest seasonality index in February, highest in July or August), including injuries caused by violence (February = 0.82; July = 1.18), transportation incidents (February = 0.87; July = 1.18), exposure to harmful substances (February = 0.81; August = 1.45) and overexertion (February = 0.86; August = 1.10). Falls, slips, and trips were the only injury event type to have greatest seasonality index in a winter month with highest and second highest seasonality indices occurring in January (1.17) and February (1.16), respectively; a second peak in falls, slips, and trips occurred the summer (July = 1.04; August = 1.03). Injuries caused by falls, slips, and trips occurred at their lowest rate in April with a seasonality index of 0.85.

Table 3 presents trend analysis of injury rate estimates, both by month and by month and injury event type, as well as the ARIMA structure used to control for serial data correlation (e.g., seasonality) in each model. Total injury rates in January 2012 were estimated to be 191.8 per 10,000 FTE, as denoted by the model's intercept. Total injury rate estimates decreased at a rate of -0.37 (95% CI = ±0.29) per month and were estimated to be 156.3 per 10,000 FTE by the end of the study period (December 2019), resulting in an overall decrease of 18.5% (95% CI = ±14.5%). Stratifying the data by month and injury event type, significant decreases were detected in monthly rates of injuries associated with contact with foreign objects and equipment (-26.9%; 95% CI = ±10.5%); transportation incidents (-23.2%; 95% CI = ±14.7%); and falls, slips, and trips (-18.1%; 95% CI = ±8.9%). Monthly rates of injuries for some injury event types, including those associated with violence; exposure to harmful substances; and overexertion and bodily reaction showed non-significant decreases.

Discussion

Using the NEISS-Work dataset, one of the US primary workplace injury surveillance programs, we analyzed rates of occupational injuries treated in US EDs from 2012 to 2019. We found that injury rates during the study period were greatest in 2012 (188.4 ±38.9 per 10,000 FTE) and lowest in 2019 (156.8 ±34.5 per 10,000). ED-treated injuries displayed a marked seasonal pattern, with seasonality indices at their greatest in summer months (July or August) and lowest during winter months (December, January, or February). Seasonality indices for rates stratified by injury event type followed a similar pattern, apart from falls, slips, and trips, which had a peak seasonality index in January. Additionally, we observed a decrease in estimated rates of occupational injuries treated in US EDs of 18.5% (95% = ±14.5%) throughout the study period.

The BLS SOII, another major US occupational injury surveillance program, also reported a decrease in occupational injury rates throughout our study period. However, SOII recorded annual injury rates of 3.7 and 3.0 per 100 FTE for 2012 and 2019, respectively, nearly double the rates estimated in our study for those years (U.S. Bureau of Labor Statistics 2013; U.S. Bureau of Labor Statistics 2020b) (Table 1). A discrepancy in occupational injury rates between these two datasets has been noted in previous literature and is likely because NEISS-Work primarily captures injuries severe enough to require ED treatment, a fraction of the total number of injuries incurred in the US (Chen 2009). In contrast, SOII captures any injury in its sample reported by an employer in accordance with OSHA recordkeeping guidelines (National Academy of Sciences 2018; Council of State and Territorial Epidemiologists 2021). As NEISS-Work and SOII have different mechanisms for capturing injuries, the fact that they both display a decrease

from 2012 to 2019 strengthens evidence that US non-fatal occupational injury rates have decreased during this period.

To the authors' knowledge, no study has used workers' compensation data to estimate trends in national occupational injury rates throughout our study period; this is expected as the US does not have a national workers' compensation system. However, state-level workers' compensation studies, such as one study from Ohio for 2007-2017, also note state-wide decreases in injury rates throughout our study period (Wurzelbacher et al. 2021). Additionally, previous literature has noted differences in occupational injury rate estimates generated via ED-based and workers' compensation data, with one study finding that occupational concussion injury rates in Kentucky measured via ED data (21.7 per 100,000 employed civilians) were higher than those reported by workers compensation (11.7 per 100,000; Slavova and Bunn 2015). This same study found that the estimated rate of injuries was highest when using linked ED, hospital discharge, and workers' compensation data (31.8 per 100,000), implying that each surveillance system has inherent strengths in capturing occupational injuries.

We noted a seasonal pattern in which injury rate estimates were greatest in a summer month (July or August) and lowest in a winter month (December, January, or February) which has been attributed in other studies to increased heat and humidity, as well as an influx of temporary workers and increased construction during summer months (Oleske and Hahn 1992; Taylor et al. 2002). A similar pattern of seasonality has been noted in previous occupational injury literature. For example, Peirce calculated seasonality indices of occupational injury rates using 2003-2010 SOII data and found that injuries peaked in seasonality in July at an index of 1.12, similar to our peak index of 1.15 in the same month for total injury rates (Pierce 2013). However, Peirce's indices were lowest in December (seasonality index = 0.86) compared to February (seasonality index = 0.87) in our study, which they suggest may be influenced by lower end-of-year reporting in SOII. Categorized by injury event type, injury rate estimates in our study followed a similar seasonality pattern except for falls, slips, and trips, which peaked in January (seasonality index = 1.17). An increased rate of fall and slip injuries in winter months, or in association with cold weather, has been noted in previous literature. For example, studies of the mining industry have found an inverse relationship between temperature and incidence of fall and slip injuries (Bell et al. 2000; Hassi et al. 2000). This association is likely influenced by workers' frequent contact with snow or icy surfaces during winter months (Chang et al. 2016), a hypothesis supported by Bentley and Haslam's finding that the majority of slip injuries in a sample of mail delivery workers involved snow or ice (Bentley and Haslam 2001). Furthermore, survey data from Bentley and Haslam's study indicate that 90% of mail delivery workers consider contact with slick surfaces to be a major contributing factor to occupational fall and slip injuries.

Several factors have likely influenced recent declines in US occupational injury rates, including reducing hazardous jobs and increased safety practices. Studies suggest that ergonomic interventions (Fathallah et al. 2008; National Research Council and Institute of Medicine Panel on Musculoskeletal Disorders and the Workplace 2001) and increasingly mechanized workplaces (Issa et al. 2019) have resulted in fewer jobsite hazards. One example of such a shift is within the logging industry, which regularly experiences injury rates far beyond the US all industry average (Janocha and Hopler 2018; Myers et al. 1998). As this industry has seen the introduction of mechanized timber harvesting in recent decades, studies show that logging companies have experienced significant decreases in injury rates after transitioning from manual (i.e., non-mechanized, chainsaw-based) to mechanized timber harvesting (Bell 2002). Similarly, increases

in occupational automation have further removed workers from the physical production process and made several workplaces safer (Autor 2015; Leso et al. 2018). In fact, one study found that for every standard deviation increase in workplace automation, occupational injuries decrease 1.2 per 100 workers (Gihleb et al. 2022). Another potential contributor to decreasing US occupational injury rates is increased globalization (Hämäläinen 2009), defined within an occupational health context as "…the transfer of manufacturing from Established Economic Markets (USA and European Community as defined by the World Bank) to 'developing' economic markets" (Schulze 2007). As laborious, high-risk manufacturing jobs are transferred to developing nations, an unintended consequence is that workers in higher income countries must find lower-risk employment (Abdalla et al. 2017). This can be seen in changing US manufacturing industry employment rates, which decreased 4.5% from 2012 to 2019 (the period analyzed in this study) (U.S. Bureau of Labor Statistics 2022a). Employment rates in some other goods-producing sectors, which have higher rates of occupational injuries relative to other sectors (U.S. Bureau of Labor Statistics 2020b), have also decreased (e.g., logging and mining employment rates decreased 31.2% for 2012-2019).

These and other employment trends may have influenced our stratified analysis, which noted significant decreases in the rate of injuries associated with certain injury event types but not others (Table 3). For example, injuries due to contact with foreign objects and equipment decreased 26.9% during our study period, more than any other injury event type. Nationally, approximately 20% of occupational injuries due to contact with objects and equipment are incurred in the manufacturing industry (National Safety Council 2023); as noted previously, however, manufacturing employment rates decreased throughout our study period (U.S. Bureau of Labor Statistics 2022a). In contrast, violence injuries decreased at the lowest rate of any injury event type throughout our study period and this decrease was not significant (-6.2% (±14.9%)). As the majority (76%) of workplace violence injuries requiring days away from work are incurred by workers in the health care and social assistance industries (National Institute for Occupational Safety and Health 2022), this finding may have been influenced by increasing employment in these industries throughout our study period (12.9% to 13.5% from 2012 to 2019, respectively) (U.S. Bureau of Labor Statistics 2022b). While these examples represent plausible associations, we cannot definitively conclude a relationship between employment in a single industry and the trends reported in our study as NEISS-Work did not include detailed industry information for the entire study period.

Some factors may have affected the proportion of occupational injuries captured by the ED-based NEISS-Work without influencing the actual number of injuries incurred by US workers. For example, the annual number of self-employed workers increased 6.4% during our study period (U.S. Bureau of Labor Statistics 2020c). US self-employed workers have been noted to have an increased risk of occupational injury (Bunn et al. 2006) yet are not required to have health insurance or workers compensation benefits which may make them less likely to seek medical care; data suggests that the proportion of US self-employed workers lacking health insurance increased throughout our study period (Rothwell and Harlan 2019). Moreover, evidence suggests that NEISS-Work underestimates the number of occupational injuries incurred by self-employed US workers, possibly because they lack health insurance (Bhandari et al. 2016). It may also be the case that more injured workers over time are seeking treatment in non-ED settings. There was an increase of more than 37% in the number of urgent care centers in the US from 2013 to 2019 (Urgent Care Association 2019), which offer significantly less-expensive treatment than US EDs (Ho et al. 2017). Thus, workers lacking access to health insurance and

workers compensation may seek care in urgent care centers for minor and non-life-threatening injuries; workers may also be seeking urgent care as opposed to ED treatment given the latter's convenience and significantly longer wait times (Khairat et al. 2021). Finally, decreasing unionization rates may have had an influence on occupational injury reporting; data from the US Bureau of Labor Statistics show that the total, all-industry unionization rate decreased from 11.3% to 10.3% throughout the study period. Previous literature suggests differential reporting of injuries by union status, with non-unionized workers being less likely to report (Altassan et al. 2018; Morse et al. 2003; Robinson and Smallman 2006). Extant literature also indicates that non-unionized workers are less likely to have health insurance than those that are unionized (U.S. Bureau of Labor Statistics, 2019), and may therefore be less likely to seek treatment than unionized workers.

This study has several strengths. One strength is that it examines all ED-treated injuries, not just those required to be reported to the BLS. The NEISS-Work dataset captures occupational injury data regardless of industry and its definition of work includes the self-employed and farm workers, giving it a wider capture of work-related injuries compared to employer-reported datasets, such as the BLS SOII. Additionally, NEISS-Work does not require an injury to be billed to workers' compensation to be included. This is a crucial strength of this dataset as a large proportion of ED-treated occupational injuries are not billed to workers' compensation (Groenewold and Baron 2013). Finally, to the authors' knowledge, this is the first study to use inferential time series techniques to quantify trends in national, all-industry monthly occupational injury data in the US for the period assessed. Specifically, ARIMA modeling, which allows for the analysis of monthly occupational injury data, is an improvement over previous methods used to measure trends in national ED-treated injury data, such as negative binomial regression (Tiesman et al. 2018), which generally cannot account for seasonality. However, other studies have used extensions of ARIMA modeling, such as interrupted time series (ITS) analysis, to assess the impact of occupational safety and health, such as US Mine Safety and Health Administration regulations (Monforton and Windsor 2010), drugfree workplace interventions (Wickizer et al. 2004), and the influence of a crash prevention program in a large law enforcement agency (Tiesman et al. 2019); ITS analysis may allow future studies to assess the impact of interventions with potential to influence national ED-treated occupational injury rates (e.g., implementation of occupational health and safety policies, changes in workers' access to health insurance, etc.) were one to be identified.

This study also has several inherent limitations. First, NEISS-Work collects occupational injury data using a probability-based survey sample design. Thus, national occupational injury estimates generated using NEISS-Work are based on a subset of US hospital EDs and include sampling error. ARIMA modeling assumes homoscedasticity of sample variances and is incapable of incorporating any error intrinsic to the NEISS-Work sampling design; incorporating survey design error within our ARIMA model, if possible, would likely increase the width of the confidence intervals presented in Table 3. Despite this, sample variances of injury rate estimates were generally comparable across the study period (Figure 1), suggesting this limitation likely did not compromise the internal validity of study findings. Second, NEISS-Work only captures injuries treated in a subset of US EDs and do not reflect any change in injury rates due to injuries treated in any other setting. Third, these findings should be discussed only in reference to national, all-industry occupational injury rates, not in any subnational or industry-specific context. Finally, these data do not indicate the severity of the injuries included in NEISS-Work and it is possible that many of the injuries included for analysis were relatively minor; literature

indicates that nearly 90% of US ED-treated injuries are not severe (Villaveces et al. 2013) and most injuries reported to NEISS-Work do not require hospital admission (Konda et al. 2015; Lipscomb et al. 2010; Reichard et al. 2015). As NEISS-Work contains data on whether a patient was hospitalized/transferred after treatment (National Institute for Occupational Safety and Health (NIOSH) Division of Safety Research 2021a), future studies should investigate if hospitalization rates of US ED-treated occupational injuries have changed in recent years. Additionally, as was reported, rates of injuries decreased significantly for some injury event types and not others. Thus, future research should also investigate factors potentially influencing these findings, including injury rate trends by industry and demographic factors.

Conclusion

To our knowledge, this is the first study to assess temporal trends in a nationally representative dataset of occupational injuries treated in US EDs from 2012 to 2019. We found that annual injury rate estimates were greatest in 2012 and lowest in 2019. Additionally, we provided quantifiable measures of trends in occupational injuries during the study period; previously, only descriptive annual statistics were available to assess trends in such data. Future research should assess the influence of potential mechanisms, such as injury underreporting or shifts in employment, that may have contributed to the trends observed in this study.

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Figures and Tables

Table 1. Mean annual occupational injuries (per 10,000 FTE) treated in United States emergency departments, by injury event type.[a]

Year	All Injuries	Violence and other injuries by persons or animals	Transportation incidents	Falls, Slips, and Trips	Exposure to harmful substances or environments	Contact with objects and equipment	Overexertion and other bodily reaction
2012	188.4 ±38.9	15.6 ±4.7	6.4 ±1.5	29.2 ± 6.0	17.9 ±3.7	65.9 ±14.0	49.6 ±11.8
2013	182.6 ±38.4	15.9 ±4.8	5.2 ±1.2	28.8 ±5.6	17.9 ±3.9	64.8 ±14.4	48.0 ±11.9
2014	183.1 ±35.6	15.3 ±3.9	5.4 ±1.2	29.8 ±5.8	17.3 ±3.9	62.0 ±12.8	50.4 ±11.6
2015	182.1 ±48.4	16.1 ±4.3	5.3 ±1.4	29.6 ±8.3	18.9 ±6.2	61.3 ±16.0	48.9 ±14.9
2016	186.8 ±47.8	16.7 ±4.4	5.2 ±1.2	29.1 ±7.9	19.3 ±6.1	58.9 ±14.3	55.0 ±17.1
2017	171.5 ±31.2	16.1 ±3.6	5.1 ±1	25.4 ±4.6	18.7 ±4.4	55.4 ±10.1	47.6 ±10.8
2018	160.9 ±34.2	14.3 ±3.5	4.4 ±1	24.8 ±5.1	17.3 ±5.0	51.8 ±10.0	45.8 ±12.5
2019	156.8 ±34.5	14.6 ±3.3	5.0 ±1.1	25.3 ±5.4	16.1 ±4.4	50.4 ±10.5	43.1 ±12.4
Total	176.2 ±30.9	15.5 ±3.5	5.2 ±0.9	27.7 ±4.8	17.9 ±3.9	58.6 ±10.4	48.5 ±10.6

[a] Numerator data (monthly ED-treated injury count estimates) are from the National Electronic Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force query system. Variances from both numerator and denominator data were used to calculate 95% CIs using a Taylor series expansion, which is reported as each injury rate estimate ± margin of error. Injury event type definitions are based on the Bureau of Labor Statistics Occupational Injury and Illness Classification System version 2.01.

Table 2. Seasonality indices[a] of occupational injuries (per 10,000 FTE) treated in United States emergency departments by injury event type.[b]

Month	All Injuries	Violence and other injuries by persons or animals	Transportation incidents	Falls, Slips, and Trips	Exposure to harmful substances or environments	Contact with objects and equipment	Overexertion and other bodily reaction
January	0.93	0.87	0.94	1.17	0.82	0.88	0.91
February	0.87	0.82	0.87	1.09	0.81	0.81	0.86
March	0.97	0.95	0.93	1.00	0.87	0.96	1.01
April	0.96	1.02	0.92	0.85	0.89	0.96	1.02
May	1.03	1.08	1.02	0.97	1.03	1.06	1.02
June	1.07	1.06	1.10	0.98	1.15	1.13	1.04
July	1.15	1.18	1.15	1.04	1.45	1.16	1.08
August	1.13	1.10	1.03	1.03	1.31	1.17	1.10
September	1.02	1.06	1.06	0.95	1.05	1.05	1.01
October	1.04	1.04	1.04	0.99	0.94	1.08	1.05
November	0.94	0.94	0.99	0.94	0.88	0.91	0.97
December	0.89	0.88	0.94	0.99	0.82	0.84	0.92

[a] Calculated by dividing the mean rate for each month by the mean monthly occupational injury rate for the entire dataset.

[b] Numerator data (monthly ED-treated injury count estimates) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via NIOSH Employed Labor Force querying system. Injury event type definitions are based on the Bureau of Labor Statistics Occupational Injury and Illness Classification System version 2.01.

Table 3. Trend analysis of monthly ED-treated occupational injury rates estimates per 10,000, 2012-2019.[a]

Injury Type	ARIMA Structure[b]	Intercept	Trend Parameter (± 95% CI)	Percent Decrease, 2012-2019 (± 95% CI)[c]
All Injuries	$(1,0,2)(1,0,0)_{12}$	191.8	**-0.37 (±0.29)**	**-18.5% (±14.5%)**
Violence	$(1,0,0)(1,0,0)_{12}$	15.9	-0.01 (±0.03)	-6.2% (±14.9%)
Transportation Incidents	$(1,0,0)(0,0,0)_{12}$	5.9	**-0.01 (±0.01)**	**-23.2% (±14.7%)**
Falls, Slips, and Trips	$(0,0,0)(1,0,0)_{12}$	30.9	**-0.06 (±0.03)**	**-18.1% (±8.9%)**
Exposure to Harmful Substances	$(1,0,0)(1,0,0)_{12}$	18.4	-0.02 (±0.05)	-9.3% (±24.9%)
Contact with Foreign Objects and Equipment	$(1,0,3)(1,0,1)_{12}$	68.1	**-0.19 (±0.08)**	**-26.9% (±10.5%)**
Overexertion and Bodily Reaction	$(1,0,0)(1,0,0)_{12}$	51.3	-0.06 (±0.09)	-12.6% (±16.3%)

Significant values **bolded.**

[a] Numerator data (monthly ED-treated injury count estimates) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via NIOSH Employed Labor Force querying system. Injury event type definitions are based on the Bureau of Labor Statistics Occupational Injury and Illness Classification System version 2.01.

[b] An $ARIMA(p,d,q)(P,D,Q)_m$ structure was used to control for serial correlation (e.g., seasonality) in monthly injury rate data, where p is the order of autocorrelation, d is the number of differences applied to the data, q is the order of moving average terms, P,D, and Q are the seasonal versions of these terms, and m is the order of seasonality (e.g., 12 for annually seasonality in monthly data). A linear trend parameter was used to measure overall decreases.

[c] Calculated by multiplying each model's trend parameter and 95% CI by 96 (i.e., the total number of months in the study period) and calculating percent difference from the model's intercept; significant decreases are bolded.

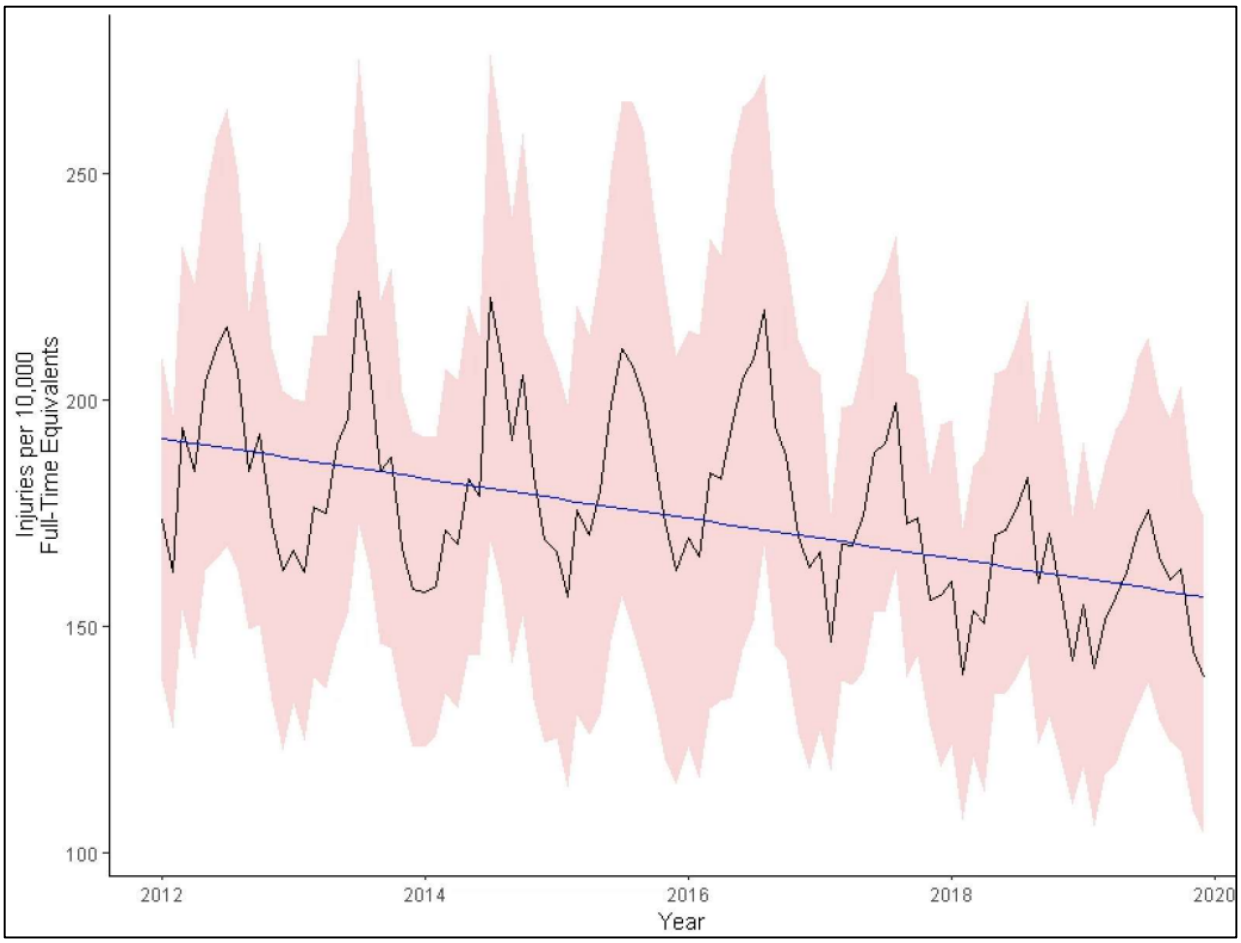
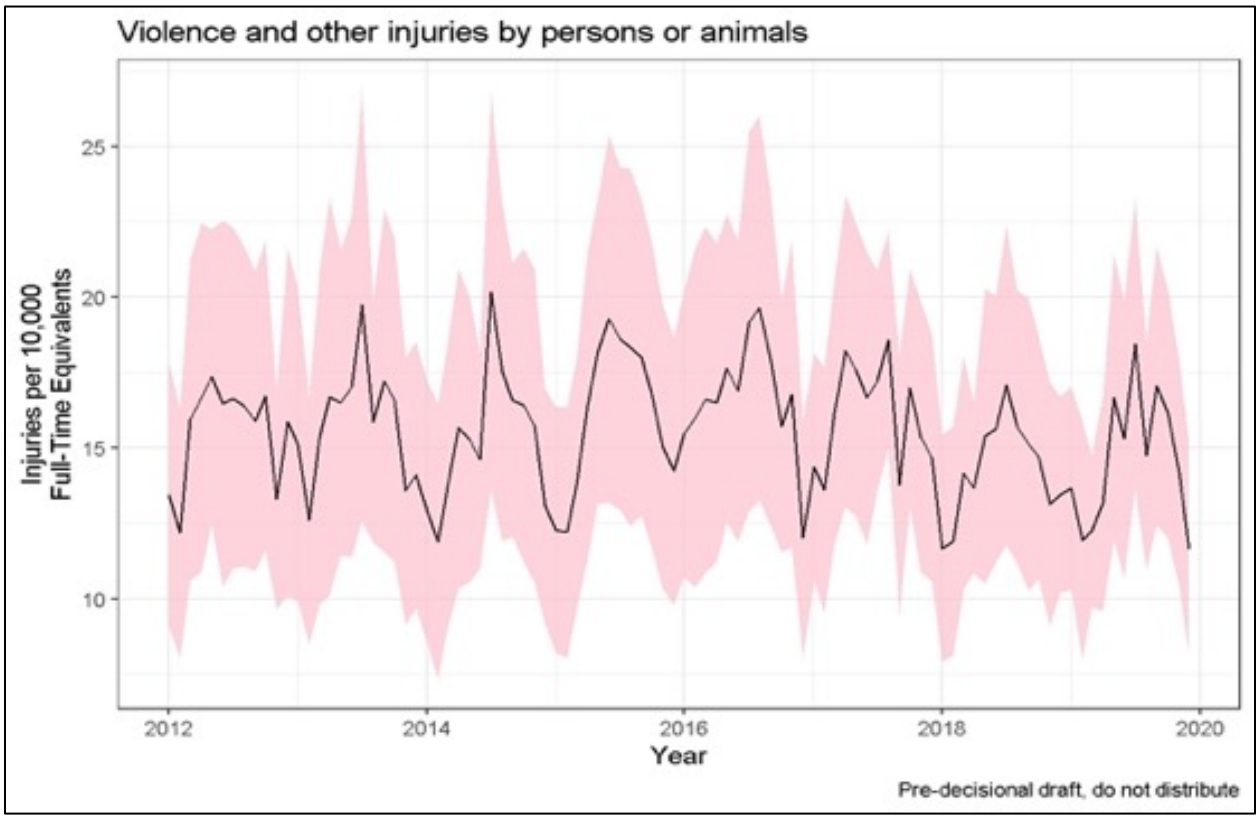


Figure 1. Monthly injury rate estimates for occupational injuries treated in US EDs, 2012-2019. [a]

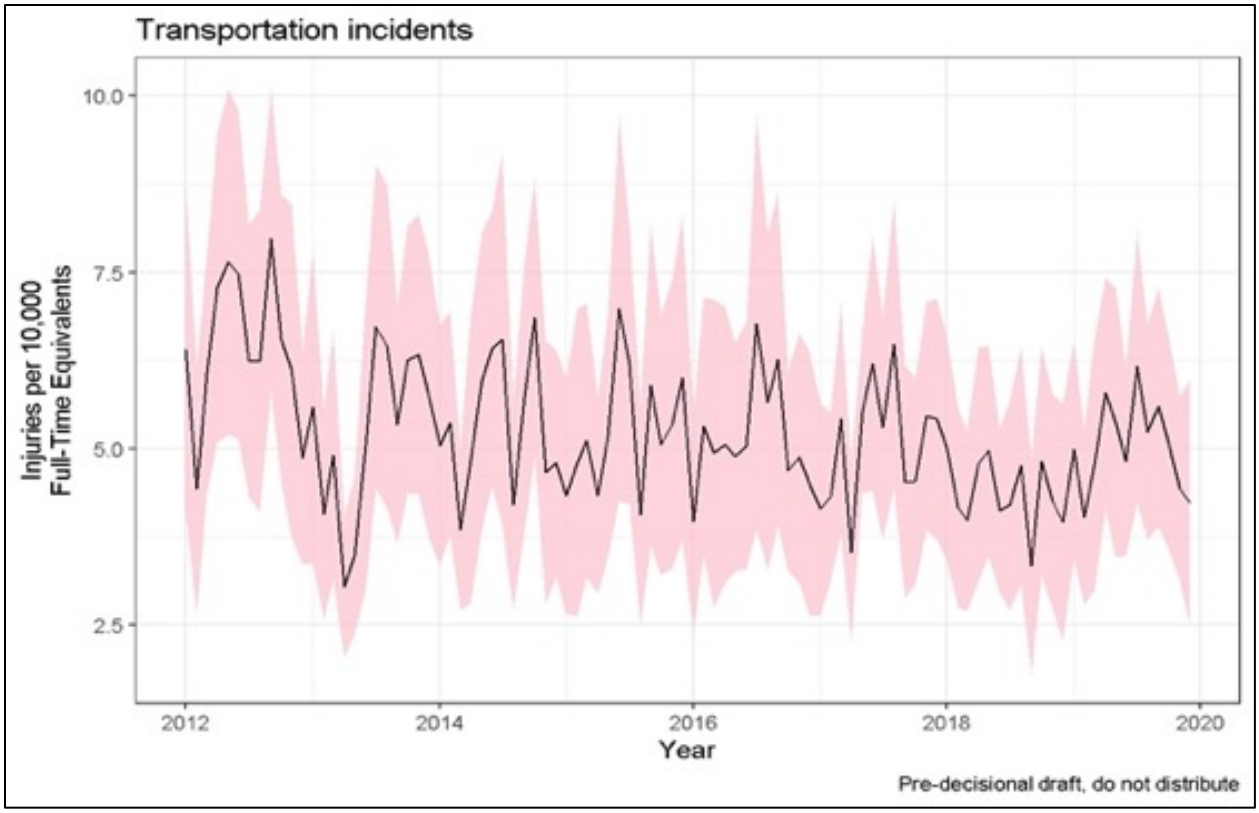
[a] Numerator data (monthly ED-treated injury count estimates) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI (represented here by red shading) using a Taylor series expansion. Blue line represents a linear trend parameter adjusted for seasonality using ARIMA modeling.

Supplementary Material



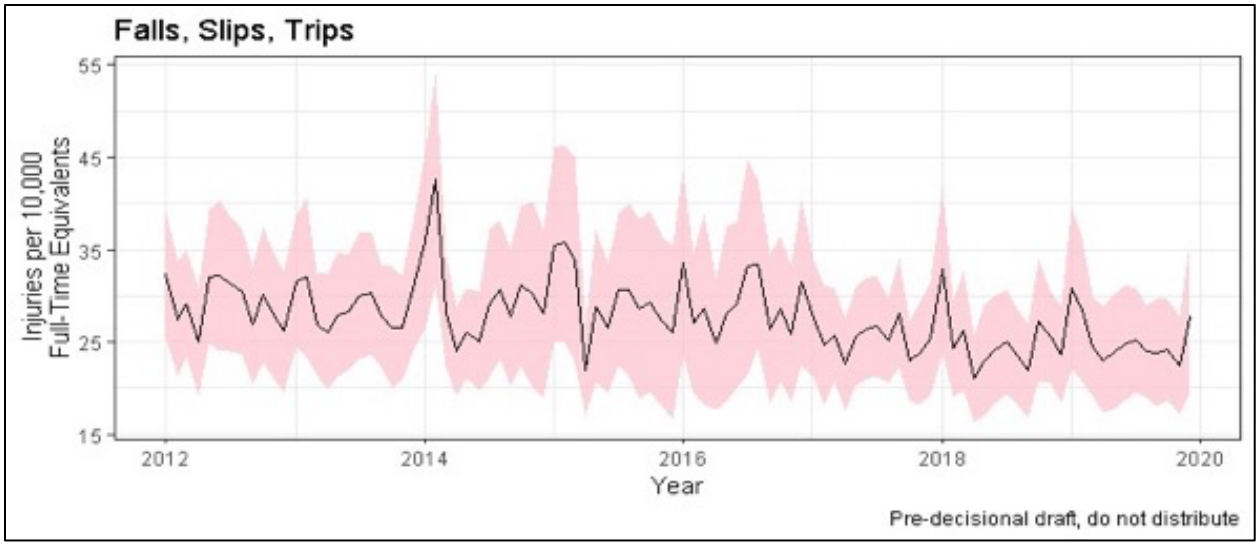
Supplementary Figure 1. Monthly injury rate estimates for occupational injuries caused by violence and other injuries by persons or animals treated in US EDs, 2012-2019.[a]

[a] Numerator data (monthly ED-treated injury count estimates associated with violence and other injuries by persons or animals) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI using a Taylor series expansion.



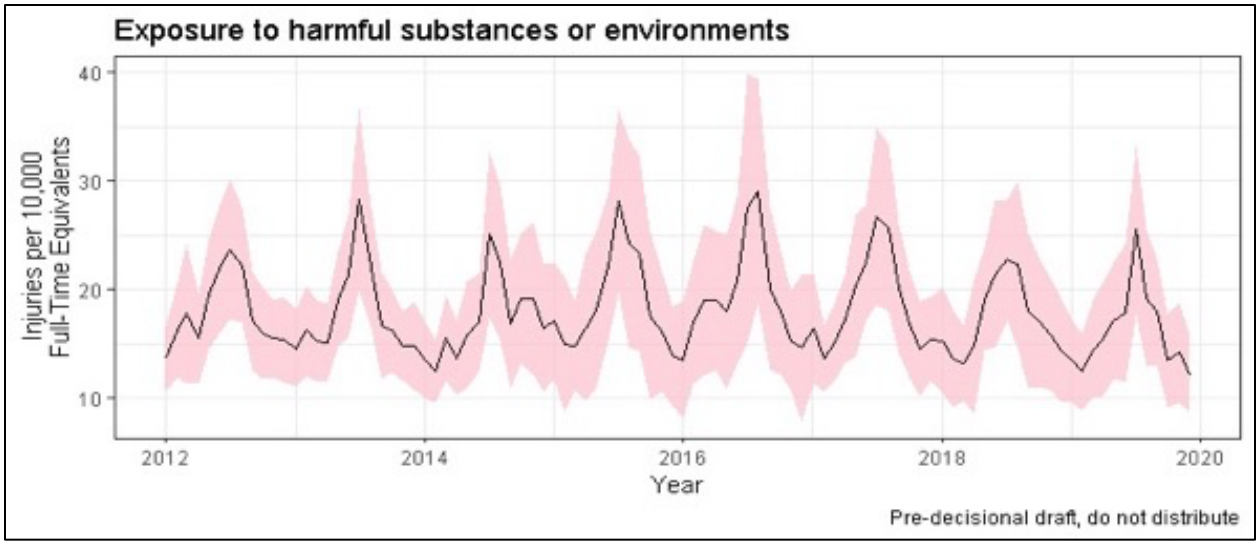
Supplementary Figure 2. Monthly injury rate estimates for occupational injuries caused by transportation incidents treated in US EDs, 2012-2019. [a]

[a]Numerator data (monthly ED-treated transportation injury count estimates) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI using a Taylor series expansion.



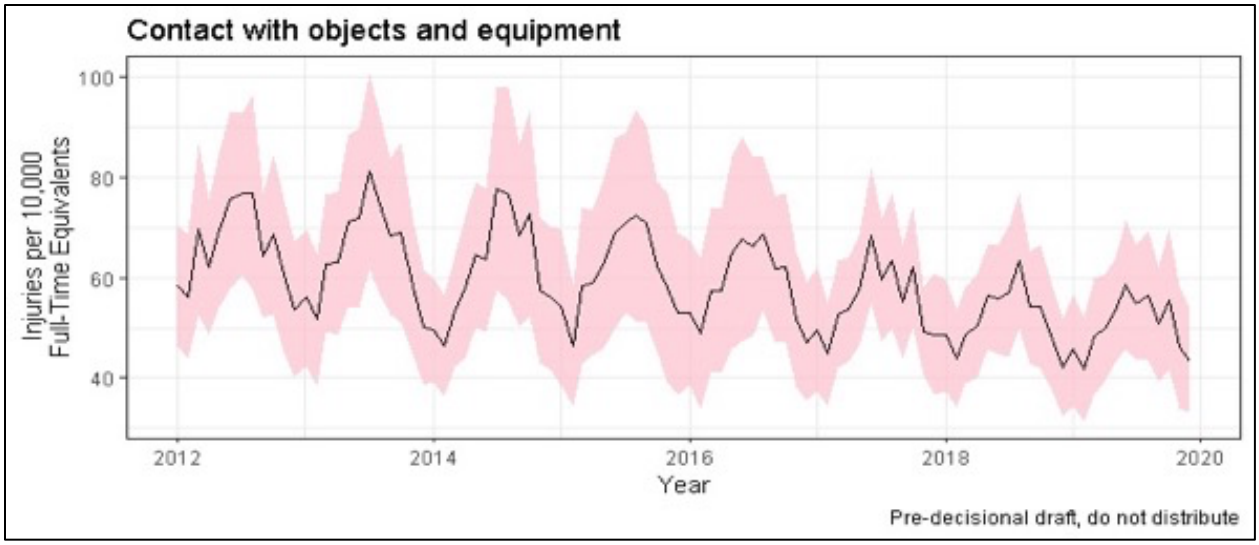
Supplementary Figure 3. Monthly injury rate estimates for occupational injuries caused by falls, slips, and trips treated in US EDs, 2012-2019. [a]

[a] Numerator data (monthly ED-treated falls, slips, and trips injury count estimates) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI using a Taylor series expansion.



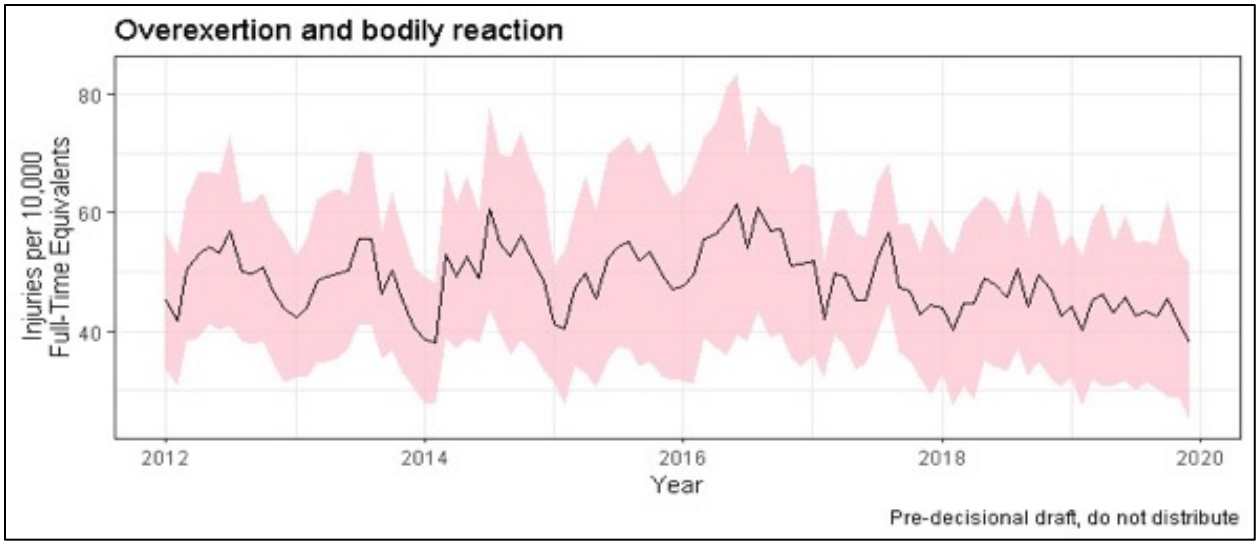
Supplementary Figure 4. Monthly injury rate estimates for occupational injuries caused by exposure to harmful substances or environments treated in US EDs, 2012-2019. [a]

[a] Numerator data (monthly ED-treated injury count estimates associated with exposure to harmful substances or environments) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI using a Taylor series expansion.



Supplementary Figure 5. Monthly injury rate estimates for occupational injuries caused by contact with objects and equipment treated in US EDs, 2012-2019. [a]

[a] Numerator data (monthly ED-treated injury count estimates associated with contact with objects and equipment) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI using a Taylor series expansion.



Supplementary Figure 6. Monthly injury rate estimates for occupational injuries caused by overexertion and other bodily reaction treated in US EDs, 2012-2019. [a]

[a] Numerator data (monthly ED-treated injury count estimates associated with overexertion and other bodily reaction) are from the National Emergency Injury Surveillance System-Occupational Supplement (NEISS-Work) dataset and were produced using the R packages 'survey' and 'srvyr'. Denominator data (FTE) were obtained from the Current Population Survey (CPS) via the NIOSH Employed Labor Force querying system. Variances from both numerator and denominator data were used to calculate for injury rate 95% CI using a Taylor series expansion.

Chapter 3

The comparative impact of decreasing prescription opioid shipments and the release of an abuse deterrent OxyContin formulation on opioid overdose fatalities in WV

Abstract

Introduction: The 2010 release of an abuse deterrent formulation (ADF) of OxyContin, a brand name extended release (ER) prescription opioid, has been cited as a major driver reduced prescription drug abuse and subsequently increasing rates of illicit opioid use and overdose. However, studies of this topic often do not account for changes in prescribing patterns or supplies of other prescription opioids that were widely abused before and after the ADF OxyContin release, including non-ER oxycodone formulations and hydrocodone. We therefore sought to compare the impact of the ADF OxyContin release to that of decreasing total prescription opioid supplies in West Virginia (WV).

Methods: Overdose and opioid shipment data were extracted from The Washington Post ARCOS (2006-2014) and the WV Forensic Drug Database (2005-2020), respectively. To overcome the lack of a fixed intervention start point we used locally estimated scatterplot smoothing (LOESS) to estimate the best point when shipments of prescription opioids to WV began decreasing, measured via dosage units and morphine milligram equivalents (MMEs). Interrupted time series analysis (ITSA) was used to compare the impact LOESS-identified prescription supply changes and the ADF OxyContin release on both prescription (oxycodone and hydrocodone) and illicit (heroin, fentanyl, and fentanyl analogues) opioid overdose deaths in WV. Models were compared using Akaike Information Criteria (AIC).

Results: ITSA models using the LOESS-identified change in prescription opioid shipments (measured via dosage units) resulted in lowest AIC for both prescription (AIC = -188.6) and illicit opioid-involved overdoses (AIC = -189.4), indicating this intervention start date resulted in the preferred model. Second lowest AIC was for models using the ADF OxyContin release (AIC = -185.5 and -185.6 for ITSA of prescription and illicit overdose, respectively).

Discussion: Our results suggest that decreasing prescription opioid shipments in response to declining sales in WV had a greater impact on changing patterns of drug overdose in the state than the ADF OxyContin release. LOESS regression was essential in allowing us to estimate the best intervention start point for our ITSA. Given these results and previous research indicating the majority of oxycodone prescribed post-ADF Oxycontin release was generic and therefore still abusable, those with opioid use disorder had multiple other opioid options to using after the ADF release.

Introduction

Opioid-involved overdose deaths have become a major public health problem in the United States (US), with more than 564,000 fatal overdoses occurring from 1999 to 2020 (Centers for Disease Control and Prevention, 2022). The opioid epidemic has been characterized by multiple waves of overdoses associated with different drug classes and routes of administration (Ciccarone, 2019; Jenkins, 2021). The first wave was associated with overdoses due to prescription opioid medications, such as oxycodone and its brand name extended-release (ER) formulation Oxycontin (van Zee, 2009). Beginning in the late 1990's, these and other prescription opioids were prescribed and dispensed at increasing rates throughout the US. As a result, fatal overdoses of prescription opioids increased in tandem (Ciccarone, 2019, 2021).

Actions taken to decrease rates of prescription medication diversion, abuse, and overdose included efforts to reduce opioid prescribing rates (Schieber et al., 2019) and prescription reformulations which sought to restrict injecting or snorting tablets, including the August 2010 release of an abuse deterrent formulation (ADF) of Oxycontin (Sessler et al., 2014). These targeted measures largely succeeded in decreasing rates of those opioid overdoses involving prescribed opioids. However, they also had the unintended consequence of diverting those suffering from untreated opioid use disorder from prescription opioids to cheaper and more available dangerous illicit alternatives, such as heroin and later fentanyl (Beletsky & Davis, 2017; Ciccarone, 2019).

The ADF Oxycontin release was widely promoted as the solution to diversion and abuse of prescription opioids; immediately following the ADF release in August 2010, sales of the non-ADF formulation ceased and Oxycontin prescriptions were solely prescribed in the ADF formulation. This formulation change has been suggested as a major driver of the transition from prescription to illicit opioid use and overdose in the US by some researchers (Cassidy et al., 2014; Cicero & Ellis, 2015) and the fundamental driver by others (Evans et al., 2019). This hypothesis is supported by decreasing rates of Oxycontin abuse and overdose after the ADF release (Cicero & Ellis, 2015; Sessler et al., 2014). However, other data indicate the majority of Oxycontin users did not start using heroin soon after the ADF release (Cicero & Ellis, 2015). In fact, a recent analysis suggests that many brand name Oxycontin users simply switched to generic ER oxycodone use following the ADF release and that falling rates of generic oxycodone prescriptions were more predictive (in comparison to the ADF OxyContin release) of subsequent increases in illicit opioid overdose at the state level (Zhang & Guth, 2021). Similarly, many previous studies on this topic have not included commonly prescribed opioids such as hydrocodone in their analyses (Cicero & Ellis, 2015; Coplan et al., 2013), an opioid which was prescribed and abused at rates comparable to Oxycontin before the ADF release (Cicero et al., 2005, 2007; Kenan et al., 2012).

Given the importance of supply side drivers of overdose (Ciccarone, 2019), omitting widely prescribed opioids from analyses limits current understanding of the transition between prescription and illicit opioid overdose in the US. Thus, using fatal opioid overdose data from West Virginia (WV), we examined the impact of decreasing opioid shipments to WV on the transition from prescription to illicit opioid overdoses in the state but no fixed date for the start of declining shipments was available . However current time series methods require a fixed stating point. Using a data-driven approach, we used LOESS regression to identify an approximate start date for the decline in opioid tablet shipments to WV given naturally occurring monthly variation in data; these points were used to inform an interrupted time series analysis (ITSA) of fatal prescription and illicit opioid overdoses in the state. ITSA assesses the impact of public health

events by quantifying trends before and after an intervention with a known start date (J. Lopez Bernal et al., 2016). We also assessed the impact of the August 2010 ADF Oxycontin release for comparison to our LOESS-informed analysis. In addition to elucidating the transition from prescription to illicit opioid overdoses in WV, this study provides a plausible framework for using ITSA to assess the impact of public health events with no intervention start date.

Methods

Data sources

Data on opioid prescription shipments in WV for 2006-2014 were obtained from a subset of Drug Enforcement Agency's (DEA) Automation of Reports and Consolidated Orders System (ARCOS) data publicly available through *The Washington Post* (The Washington Post, 2020). ARCOS tracks the flow of all schedule I/II and select schedule III/IV substances through their manufacture and subsequent distribution to points of dispersion (i.e., retail pharmacies, hospitals, practitioners, etc.). *The Washington Post* ARCOS subset contains data on individual oxycodone and hydrocodone tablet shipments, including the addresses of each shipment manufacturer/distributor and recipient, date of shipment, number of dosages (i.e., tablets) in each shipment, strength of each dose in milligrams, and morphine milligram equivalents (MME) conversion factor for each shipment (1 for hydrocodone, 1.5 for oxycodone). While this dataset only contains information on oxycodone and hydrocodone tablet shipments, *The Washington Post* reports that the prescription opioids excluded were shipped and diverted for abuse in much smaller quantities throughout the period reported (Rich et al., 2019). Quarterly dosage units were calculated using an ARCOS dataset column corresponding to the number of tablets in each shipment, while quarterly MMEs were calculated using the formula MME = Quantity × Strength × Conversion Factor (Supplemental Table S1) (Centers for Disease Control and Prevention, n.d.; Sedney et al., 2021; Winstanley et al., 2018).

WV opioid-involved overdose death data for 2005-2020 were obtained from a forensic drug database (FDD) maintained at West Virginia University through an agreement with the WV Office of the Chief Medical Examiner (OCME); the WV OCME uses a state-level, centralized death investigation system which includes comprehensive drug screenings and toxicology testing for suspected drug deaths (Dai et al., 2022). Counts of opioid-involved overdose deaths from January 2005 to December 2020 were aggregated to the quarterly level for drug-related deaths involving prescription (oxycodone or hydrocodone) or illicit opioids (heroin or a synthetic opioid other than methadone, including fentanyl, fentanyl analogs, 4-anpp, and u-47700). Proportions of deaths involving prescription or illicit opioids were calculated by dividing the quarterly aggregate of either category by the total number opioid-involved deaths in each quarter.

Statistical analysis

All statistical analyses were performed in RStudio version 4.2.1 (RStudio Team, 2022). To assess the impact of decreasing opioid prescription shipments to WV on the proportion of opioid overdose deaths associated with prescription and illicit opioids, we used an ITSA (J. Lopez Bernal et al., 2016; Schaffer et al., 2021). ITSA is a robust statistical approach in which the impact of an intervention is measured using segmented linear regression. Three potential interventions were investigated. First, two interventions denoting peak tablet shipments to WV, measured via both dosage units and MMEs. As shipments varied by quarter with no defined point when the decline began, we identified a plausible decline start point using locally estimated scatterplot smoothing (LOESS) of quarterly ARCOS data. LOESS fits weighted least squared

regression to data in several independent variable intervals and requires no global function, providing clear graphical representations of non-linear relationships. As a result, LOESS is often used to identify inflection points (i.e., changes in slope) in non-linear data (Jacoby, 2000; Ryan & Porth, 2007), including in time series data of opioid prescriptions (Ahmedani et al., 2014) and overdoses (Stevens et al., 2017). Next, an intervention for the introduction of the ADF Oxycontin (released in August 2010 or 2010 Q3) was informed by previous literature; non-ADF Oxycontin prescriptions ceased the same month that the ADF was released (Beachler et al., 2022). As there is a likely a temporal lag between changes in prescription opioid shipments and related variations in opioid overdose rates, we lagged each intervention by a transition period of two quarters. This approach is similar is used in previous analyses of prescription opioid supply in this timeframe (Mallama, 2020; Secora, 2020; Severtson et al., 2016).

Each intervention was modeled using the equation:

$$y_t = \beta_0 + \beta_1 t + \beta_2 P + \beta_3 D + \epsilon$$

where y_t is an outcome of interest (e.g. quarterly proportion of opioid overdose deaths associated with prescription or illicit opioids), β_0 is the model intercept, t is time, P is a variable representing time since the intervention (zero before the intervention, slope of one afterwards), and D is a dummy variable representing the immediate effect of the intervention (Nyugen, 2022; Penfold & Zhang, 2013). β_1, β_2, and β_3 represent the pre-intervention slope, the sustained post-intervention effect (i.e., a slope change impact known as a "ramp" variable), and the immediate post-intervention effect of an intervention (i.e., a "step-change" impact), respectively. Finally, error is denoted by ϵ and may include autoregressive integrated moving average (ARIMA) terms when data violate the linear regression assumption of data independence (i.e., the data is serially correlated). ARIMA models include lagged values of a time series' dependent variable and/or its error terms and is recommended for use in ITSA when data are not independent (J. Lopez Bernal et al., 2016, 2018). ARIMA terms were fit to opioid overdose data via inspecting autocorrelation and partial autocorrelation plots. In accordance with previous ITSA literature (Gilmour et al., 2006; Schaffer et al., 2021), the terms in the above-specified model for each identified intervention were included or excluded based on the need for control of serial correlation, preservation of model parsimony, and minimization of Akaike Information Criteria (AIC). Final ITSA models were assessed for proper fit via inspection of each model's ACF and PACF plots, as well as inspecting the significance of each model's Ljung-Box statistic (with a non-significant value considered a properly fitting model) (Ljung & Box, 1978). The AIC of each final ITSA model was used for model comparison. To compare models using AIC, we abided by the convention that when comparing two models, the model with lower AIC is better fit and that a difference of two or more AIC units is meaningful (Burnhamn & Anderson, 2002).

Results

From 2005-2020, a total of 9419 opioid-involved overdose deaths were identified in the WV FDD. The proportion of these involving illicit opioids was 0.48, while the proportion involving prescription opioids (oxycodone or hydrocodone) was 0.37. Graphical representation of the quarterly proportion of opioid-involved overdose deaths involving each opioid investigated is presented in Figure 1. During the first two quarters of the study period, illicit opioid overdoses occurred at a rate comparable to prescription opioids, likely due to a brief fentanyl overdose outbreak that occurred nationally from 2005 to 2007 (DEA Diversion Control

Division, 2016). After this, prescription opioid overdoses occurred at a rate greater than those associated with illicit opioids until approximately 2015.

LOESS regression of 2006-2014 ARCOS data indicated that maximum quarterly shipments of oxycodone and hydrocodone tablets occurred in 2011 Q3 when measured via dosage units (i.e., number of tablets) and 2012 Q4 when measured via MMEs. Graphical representation of quarterly dosage units and MMEs are presented in Figure 2 along with estimated peak total prescription shipments. Measured via dosage units, hydrocodone was shipped to WV in highest quantities, followed by non-ER oxycodone and brand name oxycodone tablets including OxyContin. Measured via MMEs, hydrocodone was shipped to WV in highest quantities until approximately 2012, when it was surpassed by non-ER oxycodone; OxyContin was shipped in third-highest quantities (measured via MMEs) after approximately 2007. The opioids products included in each category are available in Supplemental Table 2-7.

Graphical representation of each ITSA model and a corresponding counterfactual (i.e., no intervention) scenario is presented in Figure 3; the blue dotted line indicates the intervention date of interest while the grey shaded area denotes a transition period of two quarters post-intervention. ITSA informed via ADF Oxycontin release and peak ARCOS MMEs appeared to over- and underestimate, respectively, increases in illicit opioid overdoses. For all ITSA models, serial correlation was adequately controlled with an AR (1) ARIMA term (Tables 2 and 3). ITSA of the proportion of prescription opioids was best modeled using time (β_1) and ramp (β_2) functions, corresponding to significant pre- and post-intervention trends (Table 2), respectively. ITSA of illicit opioids was best modeled using only a ramp function, indicating there was no pre-intervention trend present (Table 3). No ITSA model was improved via inclusion of a step-change (i.e., immediate impact; β_3) function. For both prescription and illicit opioids, a dosage units-informed ITSA model had lowest AIC (-188.6 and -189.4 for prescription and illicit opioids, respectively), indicating best model fit, followed by models informed via ADF Oxycontin release and peak ARCOS MMEs. AIC difference between the three models was greater than two units for both prescription (Table 2) and illicit opioids (Table 3), suggesting meaningful differences between each model's performance.

Discussion

In this study, we assessed the statewide transition from prescription to illicit fatal opioid overdoses in WV. We used LOESS regression to determine the starting point for when opioid tablet shipments to WV began decreasing (measured as both dosage units and MMEs) and used these as intervention start dates in an ITSA study. We compared these to an ITSA study using the ADF Oxycontin release as an intervention start data, which is widely cited as the factor initiating a transition from prescription to illicit opioid use in the US (Cicero et al., 2012; Cicero & Ellis, 2015; Evans et al., 2019). Our findings suggest that in WV, overdose patterns began changing much closer to the time when prescription opioid shipments (measured via dosage units) began decreasing. We also accounted for an assumed six-month lag from shipment to observable effect on fatal overdose rates (Mallama, 2020; Secora, 2020; Severtson et al., 2016), indicating this observed impact was a full 1.5 years after the ADF Oxycontin release.

Changes in prescription opioid supplies have a measurable impact on use of both prescription and illicit opioids (Ciccarone, 2019; Fischer et al., 2020; Greenfield & Paoli, 2017; Werle & Zedillo, 2018). Thus, it is likely that decreasing prescription opioid supplies in WV during our study period likely contributed to increasing rates of overdoses involving illicit opioids. From 2006-2011, the WV opioid prescription dispensing rate was the highest of any US

state (Centers for Disease Control and Prevention, 2021). However, WV opioid prescription rates, measured either via dosage units or MMEs, decreased more quickly than the US average during our study period (Centers for Disease Control and Prevention, 2021; Schieber et al., 2019). These drastic supply changes may explain our finding that the ITSA study based on overall opioid shipments to WV (measured via dosage units) was the preferred model of both prescription and illicit overdose rates in our study. Moreover, our data indicate that the majority prescription opioids shipped to the state were not Oxycontin (Figure 2) or other ER oxycodone formulations; this is congruent with national data showing that the majority of oxycodone prescribed post-ADF Oxycontin release was generic and therefore abusable (Zhang & Guth, 2021). Thus, those who used OxyContin in WV likely had many other prescription options to begin using following the release of its ADF formulation. Moreover, those with opioid use disorder often prefer immediate release prescription opioid formulations as opposed to ER formulations (Cicero et al., 2017). This may be why the ADF Oxycontin release did not fit our data well as a dosage unit-based intervention.

Soon after its release, the ADF OxyContin reformulation was cited as a major contributor to subsequent increases in illicit opioid use and overdose (Cicero et al., 2012). However, analyses since the 2019 ARCOS data release by *The Washington Post* support our conclusion that changing supplies of other prescription opioids had a greater influence. For instance, Zhang and Guth assessed ARCOS, substance use data from The National Survey on Drug Use and Health (NSDUH), and opioid mortality data and found that the majority of Oxycontin users in their sample transitioned to generic oxycodone after the ADF release (Zhang & Guth, 2021). The authors also note that heroin mortality was highest in states with previously high generic oxycodone use and that illicit opioid overdose rates began increasing nearly two years after the ADF release. Our findings support and expand on those from Zhang and Guth by using ITSA, quarterly as opposed to annual data, and by including data on shipments of hydrocodone, a prescription opioid that was prescribed and abused at rates similar to Oxycontin and oxycodone before the ADF Oxycontin release (Cicero et al., 2005, 2007; Kenan et al., 2012).

While we used ARCOS data to assess prescription opioid supplies throughout our study period, analyses of other data sources support our conclusions. For example, NSDUH data indicates those using prescription pain relievers other than Oxycontin before its ADF release had 58% greater odds of heroin initiation than those using Oxycontin (Wolff et al., 2020). Similarly, in a large sample of individuals screened for substance abuse, oxymorphone and buprenorphine abuse rates increased after the ADF OxyContin release while heroin abuse rates did not change significantly (Cassidy et al., 2014). Another study using linked health insurance and National Death Index data did not find an overall effect on fatal and non-fatal overdose; the study did find a small decrease in OxyContin overdose rates (Beachler et al., 2022). Finally, a 2020 US Food and Drug Administration (FDA) joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee used multiple data sources to assess the national post-market impact of the ADF Oxycontin release. Among the meeting's findings were that while non-oral Oxycontin use decreased after the ADF release, oral use increased significantly (Mallama, 2020) and abuse of hydrocodone and other schedule II opioids increased significantly relative to Oxycontin (Secora, 2020).

In addition to elucidating the transition from prescription to illicit opioid overdose in WV, this study expands on ITSA literature seeking to identify intervention dates using data that is related to, yet separate from, a time series of interest. Notably, Gilmour et al. used previously published survey data to identify a plausible ITSA start date of the Australian heroin shortage.

Similarly, Lopez Bernal et al. used a widely accepted definition for the beginning of an economic recession (the point at which gross domestic product growth rate is negative compared to previous quarter) to assess the impact of late 2000's financial crisis on Suicide rates in Spain of (J. A. Lopez Bernal et al., 2013). While these studies provided innovative approaches, the methods used were statistically descriptive. Using LOESS regression, the inferential approach used in our study, future studies may be able to more accurately determine an intervention start date for use in an ITSA study when one is not easily defined.

This study has several strengths. For example, to the author's knowledge, we are the first to demonstrate the feasibility of LOESS regression in determining a plausible intervention start data for use in an ITSA study of substance use data. As previous substance use research has identified the difficulty in studying interventions with no known start date (Gilmour et al., 2006), this is a crucial addition to current ITSA literature. Additionally, our study assessed medical examiner data from WV, which has a highly specific drug death investigation system relative to other states (Warner & Hedegaard, 2018). However, our study also has several limitations. First, although ITSA is a powerful statistical study design and is useful in many situations in which a public health intervention has no control group, it remains an ecologic study design and therefore cannot infer causality. Despite this, we believe the methodology in this study, which investigates several possible interventions, provides a robust approach towards strengthening evidence for a specific intervention's impact as it uses ITSA to quantify the impact of several intervention points. Second, given urban/rural differences in prescription opioid abuse rates, our results may not be generalizable outside of WV, a largely rural state. Third, the medical examiner's data used in this study relies on toxicology report that cannot differentiate between formulations of the same drug. We therefore cannot assess which formulation of oxycodone (Oxycontin or generic) or hydrocodone contributed to overdose rates throughout our study period. Finally, ARCOS is limited to hydrocodone and oxycodone; while data suggests these were the primary opioids contributing to substance use disorder during the early years of the opioid epidemic in WV, other prescription opioids played a role.

Conclusion

These results suggest that the transition from prescription to illicit opioid overdose in WV may have been affected by decreasing rates of prescription opioid shipments, not the release of ADF Oxycontin as previous reported in studies of national data. This may be related to the large quantity of hydrocodone shipped to WV (relative to Oxycontin), the deterrent use of which would not have been affected by the ADF Oxycontin release. While *The Washington Post* ARCOS is compressive in its inclusion of oxycodone and hydrocodone tablet shipments, it does not include data on other prescription opioids with potential for deterrent use. Future studies should seek to elucidate the impacts of supply-side changes in prescription opioid availability in WV on other outcomes, including substance use, substance use treatment, and related co-morbidities, such as acute hepatitis C infection.

Figures and Tables

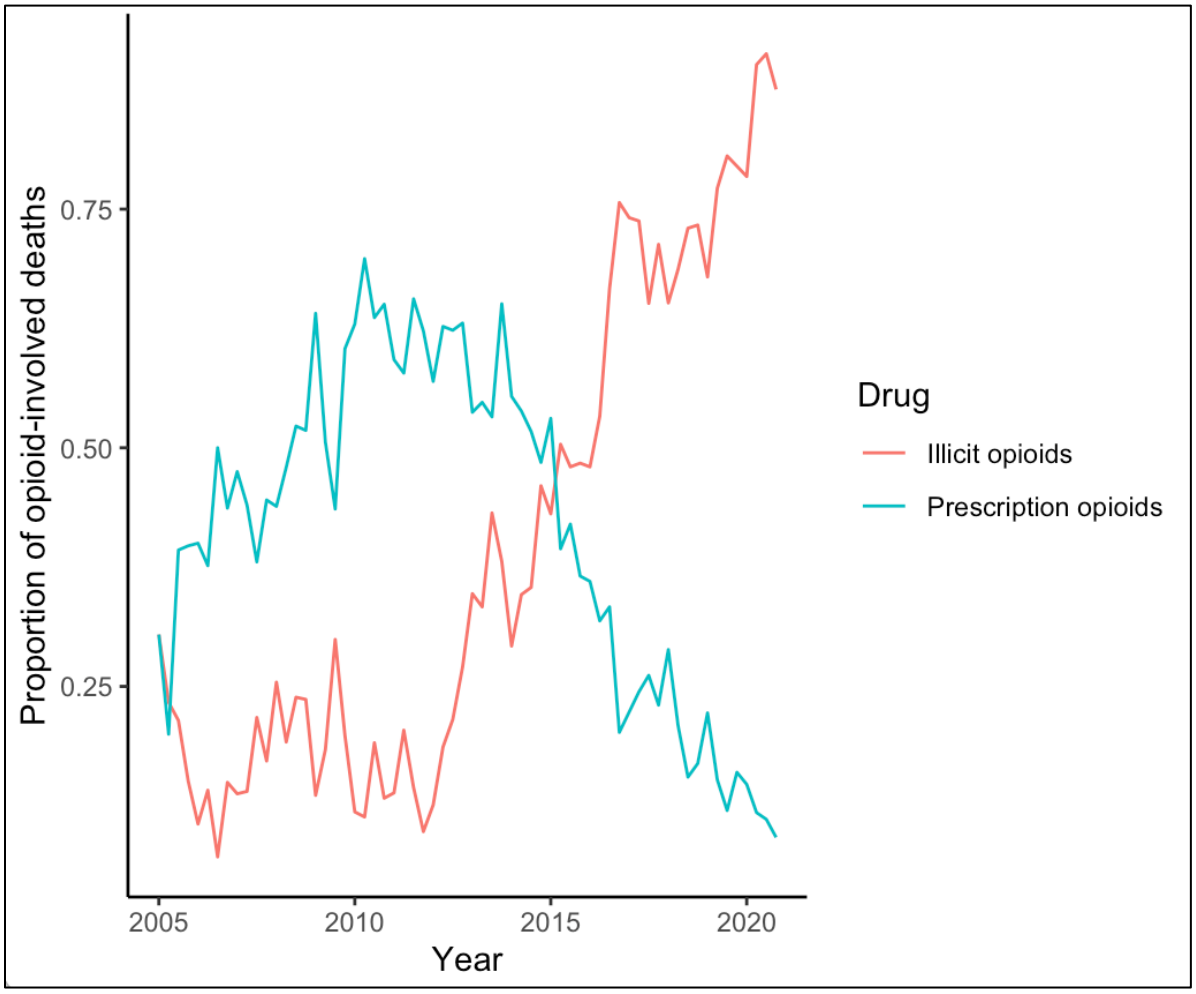


Figure 1. The quarterly proportion of opioid overdoses in WV associated with prescription and illicit opioids. [a]

[a] Prescription opioid overdoses were defined as those associated with oxycodone or hydrocodone, while illicit overdoses were defined as those involving heroin and synthetic opioids other than methadone, including fentanyl, fentanyl analogues, 4-anpp, and u-47700. Data from the West Virginia Forensic Drug Database, which compiles data from the West Virginia Office of the Chief Medical Examiner.

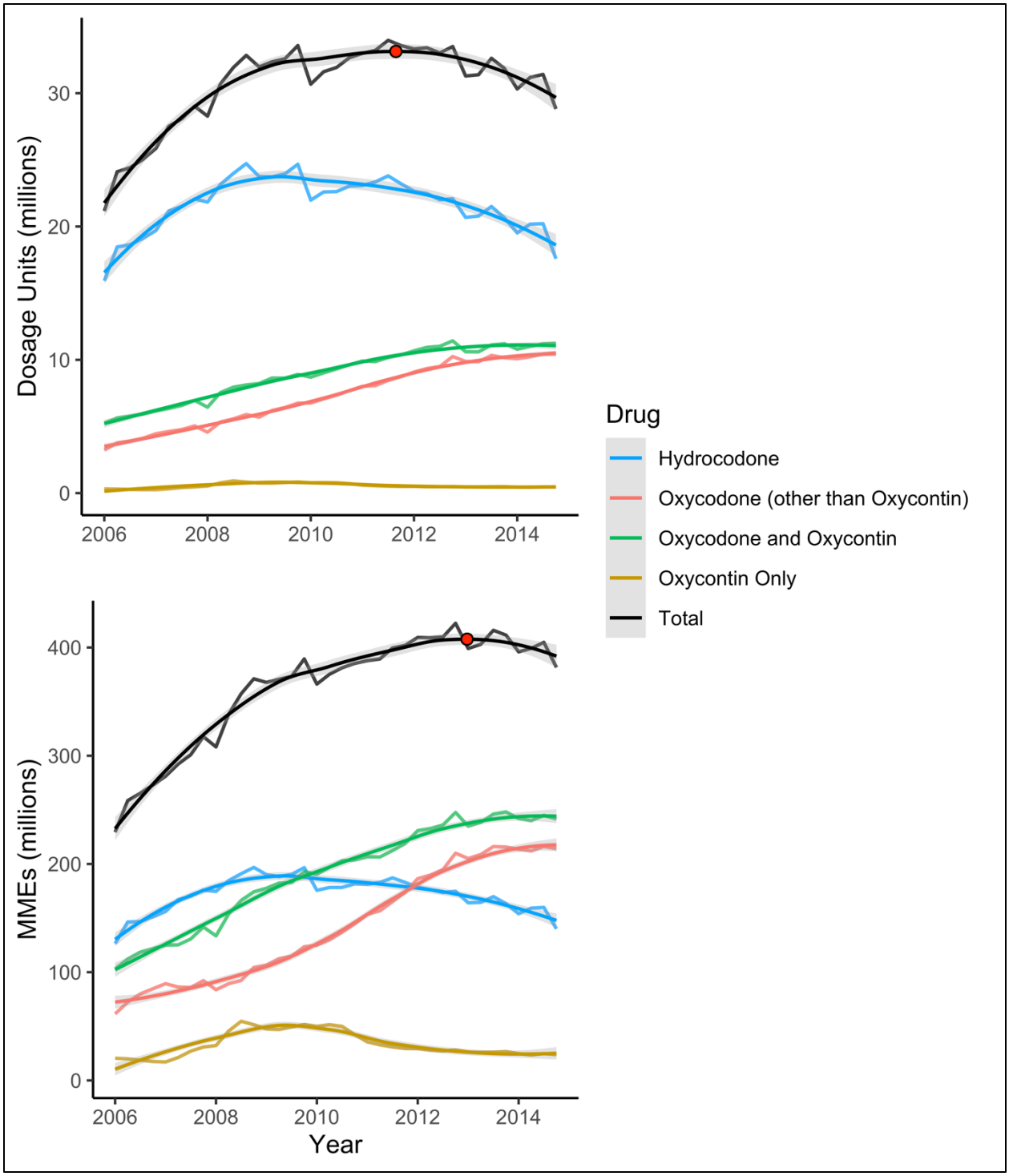


Figure 2. Quarterly opioid tablet shipments to West Virginia, both total and by individual opioid product and estimated change point in total opioid shipments indicated by red dot.[a]

[a] Data are presented measured via dosage units and morphine milligram equivalents (MMEs) and are smoothed using locally estimated scatterplot smoothing (LOESS) regression to allow for the visualization of overall trends. Peak total quarterly dosage units and MMEs were identified via LOESS and are denoted using a red dot. Data are form the Drug Enforcement Agency's Automation of Reports and Consolidated Orders System (ARCOS) database and were obtained from The Washington Post.

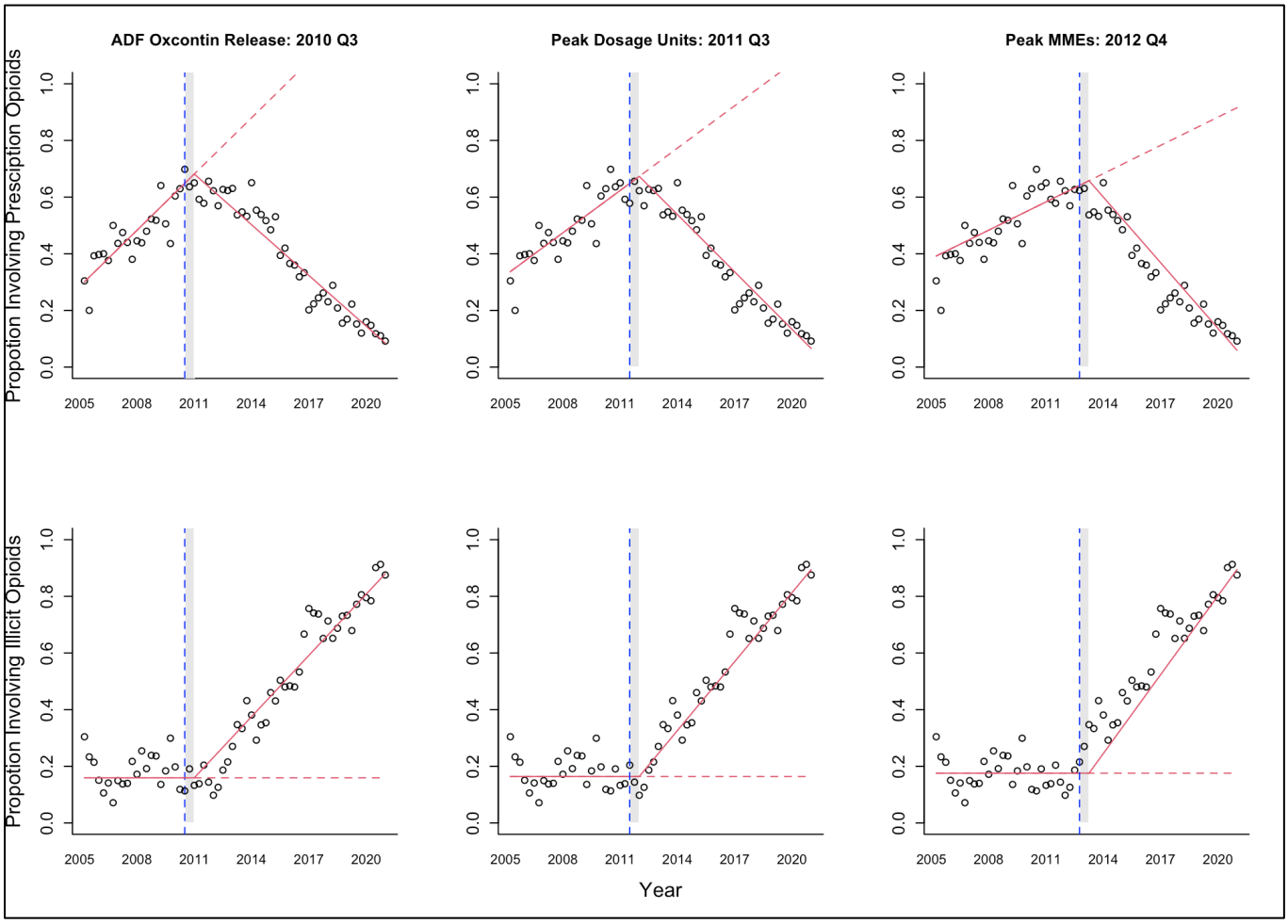


Figure 3. Graphical representation of interrupted time series analysis (ITSA)[a] of quarterly opioid-involved overdose deaths.[b]

[a] Upper and lower sub-figures represent ITSA of prescription and illicit opioid-involved overdose rates, respectively, while each column represents a unique ITSA intervention. Red lines represent estimated intervention impacts while dotted red lines represent estimated counterfactual (i.e., no intervention) trends. Blue dotted lines represent intervention start dates while grey shaded areas represent a two-quarter transition period after which the intervention impact is theorized to have begun.

[b] Prescription opioid overdoses were defined as those associated with oxycodone or hydrocodone, while illicit opioid overdoses were defined as those involving heroin and synthetic opioids other than methadone, including fentanyl, fentanyl analogues, 4-anpp, and u-47700. Data are from the West Virginia Forensic Drug Database, which compiles data from the West Virginia Office of the Chief Medical Examiner.

Table 1. Interrupted time series results of opioid-involved overdoses in West Virginia involving prescription opioids.[a]

Intervention: Oxycontin ADF released (2010 Q3)			
Parameter	Estimate	P-value	AIC [b]
AR1 (ϵ)	0.32	0.007	-185.5
Intercept (β_0)	0.28	<0.001	
Time (β_1)	0.02	<0.001	
Ramp (β_2)	-0.03	<0.001	
Intervention: Peak dosage units (2011 Q3)			
Parameter	Estimate	P-value	AIC
AR1 (ϵ)	0.25	0.042	-188.6
Intercept (β_0)	0.32	<0.001	
Time (β_1)	0.01	<0.001	
Ramp (β_2)	-0.03	<0.001	
Intervention: Peak MMEs (2012 Q4)			
Parameter	Estimate	P-value	AIC
AR1 (ϵ)	0.43	<0.001	-178.3
Intercept (β_0)	0.36	<0.001	
Time (β_1)	0.01	<0.001	
Ramp (β_2)	-0.03	<0.001	

[a] Prescription opioid overdoses were defined as those associated with oxycodone or hydrocodone. Data are from the West Virginia Forensic Drug Database, which compiles data from the West Virginia Office of the Chief Medical Examiner.

[b] Akaike Information Criteria (AIC). A lower value is considered better model fit and a difference of more than two AIC units indicates a meaningfully better-fitting model.

Table 2. Interrupted time series results of opioid-involved overdoses in west Virginia involving illicit opioids.[a]

Intervention: Oxycontin ADF released (2010 Q3)			
Parameter	Estimate	P-value	AIC [b]
AR1 (ϵ)	0.57	<0.001	
Intercept (β_0)	0.17	<0.001	-185.6
Ramp (β_2)	0.02	<0.001	
Intervention: Peak dosage units (2011 Q3)			
Parameter	Estimate	P-value	AIC
AR1 (ϵ)	0.50	<0.001	
Intercept (β_0)	0.18	<0.001	-189.4
Ramp (β_2)	0.02	<0.001	
Intervention: Peak MMEs (2012 Q4)			
Parameter	Estimate	P-value	AIC
AR1 (ϵ)	0.67	<0.001	
Intercept (β_0)	0.21	<0.001	-180.7
Ramp (β_2)	0.02	<0.001	

[a] Illicit opioid overdoses were defined as those involving heroin and synthetic opioids other than methadone, including fentanyl, fentanyl analogues, 4-anpp, and u-47700. Data are from the West Virginia Forensic Drug Database, which compiles data from the West Virginia Office of the Chief Medical Examiner.

[b] Akaike Information Criteria (AIC). A lower value is considered better model fit and a difference of more than two AIC units indicates a meaningfully better-fitting model.

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Supplemental Material

Supplemental Table 1. *Washington Post* ARCOS data variables used in the calculation of dosage units and MMEs.

Variable	ARCOS Variable Name	ARCOS Data Dictionary Description
Quantity	DOSAGE_UNIT	DEA calculated field indicating number of pills, patches or lozenges, among others, shipped as part of the transaction.
Strength	dos_str	Strength of dose in milligrams.
Conversion Factor	MME_Conversion_Factor	Morphine Milligram Equivalent, or how the specific drug compares to a morphine equivalent.

Supplemental Table 2. Hydrocodone products shown in Figure 2, measured via total dosage units and morphine milligram equivalents (MMEs) shipped to West Virginia for 2006-2014.

Product_Name	MME	Dosage_Units
ACET/HYDROCOD.BIT.,500MG&5MG/TAB	15700	3140
ACETA/HYDROCODONE.BIT - 750MG/7.5MG	126825	16910
ACETAMINOPHEN 750MG/ HYDROCODONE BIT	11250	1500
ANEXSIA 7.5MG TAB HYDROCODO.BIT ACET	13500	1800
ANEXSIA.HYDROCODONE.BITARTRATE.10MG/	1141000	114100
CO-GESIC ACETA & HYDROCODO.BIT.,5MG	2000	400
HYCODAN 5MG/TABLET	42000	8400
HYCODAN TAB. / HYDROCODONE BIT. 5MG	1000	200
HYDRO-APAP 7.5MG HYDROCOD.BIT/325MG	1350	180
HYDROCOD. BIT 5MG TAB	284360	56872
HYDROCOD. BIT 7.5MG/ACETAMINOPHEN 75	73500	9800
HYDROCOD. BIT5MG & ACET TAB	13500	2700
HYDROCOD.BIT 7.5 TAB	15752250	2100300
HYDROCOD.BIT. & ACET.;2.5MG/600MG/TA	2180547.5	872219
HYDROCOD.BIT. 5MG/HOMATROPINE.METHYL	648000	129600
HYDROCOD.BIT./ACET.,5MG & 500MG/TAB	32500	6500
HYDROCOD.BIT./ACET.,5MG & 500MG/TAB(	7500	1500
HYDROCOD.BIT./ACET.,7.5MG & 500MG/TA	234375	31250
HYDROCOD.BIT./ACET.,7.5MG & 750MG/TA	27000	3600
HYDROCOD.BIT./APAP;5MG & 500MG/TAB;B	1500	300
HYDROCOD.BIT./APAP;5MG&500MG/TAB;10X	66500	13300
HYDROCOD.BIT.& APAP,10MG/660MG/TAB	50755000	5075500
HYDROCOD.BIT.& APAP;7.5MG&750MG/TAB	21600	2880
HYDROCODO.BIT 10MG & ACETA TABLET	11310000	1131000
HYDROCODO.BIT 10MG&AC TAB	38396000	3839600
HYDROCODO.BIT 10MG&AC USP TAB	252415000	25241500
HYDROCODO.BIT 10MG&ACETAMINOPHEN USP	63000	6300
HYDROCODO.BIT 7.5MG TAB	6658500	887800
HYDROCODO.BIT.,7.5MG/APAP,750MG/TAB	32850	4380
HYDROCODO.BIT/APAP 7.5MG/750MG USP T	157967250	21062300
HYDROCODO.BIT5MG/AC TAB	353500	70700
HYDROCODONE & ACETA 5MG/500MG	1500	300
HYDROCODONE 10MG/APAP 325MG TABS	6000	600
HYDROCODONE 7.5MG;APAP 750MG TABS.	4500	600
HYDROCODONE BIT / ACETAMINOPHEN 10MG	66464000	6646400
HYDROCODONE BIT & ACETA 7.5MG/500MG	38507775	5134370
HYDROCODONE BIT & ACETAMINOPHEN 5MG/	1464000	292800
HYDROCODONE BIT & ACETAMINOPHEN 7.5M	1950000	260000

HYDROCODONE BIT 5MG/ACETAMINOPHEN 50	168557040	33711408
HYDROCODONE BIT. & ACETA 10MG/325MG	696000	69600
HYDROCODONE BIT. & ACETA 10MG/500MG	1224000	122400
HYDROCODONE BIT. & ACETA 5MG/325MG T	21000	4200
HYDROCODONE BIT. & ACETA 5MG/500MG T	1639500	327900
HYDROCODONE BIT. & ACETA. 7.5MG/750M	479250	63900
HYDROCODONE BIT. & IBUPROFEN 7.5MG/2	750	100
HYDROCODONE BIT. & IBUPROPHEN 7.5MG/	1058250	141100
HYDROCODONE BIT. 10MG/ACETAMINOPHEN	915367000	91536700
HYDROCODONE BIT. 5MG/ACETA. 325MG TA	5500	1100
HYDROCODONE BIT. 7.5MG/ACETAMINOPHEN	59728931.25	7963857.5
HYDROCODONE BIT.,7.5MG/ACET.500MG/TA	900	120
HYDROCODONE BIT./ACET.,7.5MG & 650MG	75176250	10023500
HYDROCODONE BIT./ACETA 10MG/325MG TA	98090000	9809000
HYDROCODONE BIT./ACETA 10MG/500MG US	1302000	130200
HYDROCODONE BIT./ACETA 5MG/325MG TAB	11471000	2294200
HYDROCODONE BIT./ACETA 5MG/325MG USP	9500	1900
HYDROCODONE BIT./ACETA 7.5MG/325MG T	18059250	2407900
HYDROCODONE BIT./ACETA 7.5MG/500MG 1	53250	7100
HYDROCODONE BIT./ACETA. 10MG/325MG U	2000	200
HYDROCODONE BIT./ACETA. 7.5MG/325MG	1500	200
HYDROCODONE BIT./ACETA. TABLETS USP	500	100
HYDROCODONE BIT./ACETAM. TABS. 5MG/3	25500	5100
HYDROCODONE BIT./ACETAMIN. TABS. 7.5	34500	4600
HYDROCODONE BIT./ACETAMINOPHEN 10MG/	10000	1000
HYDROCODONE BIT./ACETAMINOPHEN TABS.	171344900	22863430
HYDROCODONE BIT./APAP 10MG/325MG TAB	41616000	4161600
HYDROCODONE BIT./APAP 10MG/650MG TAB	9368000	936800
HYDROCODONE BIT./APAP 10MG/750MG TAB	2000	200
HYDROCODONE BIT./APAP 5MG/325MG TABL	295400	59080
HYDROCODONE BIT./APAP 7.5MG/325MG TA	8160750	1088100
HYDROCODONE BIT./APAP 7.5MG/650MG TA	1120500	149400
HYDROCODONE BIT./APAP 7.5MG/750MG 10	21750	2900
HYDROCODONE BIT./IBUPROFEN;7.5MG & 2	9106500	1214200
HYDROCODONE BIT.&ACETA 10MG/660MG TA	91000	9100
HYDROCODONE BIT.7.5MG/ACETAMINOPHEN	418473750	55796500
HYDROCODONE BIT/ ACETAMINOPHEN 5MG/5	47000	9400
HYDROCODONE BIT/ACETA 10MG/325MG USP	243305000	24330500
HYDROCODONE BIT/ACETA 10MG/500MG USP	463392000	46339200
HYDROCODONE BIT/ACETA 5MG/325MG TABL	136000	27200
HYDROCODONE BIT/ACETA 5MG/325MG USP	52575500	10515100

HYDROCODONE BIT/ACETA 7.5MG/325MG US	123987750	16531700
HYDROCODONE BIT/ACETA 7.5MG/500MG US	507744750	67699300
HYDROCODONE BIT/ACETAMINOPHEN 10MG/3	29732500	2973250
HYDROCODONE BIT/ACETAMINOPHEN 5MG/32	15350	3070
HYDROCODONE BIT/ACETAMINOPHEN 5MG/50	507248500	101449700
HYDROCODONE BIT/ACETAMINOPHEN 7.5MG/	19050	2540
HYDROCODONE BIT/APAP 10MG/325MG TABL	2455200	245520
HYDROCODONE BIT/APAP 10MG/500MG TABL	468000	46800
HYDROCODONE BIT/APAP 5MG/325MG TABLE	2266200	453240
HYDROCODONE BIT/APAP 5MG/500MG TABLE	594000	118800
HYDROCODONE BIT/APAP 7.5MG/325MG TAB	1612950	215060
HYDROCODONE BIT/APAP 7.5MG/500MG TAB	480600	64080
HYDROCODONE BIT/HOMATROPINE METHYLBR	880000	176000
HYDROCODONE BIT/IBUPROFEN 5MG/200MG	7500	1500
HYDROCODONE BIT/IBUPROFEN 10MG/200MG	2.00E+05	20000
HYDROCODONE BIT/IBUPROFEN 2.5MG/200M	3750	1500
HYDROCODONE BIT/IBUPROFEN 7.5MG/200M	2220750	296100
HYDROCODONE BITARTARATE.2.5MG & ACET	5364250	2145700
HYDROCODONE BITARTRATE / ACETAMINOPH	15000	1500
HYDROCODONE BITARTRATE & ACETA 10MG/	12366000	1236600
HYDROCODONE BITARTRATE & ACETA 5MG/3	7313000	1462600
HYDROCODONE BITARTRATE & ACETA 7.5MG	98076675	13076890
HYDROCODONE BITARTRATE & ACETAMINOPH	51201750	6747400
HYDROCODONE BITARTRATE 10MG;ACETAMIN	151000	15100
HYDROCODONE BITARTRATE 10MG;GUAIFENE	82000	8200
HYDROCODONE BITARTRATE 10MG/ACETAMIN	293905800	29390580
HYDROCODONE BITARTRATE 5MG TAB	1650	330
HYDROCODONE BITARTRATE 5MG/ACETAMINO	64066900	12813380
HYDROCODONE BITARTRATE 7.5MG /ACETAM	75600	10080
HYDROCODONE BITARTRATE 7.5MG & ACETA	29246250	3899500
HYDROCODONE BITARTRATE 7.5MG/ACETAMI	80486250	10731500
HYDROCODONE BITARTRATE AND ACETA 10M	23923000	2392300
HYDROCODONE BITARTRATE AND ACETA 5MG	21405000	4281000
HYDROCODONE BITARTRATE AND ACETA 7.5	23453250	3127100
HYDROCODONE BITARTRATE AND ACETAMINO	7500	1000
HYDROCODONE BITARTRATE/ APAP TABLETS	20400	3080
HYDROCODONE BITARTRATE/ APAP TABS US	32250	4300
HYDROCODONE BITARTRATE/ACETA 2.5MG/3	250	100
HYDROCODONE BITARTRATE/ACETA 7.5MG/3	43074000	5743200
HYDROCODONE BITARTRATE/APAP 10MG/500	73178000	7317800
HYDROCODONE BITARTRATE/IBUPROFEN 5MG	8500	1700

HYDROCODONE BITARTRATE/IBUPROFEN 7.5	39000	5200
HYDROCODONE BITARTRATE/IBUPROPHEN 7.	21000	2800
HYDROCODONE.BIT & ACETA 10MG & 500M	159945500	15994550
HYDROCODONE.BIT 7.5MG/ACETAMINAOPHEN	21000	2800
HYDROCODONE.BIT. & ACETA 5MG & 500M	68102000	13620400
HYDROCODONE.BIT. & ACETA, 10MG & 500	18500	1850
HYDROCODONE.BIT./ACET.,10MG & 325MG/	369246500	36924650
HYDROCODONE.BIT/IBUPROFEN 10MG/200MG	525000	52500
HYDROCODONE.BITARTRATE 10MG & ACETAM	497000	49700
HYDROCODONE.BITARTRATE 10MG/APAP 650	18674000	1867400
HYDROCODONE.BITARTRATE 2.5MG/IBUPROF	3750	1500
HYDROCODONE.BITARTRATE 7.5MG/APAP 65	1872750	249700
HYDROCODONE.BITARTRATE 7.5MG/APAP 75	7008750	934500
HYDROCODONE.BITARTRATE/ACETA 10MG/50	1000	100
HYDROCODONE.BITARTRATE/IBUPROFEN 7.5	22134750	2951300
HYDROCODONE.BITRATRATE.10MG/ACETAMIN	13430000	1343000
HYDROCODONE/ACETAMINOPHEN 5MG/500MG	13909500	2781900
HYDROCODONE/APAP - 5MG/500MG TABLET	3000	600
HYDROCODONE/APAP 10MG/325MG - 10MG H	4200	420
HYDROCODONE/APAP 10MG/500MG TABLETS	12000	1200
HYDROCODONE/APAP 5MG/500MG TABLETS	594400	118880
HYDROCODONE/APAP 5MG/500MG (LORTAB G	4000	800
HYDROCODONE/APAP 7.5MG/200MG TABS.	1972500	263000
HYDROCODONE/IBUPROFEN 5MG/200MG TABL	127000	25400
HYDROCODONE/IBUPROFEN 7.5MG/200MG TA	22771500	3036200
IBUDONE HYDROCODONE BIT./IBUPROFEN 1	73800	7380
IBUDONE/HYDROCODONE BIT./IBUPROFEN	59900	11980
IBUDONE/HYDROCODONE BIT./IBUPROFEN T	85500	10400
LORCET HYD.BIT10MG/ACET650MG TAB	3543000	354300
LORCET HYD.BIT10MG/ACET650MG TAB (4	4000	400
LORCET PLUS HYDROCODO.BIT 7.5/ACET65	919500	122600
LORCET+ HYDROCODO.BIT7.5MG/ACET650MG	75000	10000
LORTAB 10 TAB HYDROCODO.BIT & AC	908000	90800
LORTAB 10MG/500MG/TAB,HYDROCOD.BIT.&	8922000	892200
LORTAB 5 HYDROCODO/AC TAB	996500	199300
LORTAB 7.5 HYD.BIT/AC TAB	718500	95800
LORTAB 7.5MG HYDROCODONE.BIT / 500MG	4953000	660400
MAXIDONE;HYDROCODONE BIT./ACET.,10MG	45000	4500
NORCO 5/325;5MG HYDROCOD.BIT. & 325M	149500	29900
NORCO HYDROCODO.BIT./ACET.,10MG & 32	2009000	200900
NORCO TAB - HYDROCODONE BIT/ACETA 10	455000	45500

NORCO TAB - HYDROCODONE BIT/ACETA 7.	207750	27700
NORCO;7.5MG HYDROCOD.BIT.+ 325MG ACE	379500	50600
P-V-TUSSIN TABS;5MG HYDROCODO.BIT. &	17500	3500
PNEUMOTUSSIN TABS;2.5MG HYDROCOD.BIT	1000	400
REPREXAIN - HYDROCODONE BIT./IBUPROP	985175	127050
REPREXAIN - HYDROCODONE.BIT. 5MG/IBU	3600	720
REPREXAIN (HYDROCODONE BITARTRATE/IB	7000	700
TUSSEND;5MG HYDROCOD.BIT./TAB	1000	200
TUSSIGON 5MG HYD.BIT&HOMA MBR 1.5MG/	1151000	230200
TUSSO HC HYDRO.BIT.10MG;GUAIF.1200MG	2000	200
VICODIN ES HYDROCODONE BITRATE/ACETA	1053750	140500
VICODIN ES TABLETS 7.5MG HYDROCODONE	5898750	786500
VICODIN HP HYDROCODONE BITARTRATE/AC	1418000	141800
VICODIN HP TABLETS 10MG HYDROCODONE.	2366000	236600
VICODIN HYDROCODONE BITARTRATE/ACETA	797000	159400
VICODIN TABLETS 5MG HYDROCODONE.BIT	756235	151247
VICOPROFEN TABLETS 7.5MG HYDROCODONE	1156500	154200
VICOPROFEN;7.5MG HYDROCOD.BIT.& 200M	1800	240
XODOL - HYDROCODONE.BIT 10MG & ACETA	929200	92920
XODOL 5MG HYDRO. BIT.;300MG ACET. TA	354000	70800
XODOL 7.5/300MG HYDROCODONE.BIT. & A	108750	14500
XODOL 7.5MG HYDROCODONE BIT. ;300MG	678750	90500
XODOL HYDROCODONE.BITARTRATE 5MG/ACE	167000	33400
XODOL- HYDROCODONE BIT/APAP 10MG/300	17000	1700
XODOL- HYDROCODONE BIT/APAP 5MG/300M	1500	300
XODOL- HYDROCODONE BIT/APAP 7.5MG/30	8250	1100
XODOL;10MG HYDRO.BIT.;300MG ACET. TA	2507000	250700
XPECT-HC/HYDRO.BIT.5MG/GUAIFENESIN 6	35300	7060
ZTUSS/HYDRO.BIT.5MG/PSEUDOE.HC30MG/G	4000	800
ZYDONE TABS;10MG HYDROCOD.BIT.& 400M	4503000	450300
ZYDONE TABS;5MG HYDROCOD.BIT.& 400MG	211500	42300
ZYDONE TABS;7.5MG HYDROCOD.BIT.& 400	1719750	229300

Supplemental Table 3. Generic extended-release oxycodone products shown in Figure 2, measured via total dosage units and morphine milligram equivalents (MMEs) shipped to West Virginia for 2006-2014.

Product_Name	MME	Dosage_Units
OXYCOD.HCL ER TABS;10MG/TAB	1582500	105500
OXYCOD.HCL ER TABS;20MG/TAB	4455000	148500
OXYCOD.HCL ER TABS;40MG/TAB	7254000	120900
OXYCOD.HCL ER TABS;80MG/TAB	1848000	15400
OXYCODONE 10MG ER TABLETS	90000	6000
OXYCODONE 20MG ER TABLETS	279000	9300
OXYCODONE 40MG ER TABLETS	792000	13200
OXYCODONE 80MG ER TABLETS	936000	7800
OXYCODONE HCL 10MG ER TABLET	6000	400
OXYCODONE HCL 10MG ER TABLETS	13500	900
OXYCODONE HCL 20 MG ER TABLETS	33000	1100
OXYCODONE HCL 20MG ER TABLETS	1755000	58500
OXYCODONE HCL 40MG ER TABLET	30000	500
OXYCODONE HCL 40MG ER TABLETS	54000	900
OXYCODONE HCL 80MG ER TABLET	12000	100
OXYCODONE HCL 80MG ER TABLETS	96000	800
OXYCODONE HYDRCHLORIDE 40MG EXTENDED	34134000	568900
OXYCODONE HYDROCHLORIDE - ER - 80MG/	37704000	314200
OXYCODONE HYDROCHLORIDE EXTENDED REL	4671000	311400
OXYCODONE HYDROCHLORIDE EXTENDED-REL	18843000	628100
OXYCODONE.HCL ER 10MG TABS	2146500	143100
OXYCODONE.HCL ER 20MG TABS	8127000	270900
OXYCODONE.HCL ER 40MG TABS	16116000	268600
OXYCODONE.HCL ER 80MG TABS	11940000	99500
OXYCODONE.HCL ER TABS;80MG/TAB	756000	6300

Supplemental Table 4. Generic non-extended-release oxycodone products shown in Figure 2, measured via total dosage units and morphine milligram equivalents (MMEs) shipped to West Virginia for 2006-2014.

Product_Name	MME	Dosage_Units
ACET/OXYCOD.HCL;500MG&5.35MG/TAB	817747.5	101900
OXYCOD.HCL IR TABS;5MG/TAB	303000	40400
OXYCOD.HCL/APAP TABS;7.5MG & 500MG/T	549000	48800
OXYCOD.HCL/APAP;10MG & 650MG/TAB,BOT	3139500	209300
OXYCOD.HCL/APAP;2.5MG & 325MG/TAB;BO	117000	31200
OXYCODO.HCL 5.35MG/TAB	5034885	627400
OXYCODONE & ACETAMINOPHEN 10MG/325MG	129000	8600
OXYCODONE AND ACETA 7.5MG/325MG USP	6996375	621900
OXYCODONE AND ACETA 10MG/325MG TABLE	25446000	1696400
OXYCODONE AND ACETA 7.5MG / 500MG TA	19280250	1713800
OXYCODONE AND ACETAMINOPHEN 10MG/325	307500	20500
OXYCODONE AND ACETAMINOPHEN 7.5MG/32	2176875	193500
OXYCODONE HCI 20 MG TABLETS USP	73062000	2435400
OXYCODONE HCI 10MG TABLETS USP	92359500	6157300
OXYCODONE HCI 5MG TABLETS	23661750	3154900
OXYCODONE HCI/APAP 5/325MG TABLETS	18000	2400
OXYCODONE HCL & ACETA 10MG/325MG USP	789000	52600
OXYCODONE HCL & ACETA 5MG/325MG USP	102000	13600
OXYCODONE HCL & ACETA 7.5MG/325MG US	279000	24800
OXYCODONE HCL & IBUPROPHEN 5MG/400MG	158250	21100
OXYCODONE HCL & NIACIN 7.5MG/30MG US	18000	1600
OXYCODONE HCL 10MG CR TABLETS	427500	28500
OXYCODONE HCL 10MG IR TABLET	25068000	1671200
OXYCODONE HCL 10MG IR TABS	802500	53500
OXYCODONE HCL 10MG TABLET USP; 10 X	4500	300
OXYCODONE HCL 10MG TABLET USP; 100 T	15000	1000
OXYCODONE HCL 10MG TABLETS	96000	6400
OXYCODONE HCL 10MG TABS	4939500	329300
OXYCODONE HCL 10MG USP TABLETS	127500	8500
OXYCODONE HCL 15MG IR TABLET	164250	7300
OXYCODONE HCL 15MG IR TABS	13578750	603500
OXYCODONE HCL 15MG TABLET USP; 100 T	132750	5900
OXYCODONE HCL 15MG TABLETS	28235250	1254900
OXYCODONE HCL 15MG TABLETS, 100 CT	179892000	7995200
OXYCODONE HCL 15MG TABLETS, 100CT	272250	12100
OXYCODONE HCL 15MG TABLETS, USP	35113500	1560600

OXYCODONE HCL 15MG USP TABLETS	251417250	11174100
OXYCODONE HCL 20MG CR TABLETS	21000	700
OXYCODONE HCL 20MG IR BLEND TABS	984000	32800
OXYCODONE HCL 20MG IR TABLET	19824000	660800
OXYCODONE HCL 20MG TABLET USP; 100 T	111000	3700
OXYCODONE HCL 20MG TABLETS	534000	17800
OXYCODONE HCL 20MG USP TABLETS	234000	7800
OXYCODONE HCL 30MG IR TABLET	153000	3400
OXYCODONE HCL 30MG IR TABS	20614500	458100
OXYCODONE HCL 30MG TABLET USP; 100 T	679500	15100
OXYCODONE HCL 30MG TABLETS	45859500	1019100
OXYCODONE HCL 30MG TABLETS, 100 CT	368158500	8181300
OXYCODONE HCL 30MG TABLETS, 100CT	261000	5800
OXYCODONE HCL 30MG TABLETS, USP	56281500	1250700
OXYCODONE HCL 30MG USP TABLETS	531652500	11814500
OXYCODONE HCL 40MG CR TABLETS	60000	1000
OXYCODONE HCL 40MG TABS	43866000	731100
OXYCODONE HCL 5MG IR TABLET	240750	32100
OXYCODONE HCL 5MG TABLET USP; 10 X 1	111750	14900
OXYCODONE HCL 5MG TABLET USP; 100 TA	42750	5700
OXYCODONE HCL 5MG TABLETS	4566750	608900
OXYCODONE HCL 5MG TABLETS, 100CT	42000	5600
OXYCODONE HCL 5MG TABLETS, USP	9674250	1289900
OXYCODONE HCL 5MG USP TABLETS	21885750	2918100
OXYCODONE HCL 5MG/IBUPROFEN 400MG TA	237750	31700
OXYCODONE HCL 80MG CR TABLETS	144000	1200
OXYCODONE HCL 80MG TABS	39948000	332900
OXYCODONE HCL AND ASPIRIN 4.8355MG/3	195112.425	26900
OXYCODONE HCL USP & IBUPROFEN 5MG/40	109500	14600
OXYCODONE HCL/ACETAMINOPHEN 10MG/325	447124500	29808300
OXYCODONE HCL/ACETAMINOPHEN 10MG/650	8418000	561200
OXYCODONE HCL/ACETAMINOPHEN 2.5MG/32	223500	59600
OXYCODONE HCL/ACETAMINOPHEN 5MG/325M	403299000	53773200
OXYCODONE HCL/ACETAMINOPHEN 7.5MG/32	108936000	9683200
OXYCODONE HCL/ACETAMINOPHEN 7.5MG/50	2665125	236900
OXYCODONE HCL/ACETAMINOPHEN TABLET U	4084500	544600
OXYCODONE HCL/ACETAMINOPHEN TABS 10M	146827500	9788500
OXYCODONE HCL/ACETAMINOPHEN TABS 5MG	33074250	4409900
OXYCODONE HCL/ACETAMINOPHEN TABS. 10	24906000	1660400
OXYCODONE HCL/ACETAMINOPHEN TABS. 7.	2730375	242700
OXYCODONE HCL/ASPIRIN 4.8355/325MG T	163198.125	22500

OXYCODONE HYDROCHLORIDE 10MG TABLETS	453000	30200
OXYCODONE HYDROCHLORIDE 15MG TABLET	69750	3100
OXYCODONE HYDROCHLORIDE 15MG TABLETS	281826000	12525600
OXYCODONE HYDROCHLORIDE 20MG TABLETS	1782000	59400
OXYCODONE HYDROCHLORIDE 20MG TABS.	6174000	205800
OXYCODONE HYDROCHLORIDE 30MG TABLET	710356500	15785700
OXYCODONE HYDROCHLORIDE 40MG TABLETS	3660000	61000
OXYCODONE HYDROCHLORIDE 40MG TABS.	11334000	188900
OXYCODONE HYDROCHLORIDE 5MG TABS USP	797250	106300
OXYCODONE HYDROCHLORIDE 5MG&ACETAMIN	15054000	2007200
OXYCODONE HYDROCHLORIDE 80MG TABLETS	4368000	36400
OXYCODONE HYDROCHLORIDE 80MG TABS.	13320000	111000
OXYCODONE HYDROCHLORIDE CONTROLLED R	144000	2800
OXYCODONE HYDROCHLORIDE CR 20MG TABL	20343000	678100
OXYCODONE HYDROCHLORIDE TABLETS 5MG	81765000	10902000
OXYCODONE HYDROCHLORIDE TABLETS USP	152565750	6780700
OXYCODONE HYDROCHLORIDE TABS. 10MG	1006500	67100
OXYCODONE HYDROCHLORIDE USP 30MG TAB	232398000	5164400
OXYCODONE.HCL 10MG / APAP 650MG TABL	89059500	5937300
OXYCODONE.HCL 5MG IR (10 X 10 BLISTE	22500	3000
OXYCODONE.HCL 5MG IR TAB	2973750	396500
OXYCODONE.HCL/APAP 10MG/325MG TABS	166764000	11117600
OXYCODONE.HCL/APAP 7.5MG/325MG TABS	37197000	3306400
OXYCODONE.HCL/APAP TABLETS, 7.5MG/50	17239500	1532400
OXYCODONE/APAP 5MG/325MG TABS.	10125	1350

Supplemental Table 5. OxyContin products shown in Figure 2, measured via total dosage units and morphine milligram equivalents (MMEs) shipped to West Virginia for 2006-2014. Bolded rows denoted abuse-deterrent formulations.

Product_Name	MME	Dosage_Units
OXYCONTIN - 10MG OXYCODONE.HCL CONTR	14522400	968160
OXYCONTIN - 40MG OXYCODONE.HCL CONTR	232012800	3866880
OXYCONTIN - 80MG OXYCODONE.HCL CONTR	290431200	2420260
OXYCONTIN (OXYCODONE.HCL) CONTROLLED	76090950	2536365
OXYCONTIN 10MG OXYCODONE HCL CR TABL	**19325400**	**1288360**
OXYCONTIN 15MG CONTROLLED RELEASE OX	1512000	67200
OXYCONTIN 15MG OXYCODONE HCL CR TABL	**6472800**	**287680**
OXYCONTIN 20MG OXYCODONE HCL CR TABL	**62755800**	**2091860**
OXYCONTIN 30MG COTROLLED RELEASE OXY	18346500	407700
OXYCONTIN 30MG OXYCODONE HCL CR TABL	**38507400**	**855720**
OXYCONTIN 40MG OXYCODONE HCL CR TABL	**123261600**	**2054360**
OXYCONTIN 60MG COTROLLED RELEASE OXY	48069000	534100
OXYCONTIN 60MG OXYCODONE HCL CR TABL	**68443200**	**760480**
OXYCONTIN 80MG OXYCODONE HCL CR TABL	**189686400**	**1580720**

Supplemental Table 6. Brand name oxycodone products (other than OxyContin) shown in Figure 2, measured via total dosage units and morphine milligram equivalents (MMEs) shipped to West Virginia for 2006-2014.

Product_Name	MME	Dosage_Units
COMBUNOX - 5MG / 400MG OXYCODONE.HCL	1065000	142000
ENDOCET - 10MG OXYCODONE.HCL/325MG A	243274500	16218300
ENDOCET - 7.5MG OXYCODONE.HCL/325MG	35419500	3148400
ENDOCET OXYCODO HCL5MG&AC TAB	34386000	4584800
ENDOCET TABS - 10MG OXYCODONE.HCL &	140868000	9391200
ENDOCET TABS;7.5MG OXYCODONE.HCL & 5	18250875	1622300
ENDODAN OXYCODONE & ASP, USP 4.8355M	501199.575	69100
MAGNACET 10MG/400MG OXYCODONE HCL/AC	885000	59000
MAGNACET 5MG/400MG OXYCODONE HCL/ACE	3000	400
MAGNACET 7.5MG/400MG OXYCODONE HCL/A	43875	3900
MAGNACET TM /OXYCODONE 10MG;ACET.400	361500	24100
MAGNACET TM OXYCODONE 2.5MG ACET. TA	3750	1000
MAGNACET TM OXYCODONE 5MG;ACETA. 400	27000	3600
MAGNACET TM OXYCODONE 7.5MG;ACET.400	65250	5800
MAGNACET-OXYCODONE HCL/APAP 10MG/400	1500	100
PERCOCET (OXYCODONE HCL/ACETA) 5MG/3	2325000	310000
PERCOCET TABLETS 10MG OXYCODONE HCL/	8898000	593200
PERCOCET TABLETS OXYCODONE HCL 7.5MG	929250	82600
PERCODAN - 4.8355MG OXYCODONE.HCL &	455504.1	62800
PERLOOX OXYCODONE.HCL 5MG/ACETAMINOP	12750	1700
PERLOXX OXYCODONE.HCL 10MG/ACETAMINO	40500	2700
PERLOXX OXYCODONE.HCL 7.5MG/ACETAMIN	9000	800
PRIMALEV OXYCODONE HCL 10MG & ACETA	109500	7300
PRIMALEV OXYCODONE HCL 2.5MG & ACETA	375	100
PRIMALEV OXYCODONE HCL 5MG & ACETA 3	27000	3600
PRIMALEV OXYCODONE HCL 7.5MG & ACETA	4500	400
PRIMLEV - OXYCODONE HCI/ACETAMINOPHE	25875	1800
ROXICET - OXYCODONE.HCL & ACETA 5MG/	18892500	2519000
ROXICODONE - 15MG OXYCODONE HCL TABL	69750	3100
ROXICODONE - 30MG OXYCODONE HCL TABL	715500	15900
ROXICODONE (OXYCODONE HCI);30MG;100	1944000	43200
ROXICODONE (OXYCODONE HCL) 15MG TABS	2772000	123200
ROXICODONE (OXYCODONE HCL) 30MG TABS	7137000	158600
ROXICODONE (OXYCODONE HCL) 5MG TABS.	381750	50900
ROXICODONE 5MG TAB	17250	2300

ROXICODONE TABS;15MG OXYCODONE.HCL/T	182250	8100
ROXICODONE TABS;30MG OXYCODONE.HCL/T	369000	8200
ROXICODONE TABS.;(OXYCODONE HCl);15M	1599750	71100
ROXICODONE TABS.(OXYCODONE HCl);5MG;	92250	12300
ROXILOX OXYCO HCL 5MG &ACE500MG TAB	3714750	495300
XARTEMIS XR - OXYCODONE HCL/ACETA 7.	142875	12700
XOLOX - OXYCODONE HCL/ACETA 10MG/50	55500	3700

Chapter 4

Forecasting US opioid overdose deaths: A comparison of time series methods

Abstract

Introduction: Opioid-involved overdose fatalities are a major contributor to U.S. mortality and present a significant challenge to the nation's public health infrastructure. Time series forecasting has been used to predict future trends in fatal opioid overdose. However, few studies have compared forecasting methods when applied to US opioid overdose rates. Thus, the objective of this study was to examine the predictive accuracy of forecasts generated via different time series models when applied to US opioid overdose mortality data.

Methods: Monthly opioid-involved overdose mortality data for 1999 to 2019 were extracted from CDC WONDER. The forecasting performance of ARIMA (Autoregressive Integrated Moving Average), ETS (Error, Trend, and Seasonality), and Facebook Prophet models was assessed using time series cross validation. Forecast bias was evaluated using mean average percent error (MAPE). Forecast coverage probability was assessed via Winkler scores, which measures a prediction interval's ability to include true values while preserving precision. Forecasts were assessed both overall and stratified by type of opioid involved.

Results: While ARIMA modeling provided most accurate forecasts overall, each model delivered accurate forecasts before fentanyl-involved overdoses began increasing in 2014. From 2014 onward, ETS models delivered best predictive coverage probability, including for heroin and fentanyl. Prophet models underperformed relative to ARIMA and ETS.

Conclusion: ETS models delivered best predictive coverage probability of US opioid-involved overdose rates, including adjusting after large surges in overdoses associated with illicitly manufactured fentanyl. This implies that this approach adapts well to unexpected shifts in overdose rates. Future research should consider ETS modeling when planning for future resource allocation related to drug overdose mortality.

Introduction

The United States (US) opioid epidemic is one of the nation's most pressing public health emergencies. The crisis has placed a significant burden on the nation's public health (Gomes et al. 2018), healthcare (Hsu et al. 2017), and economic (Florence et al. 2021) infrastructures, with more than 500,000 opioid-involved overdose deaths occurring since 1999 (Centers for Disease Control and Prevention 2022). The epidemic has been characterized by temporally distinct waves, each defined by specific classes or combinations of prescription or illicit drugs driving overdoses (Ciccarone 2019; Jenkins 2021). Introduction of the potent synthetic opioid fentanyl, the cost and availability of prescription opioids, and poor availability of opioid use disorder treatment have resulted in rapidly changing patterns of drug overdoses (Congressional Budget Office 2022; Gladden et al. 2016; Winstanley et al. 2020). This has made it difficult for public health practitioners to project resource needs associated with the prevention of future overdoses.

One method for predicting future overdose rates is time series forecasting, which statistically models historical data to predict future rates of events (Hyndman and Athanasopoulos 2021a). Published researched has demonstrated this approach's ability to accurately forecast opioid overdose rates at the zip code (Bauer et al. 2023), county (Marks et al. 2021), and state level (Mukherjee et al. 2020□). A number of studies have produced forecasts of national opioid overdose rates with the goal of aiding in national policy planning and resource allocation, including using advanced forecasting methods such as (Sumner et al. 2022). In addition, few studies have assessed national forecast accuracy stratified by opioid type (e.g., prescription opioids, heroin, fentanyl, etc.), limiting information on the applicability of forecasting methods to different substance use scenarios. Moreover, studies of national overdose forecasts often omit information pertaining to their forecasts' prediction intervals, which give an impression of a forecast's uncertainty (Christoffersen 1998). Specifically, these studies do not assess prediction coverage probability (Matero et al. 2023; Sumner et al. 2022), which is the capability of a forecast's prediction interval to include actual/observed future values. Doing so would give researchers and public health stakeholders information on how well their forecasting methods can predict future rates of disease.

To address limitations in extant opioid forecasting literature, including a lack of comparative time series analysis and the exclusion of prediction coverage probability assessment, we report findings from a comparative forecasting analysis. We compared the ability of three time series models (autoregressive integrated moving average (ARIMA), state-space exponential smoothing (ETS), and Facebook Prophet) to generate 24-month forecasts of U.S. opioid-involved poisoning mortality rates, both overall and stratified by type of opioid involved. In addition to assessing forecast accuracy using traditional approaches, we measured each forecast's prediction coverage probability using Winkler Scores, which measure a forecast prediction interval's ability to include actual/observed values while maintaining relative precision.

Methods

Data source

Monthly opioid-involved poisoning death counts for 1999-2019 were obtained from the CDC WONDER database, which compiles mortality data collected through state death certificate registries (Centers for Disease Control and Prevention 2022). While opioid-related poisoning mortality data for 2020 was available at the time of analysis, previous literature indicates that extant forecasting approaches did not anticipate the large increase in overdose rates that occurred

during the COVID-19 pandemic due to the disruption of healthcare services (Cartus et al. 2022). As the goal of this study was to inspect forecasting accuracy and precision, and not to quantify the impact of the pandemic on poisoning rates, including 2020 would have detracted from our study's aim and been of limited value. Opioid-involved poisoning deaths were defined as those with an ICD-10 underlying cause of death (UCOD) code listed as drug poisoning and an ICD-10 multiple cause of death (MCOD) code listed as poisoning by opium, heroin, other opioids (largely prescription opioids excluding methadone, hereafter labeled "prescription opioids"), methadone, other synthetic narcotics (largely fentanyl and its analogs, hereafter labeled "fentanyl"), or unspecified narcotics. Since CDC WONDER does not report population or age-adjusted rates at the monthly level, monthly all-cause mortality for 1999-2019 was used to calculate the rate of opioid-related overdoses per 1,000 fatality rates.

Statistical Analysis

All statistical analyses were conducted using RStudio version 2022.07.2+576 (Rstudio Team 2022). Time series modeling and forecasting was conducted using the 'fable'(O'Hara-Wild et al. 2021a) and 'fabletools'(O'Hara-Wild et al. 2021b) Rstudio packages. Three time series approaches were compared in this study: autoregressive integrated moving average (ARIMA) (Hyndman and Athanasopoulos 2021g), state-space exponential smoothing (ETS) (Hyndman and Athanasopoulos 2021f), and Facebook Prophet (Taylor and Letham 2018) modeling. Each method was used to model overall monthly total opioid-involved overdose mortality and overdose mortality stratified by ICD-10 MCOD codes; opium is associated with a negligible number of deaths in the US (<10 annually) and was therefore excluded from our stratified analysis. Each of these models is described below:

Autoregressive integrated moving average (ARIMA) modeling is a common approach for modeling data showing autocorrelation in which a time series is regressed on its previous, or lagged, values and error terms through autoregressive (AR) and moving average (MA) processes, respectively. In addition, non-stationarity of a time series, or changes in mean or variance over time, is controlled through differencing. Let Y_t be the opioid-involved poisoning mortality rate at $t = 1, 2, \ldots T$, where T is the length of the time series. In full, a time series may be modeled via ARIMA through the equation:

$$Y_t = c + (\phi_1 Y_{t-1} + \phi_2 Y_{t-2} + \cdots + \phi_p Y_{t-p}) + e_t - (\theta_1 e_{t-1} + \theta_2 e_{t-2} + \cdots + \theta_q e_{t-q})$$

where c is a constant or model intercept; ϕ_p and θ_q are parameters of the model for the AR and MA components, respectively; e is random noise at time t; and p and q denote the lag terms for the AR and MA components, respectively. Additionally, ARIMA models may be expanded to include seasonally lagged autocorrelation, differencing, or moving error terms denoted by P, D, and Q, respectively.

State-space exponential smoothing (ETS) models (also known as error, trend, and seasonality models) incorporate information on how the components of a time series (i.e., error, trend, and seasonality) interacts with one another. An advantage of ETS models is their state space form, which incorporates different types of error, trend, and seasonality. A framework for defining state pace ETS models, proposed by Hyndman, is based on whether each term is additive (A), multiplicative (M), or not present (N); additive terms are constant whereas multiplicative terms increase or decrease in amplitude throughout a time series (Hyndman and Athanasopoulos 2021b). Additionally, trend terms can be additive or multiplicative damped

(denoted by Ad and Md, respectively), referring to a slowing of a time series trend. As previously, let Y_t be the opioid-related overdose rate at month *t*. A time series may be modeled via ETS through the nested equations:

$$Y_t = w(v_{t-1} - 1) + r(v_{t-1} - 1)e_t$$

$$v_t = f(v_{t-1} - 1) + g(v_{t-1} - 1)e_t$$

where v_t is the state vector containing trend and seasonal components; $w(v_{t-1} - 1)$ is measurement function representing different types of seasonality and trend; $f(v_{t-1} - 1)$ is the transition function indicating how the model's trend, seasonality, and error components interact; and $g(v_{t-1} - 1)$ is the persistence function, which is a vector of smoothing parameters indicating how responsive the model is to changes in the data. The $r(v_{t-1} - 1)$ function represents model error, with additive error taking the form $r(v_{t-1} - 1) = 1$ and multiplicative error takes the form $r(v_{t-1} - 1) = w(v_{t-1} - 1)$. There are 30 possible ETS model structures based on different types of error, trend, and seasonality, each of which have been described in mathematical detail elsewhere (Hyndman and Athanasopoulos 2021b).

Facebook Prophet models were first introduced by Facebook in 2017 as the corporation's solution for forecasting "at-scale" or forecasting in a within a wide variety of settings and disciplines (Taylor and Letham 2018). As previously, let Y_t be the opioid-related overdose rate at month t. The prophet model would take the following form:

$$Y_t = g(t) + s(t) + h(t) + e_t$$

where *g(t)* is the trend function (taking the form of either additive, multiplicative, or no trend), *s(t)* denotes seasonality, *h(t)* is a holiday function (i.e., regularly predictable outliers which are not accounted for by seasonal fluctuation), and e_t is the error term. The trend term *g(t)* is composed of changepoints, which allows for piecewise linear regression (Hyndman and Athanasopoulos 2021c). Additionally, the seasonal term *s(t)* is modeled via a pre-specified (default of ten) number of Fourier transformations, which allows for a high degree of flexibility in modeling periodicity (Hyndman and Athanasopoulos 2021c). To produce Prophet models of monthly opioid-related overdose data, we used the 'fable.prophet' Rstudio package (O'Hara-Wild et al. 2022), which extends use of the 'fable' (O'Hara-Wild et al. 2021a) and 'fable.tools' (O'Hara-Wild et al. 2021b) to the package 'prophet'; the 'prophet' package automatically selects changepoints, seasonality, and other model attributes automatically using a Bayesian approach (Taylor and Letham 2022).

We used a time series cross validation (TSCV) to evaluate each model's forecasting ability (Hyndman and Athanasopoulos 2021d). We used a starting test set of five years and forecast length 24 months of data, increasing the training set length by one month per forecast for a total of 157 forecasts per dataset; the TSCV process is explained in detail in Supplementary Figure S1. To further improve forecasting validity within our, framework, modeling parameters were selected separately for each forecast and models were generated/selected automatically using the 'forecast' package, which selects an optimal model by minimizing Akaike information criteria (AIC) (O'Hara-Wild et al. 2021a). Forecast bias was evaluated by calculating mean average percent error (MAPE), given by the equation:

$$MAPE = \frac{\sum_{t=1}^{h} \frac{|X_t - \hat{X}_t|}{X_t} \times 100}{h}$$

where X_t is the actual value of a time series' test set, $\hat{X}_t$ is the forecast value, and h is the total number of observations forecast. One advantage of MAPE is that it is not scale-dependent, meaning it can be compared across forecasts of time series from different dependent variables. Statistical predictive coverage probability of each model was assessed via mean 95% CI width, percent coverage (i.e., what percent of observed values are included in a forecast's 95% CI), and Winkler scores. Winkler scores assess interval accuracy by assigning penalties to forecasts based on how far outside of a specified interval an observed value lies, with a greater distance from the interval equating to a greater penalty; Winkler scores of forecast distributions that include the observed value are simply the length of the interval. The mathematics of Winkler score calculations have been specified elsewhere (Hyndman and Athanasopoulos 2021e; Winkler 1972). Winkler scores are scale-dependent and cannot be compared across models with different dependent variables.

Results

Graphical representation of monthly US opioid-related overdose fatality deaths per 1,000 all-cause mortality is presented in Figure 1. Prescription opioid overdoses occurred at the highest rate until approximately 2014, when heroin and fentanyl were responsible for the majority of opioid-involved overdoses. While each model accurately forecasted national overdose mortality throughout the first decade assessed, each under-estimated overdose rates from 2014 onward (Figure 2). Despite this, ARIMA and ETS delivered most accurate forecasts from 2014 on (MAPE = 10.6 and 10.8 for ARIMA and ETS, respectively), while ETS provided best coverage probability (Winkler score = 15.1).

ARIMA provided most accurate point forecasts of total/any opioid overdose rates; ETS provided most precise prediction intervals for this category, indicated by lowest Winkler scores (Table 1). Stratified by MCOD code, prescription opioid forecasts had highest point accuracy, while fentanyl forecasts were least accurate. For all MCOD strata, ETS-generated forecasts had the most precise probability coverage, indicated by lowest Winkler scores (Table 2). Similar bias and predictive coverage probability patterns were observed when analysis was stratified by state-level drug death reporting specificity (supplementary tables S1 and S2).

Figures 3A and 3B display forecast accuracy and coverage probability throughout 24-month forecasts, respectively. ARIMA had lowest MAPE throughout 95.8% of 24-month forecasts for total opioid-involved drug deaths and throughout 100% of 24-month forecasts for heroin. ARIMA and ETS has lowest MAPE throughout 75% and 25% of other and synthetic narcotics 24-month forecasts, respectively. Prophet and ARIMA modeling had lowest MAPE for 75% and 16.7% of methadone overdose forecasts, respectively, while Prophet and ETS modeling provided lowest MAPE for 66.7% and 33.3% of forecasts for other and unspecified narcotics, respectively. ETS had best coverage probability throughout 24-month forecasts for all strata, with the exception other and unspecified narcotics, for which ARIMA modeling had lowest Winkler score throughout 54.2% of 24-month forecasts. Prophet modeling produced highest Winkler scores throughout all 24-month forecasts.

Discussion

This study provides a rigorous assessment of three time series models in their ability to forecast national 24-month opioid-involved overdose death rates. We evaluated forecasts both in terms of point accuracy and predictive coverage probability, which is often omitted from opioid overdose forecasting studies. While ARIMA modeling provided most accurate point estimates of national total opioid-related overdoses (Table 1), ETS provided best predictive coverage probability (Table 2; Figure 3B). This general pattern was observed overall, as well as stratified by the type of opioid involved in overdoses (Table 2) and state-level drug death reporting specificity (Supplemental Table S2).

Throughout the first decade assessed (2004-2013), each model forecasted overdose rates with relative accuracy (Figure 2). During this period, overdoses were primarily driven by prescription opioids, which increased steadily until approximately 2011 (Figure 1). Methadone, which was similarly well-forecasted, decreased steadily throughout the forecast period after initially increasing in 1999-2006. Prescription opioids and methadone supplies mostly originate from licit sources, such as pharmacies and medication-assisted treatment programs, respectively, which change slowly relative to shifts in illicit drug supplies. Conversely, published research indicates that increases in fentanyl overdoses during epidemic's third wave (beginning in 2014) were principally attributable to a large, sudden increase in drug lethality associated with introduction of illicit fentanyl into the the US beginning in 2013 (Gladden et al. 2016; Rosenblum et al. 2020). The concomitant increase in fentanyl-related overdose deaths in 2014 was sudden relative to changes in prescription opioid and methadone overdoses; this is likely why forecasts were least accurate for fentanyl. As time series forecasts are generated using historical data,

Given the sudden nature of the fentanyl-dominated phase of the epidemic, it is notable that ETS-generated forecasts consistently provided higher precision as assessed from winker scores during this period and were the fastest model to adjust to the sudden change represented by the introduction of lethal fentanyl. As a forecast's 95% prediction interval represents a range of statistically likely future outcomes (Christoffersen 1998), this finding has important implications towards resource planning, particularly as synthetic opioid overdoses continue to rise and use of non-opioid substances, such as psychostimulants, begin driving new waves of the epidemic (Dai et al. 2022; Jenkins 2021). ETS's ability to adapt to the fentanyl transition period may be related to its state-space form, which includes transition and persistence functions, which determine how different time series components (i.e., error, trend, and seasonality) interact and adapt to changes in time series data (Hyndman and Athanasopoulos 2021f).

As noted, we did not extend our analysis into the COVID -19 pandemic (March 2020 and beyond). Opioid overdoses increased drastically during this unprecedented and unexpected event due to increased drug use in isolation and a large shift in resource allocation away from overdose prevention (Ghose et al. 2022). It is likely that ETS will be the model that adjusts fastest to this sudden change. As time series forecasting uses historical data to predict future rates of events, erroneous predictions in the presence of unexpected events are a noted limitation of the field (Naess et al. 2015). As noted, this is likely why fentanyl forecasts were least accurate in our study. However, forecasting can still be useful in such situations; using a forecast to represent a counterfactual scenario, excess burden associated with an unanticipated event can be estimated. In fact, Cartus et al. used this approach to estimate excess opioid overdose fatalities associated with the COVID-19 pandemic (Cartus et al. 2022). While studies using this approach often use fixed origin forecast validation (Inada et al. 2021), TSCV is preferred as it creates a more reliable

depiction of pre-event, and therefore "expected" post-event trends (Borrego-Morell et al. 2021; Nguyen et al. 2022; Schleimer et al. 2021).

In addition to its strengths, such as the use TSCV, comparisons of multiple models, and individual drug involvement stratification, our study has several limitations. One limitation is lack of inclusion of spatial dependence, where states who share common borders have similar death reporting standards; the inclusion of this characteristic would likely improve our forecasting accuracy. Previous studies have accounted for this by including spatiotemporal data through a variety of techniques, including Bayesian and machine learning methods (Campo et al. 2020; Hepler et al.). Second, the methods used to compare between time series models did not include measures of statistical significance. This prevented us from determining whether one method better predicted opioid-involved mortality. Finally, we did not include temporal changes in important drivers of overdose mortality, such as socioeconomic trends, access to evidence-based harm reduction, or polysubstance use. Including such data as has been done in other modeling studies (Irvine et al. 2022), would likely improve forecasting accuracy and expound upon the roles each plays in temporal patterns of drug overdose mortality. Future research directions include incorporating these into modeling approaches, as well as comparing the models used in our study to more complex approaches, including machine learning and ensemble modeling.

Conclusions

Given the marked role of opioid overdoses in driving US mortality, it is imperative that public health stakeholders are provided with accurate overdose forecasts. We assessed three time series modeling approaches in their ability to forecast opioid overdose mortality. While each model provided adequate forecasts before the introduction of fentanyl, ETS forecast prediction intervals captured the temporal volatility associated with the fentanyl era while maintaining relative precision. This suggests ETS models may estimate a range of future opioid overdose rates with potential to aid in resource allocation planning and can more quickly adjust for sudden dramatic changes.

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Tables and Figures

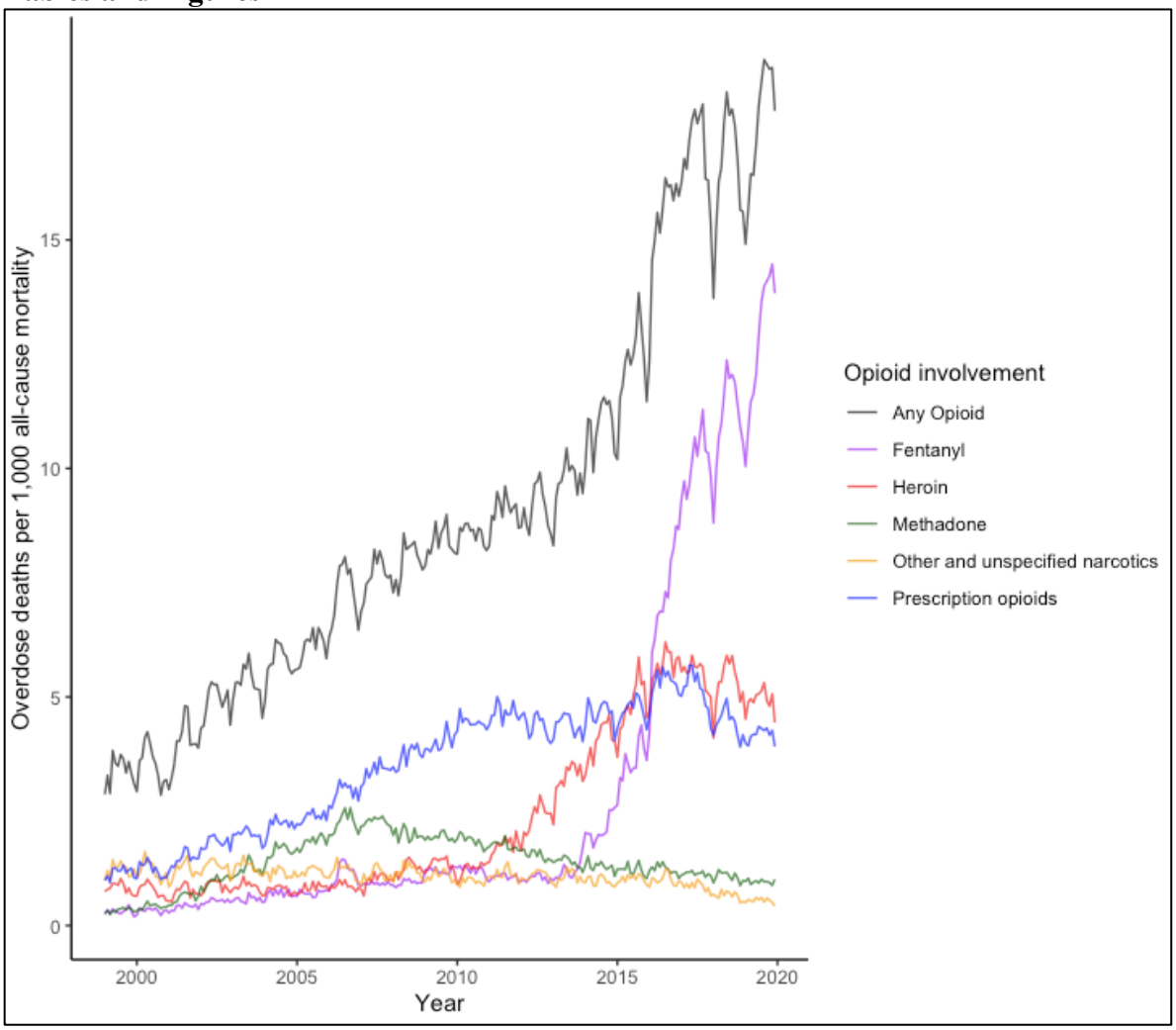

Figure 1. Monthly national opioid-related overdose fatality deaths per 1,000 all-cause mortality by individual drug involvement, for 1999-2019.[a]

[a] Numerator data are opioid overdose death counts, defined as deaths with an ICD-10 underlying cause of death codes for poisoning (X40–X44, X60–X64, X85, or Y10–Y14) and an ICD-10 multiple cause of death code indicating opium (T.40), heroin (T40.1), other opioids (T40.2; labeled "Prescription opioids"), methadone (T40.3), other synthetic narcotics (T40.4; labeled "Fentanyl"), or other and unspecified narcotics (T40.6) overdose as a contributing cause of death. Opium is associated with a negligible number of deaths in the US (<10 annually) and was therefore excluded from our stratified analyses. Denominator data are all cause mortality counts. Data from CDC WONDER.

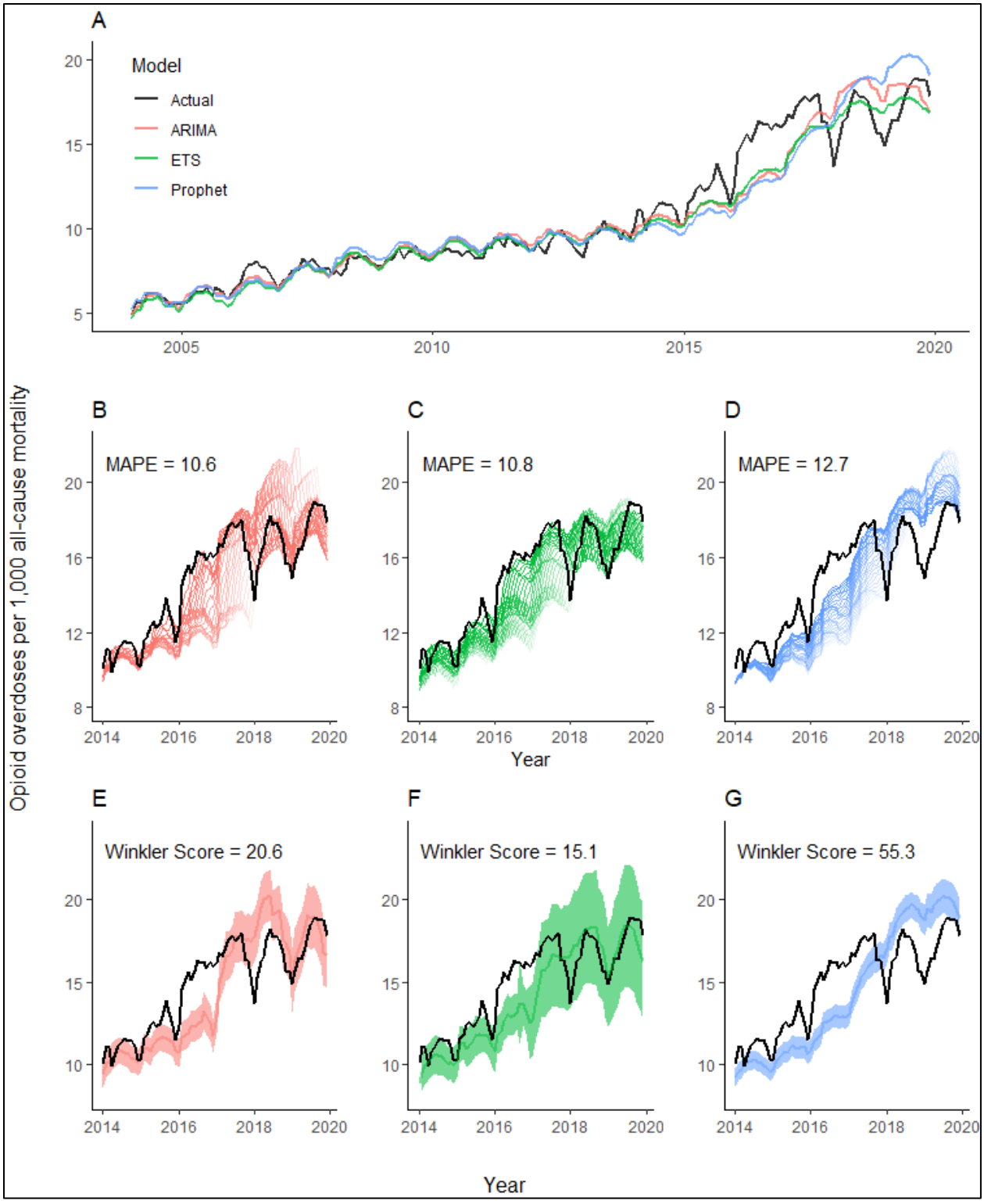

Figure 2. Forecast accuracy and coverage probability for the period assessed (2004-2019). [a]

[a] Each model provided relatively accurate forecasts until the fentanyl-dominated period from 2014 onwards (A). To highlight prediction accuracy during the fentanyl period, point forecasts for individual 24-month forecasts generated

via ARIMA (B), ETS (C), and Facebook Prophet (D) models are presented. For B-D, distance between a forecast value and the time it originates from is denoted by transparency (i.e., one-month forecasts are least transparent, 24-month forecast most) and mean MAPE for 2014-2019 is presented for each model. Mean 95% CI of forecasts generated via each model at 12-months are presented in are presented (E-G) with mean Winkler score for each model for 2014-2019.

Table 1. Mean absolute percent error (MAPE) estimates of national 24-month opioid overdose death rate forecasts for ARIMA, ETS, and Prophet models, stratified by opioid involvement.

	MAPE (%)		
Opioid involvement	**ARIMA**	**ETS**	**Prophet**
Any opioid	5.5	6.8	6.7
Heroin	15.7	16.9	19.2
Methadone	11.2	11.9	10.7
Other and unspecified narcotics	15.6	13.6	14.6
Prescription opioids	8.8	8.6	10.2
Fentanyl	21.0	21.4	25.8

Table 2. Predictive coverage probability of national 24-month opioid overdose death rate forecasts for ARIMA, ETS, and Prophet models, stratified by opioid involvement.

	95% CI Width			% Coverage			Winkler Score		
Opioid involvement	**ARIMA**	**ETS**	**Prophet**	**ARIMA**	**ETS**	**Prophet**	**ARIMA**	**ETS**	**Prophet**
Any opioid	2.1	3.2	1.3	73%	86%	49%	14.4	9.0	24.0
Heroin	1.0	2.1	0.5	69%	81%	30%	5.3	4.3	15.4
Methadone	0.9	1.3	0.4	93%	100%	71%	1.9	1.4	3.1
Other and unspecified narcotics	0.6	0.5	0.4	92%	89%	84%	0.8	0.8	1.0
Prescription opioids	1.1	1.5	0.6	79%	93%	42%	4.1	2.5	8.6
Fentanyl	1.7	4.5	0.8	70%	75%	42%	16.8	14.5	31.8

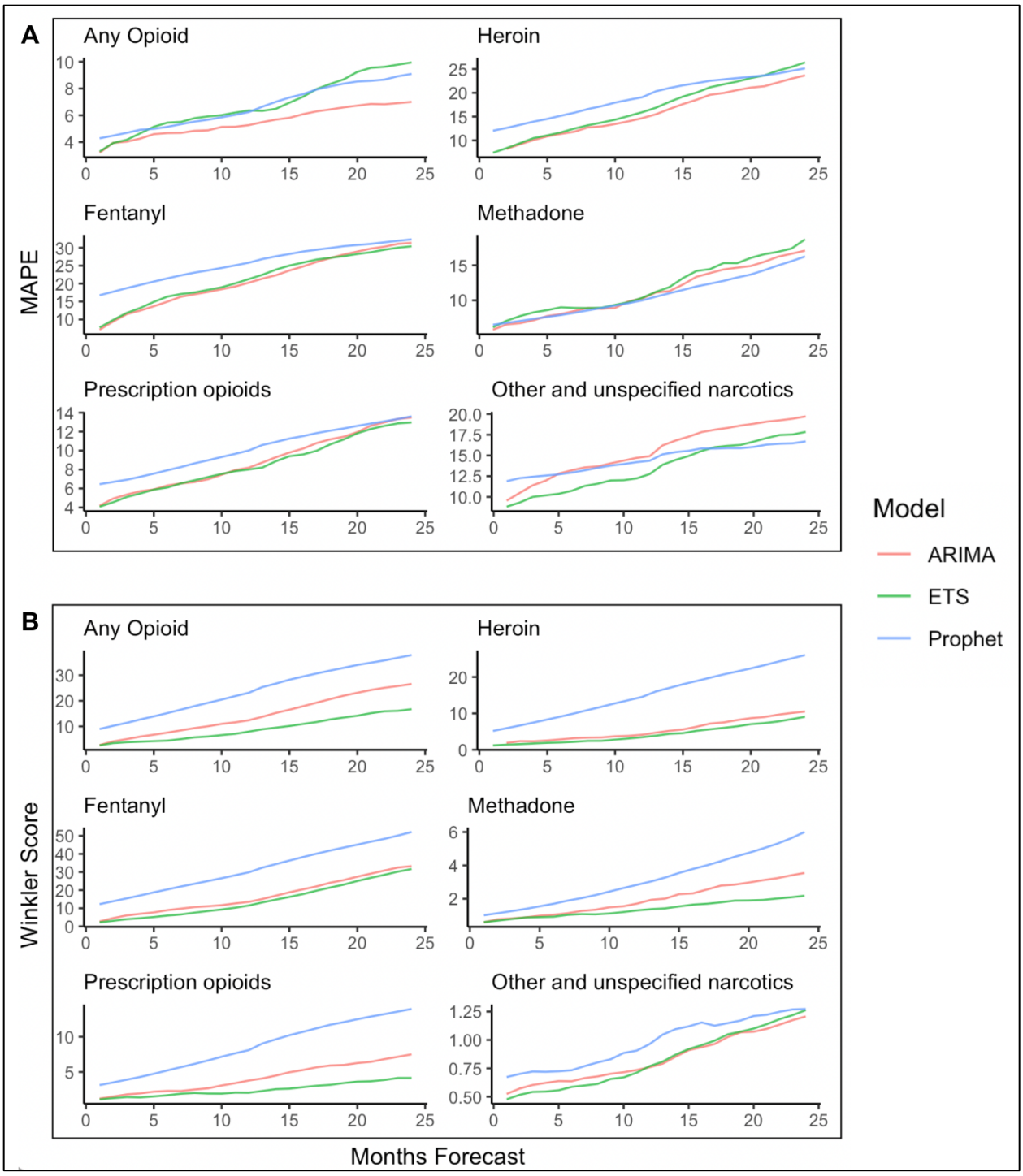

Figure 3. Mean absolute percent error (MAPE) estimates (A.) and predictive coverage probability (B.) throughout 24-month forecasts by opioid involvement and model assessed, represented by MAPE and Winkler score, respectively.

Supplementary Material

Time series cross validation procedure.

Time series cross validation is a robust method of forecast validation which has seen recent use in COVID-19 forecast evaluation (Atchadé et al. 2021; Atchadé and Sokadjo 2022; Cerqueira et al. 2019). TSCV assesses the accuracy of a given model by sub-setting time series data into training (i.e., a subset of the time series to be modeled) and test sets (i.e., a subset of the time series not modeled and compared against to assess forecasting accuracy) on a rolling basis. TSCV is preferred to using a single training and test set method (Figure S1A) as it produces forecasts using several lengths of data, increasing a given forecast's generalizability beyond a single temporally defined scenario (Bergmeir et al. 2018; Song et al. 2021).

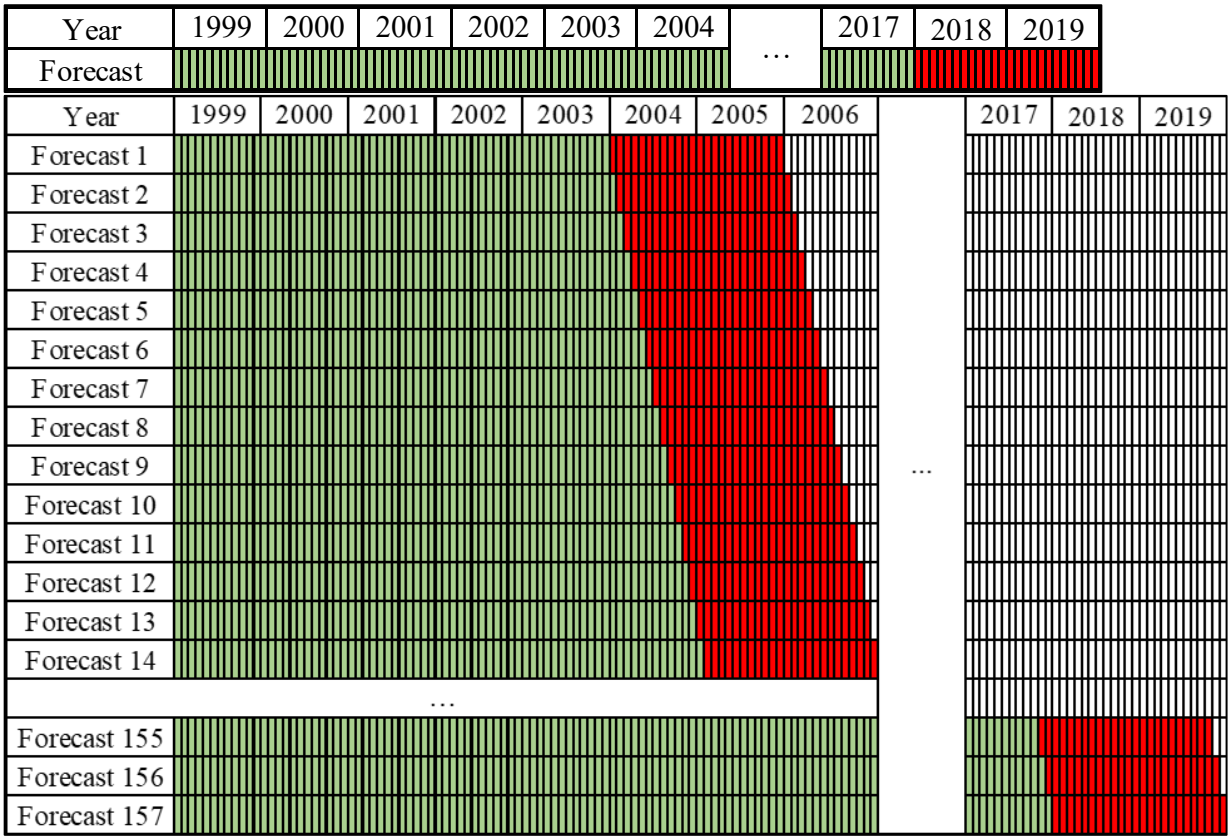

Figure S1. Graphical representation of a fixed origin approach towards evaluating forecasting accuracy (A), compared to the time series cross validation approach used in this study (B). [a]

[a] The accuracy of time series forecasts is assessed using training and test sets; a training set is composed of data used to model a time series (shown here in green), while a test is composed of data used only to compare the accuracy of a forecast generated from the test set model (shown here in red). In a single training and tests set approach, training and test sets of a single length are used to evaluate forecasting accuracy. In contrast, time series cross-validation approach, training and tests sets) are moved throughout a dataset in by pre-specified intervals. In this example, which illustrates the methodology used in our study, training sets increase in length by one-month intervals, while test sets remain at a length of 24 months.

Analysis stratified by state-level drug death reporting specificity

Given high variability in drug-specific overdose reporting by state (Warner and Hedegaard 2018), we conducted a stratified version of our analysis by state-level proportion of overdose death certificates for which no specific drug was listed as a contributing cause of death. This was determined by calculating the proportion of drug poisoning-associated death certificates (i.e., those with ICD-10 UCOD codes X40–X44, X60–X64, X85, or Y10–Y14) that listed a specific drug as a contributing cause (i.e., those with ICD-10 MCOD code within the range T36–T50.8) for the year 1999-2019 and subtracting this value from one. Based on these values, four strata were used: <5%, 5-15%, 15-25%, and >25% of drug-related death certificates having no specific drug listed (Figure S1). Results from this analysis did not overall differ from our non-stratified analysis. Results are shown in Tables S1-S2.

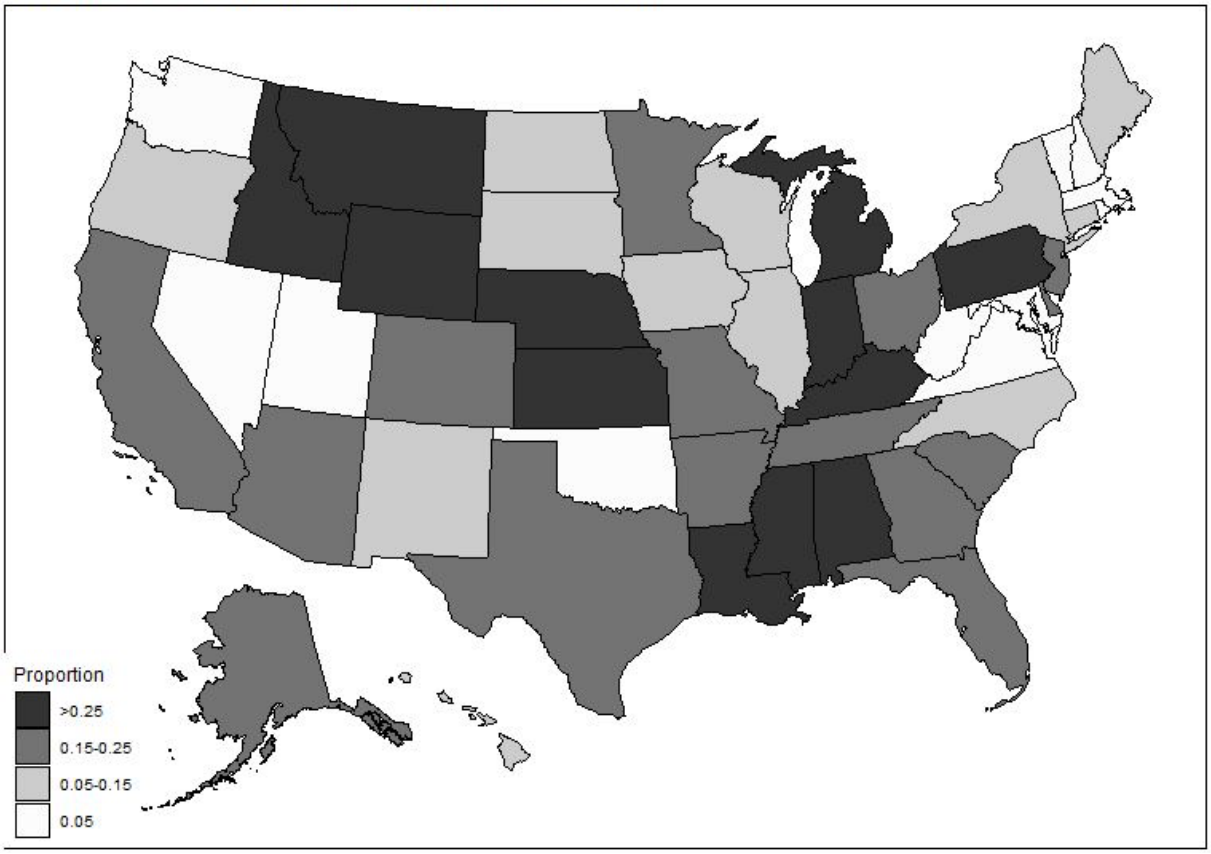

Figure S2. Geographical representation of strata used to represent state-level of proportion of death certificates with no drug specified, 1999-2019.[a]

[a] Values creating by determining the proportion of drug-induced deaths (i.e., those with ICD-10 underlying cause of death codes X40–X44, X60–X64, X85, or Y10–Y14) with no drug specified (i.e., those with ICD-10 multiple cause of death code within the range T36–T50.8) and subtracting this value from one. Data from CDC WONDER.

Table S1. Forecast bias of national 24-month opioid overdose death rate forecasts for ARIMA, ETS, and Prophet models, stratified by opioid involvement and state-level drug death reporting specificity.

% of Death Certificates with no Drug Listed	MAPE		
	ARIMA	ETS	Prophet
<5%			
Any Opioid	8.7	8.1	8.9
Heroin	23.1	23.2	28.7
Methadone	17.9	18.2	18.7
Other and unspecified narcotics	27.1	25.6	35.0
Prescription opioids	13.5	13.4	14.1
Fentanyl	23.3	22.0	24.7
5-15%			
Any Opioid	12.1	11.9	13.8
Heroin	23.0	24.1	26.3
Methadone	17.2	18.8	17.6
Other and unspecified narcotics	30.4	27.7	27.9
Prescription opioids	13.4	12.3	14.7
Fentanyl	30.5	30.5	34.3
15-25%			
Any Opioid	8.3	8.5	7.3
Heroin	16.2	15.1	19.3
Methadone	14.8	13.3	15.2
Other and unspecified narcotics	16.3	15.8	16.3
Prescription opioids	11.2	11.3	11.1
Fentanyl	22.4	22.1	24.8
>25%			
Any Opioid	8.9	9.6	8.7
Heroin	25.9	26.4	27.2
Methadone	20.6	19.8	21.2
Other and unspecified narcotics	23.6	23.7	24.7
Prescription opioids	14.2	15.3	14.1
Fentanyl	28.5	28.0	31.5

Table S2. Statistical predictive coverage probability of national 24-month opioid overdose death rate forecasts for ARIMA, ETS, and Prophet models, stratified by opioid involvement and state-level drug death reporting specificity.

% of Death Certificates with no Drug Listed	95% CI Width			Coverage			Winkler Score		
	ARIMA	ETS	Prophet	ARIMA	ETS	Prophet	ARIMA	ETS	Prophet
<5%									
Any Opioid	5.2	5.7	3.1	88%	90%	50%	15.3	13.4	34.1
Heroin	1.9	4.2	1.2	62%	80%	38%	9.8	6.8	25.3
Methadone	2.4	2.8	1.3	85%	91%	70%	4.0	3.1	7.3
Other and unspecified narcotics	2.3	2.3	1.7	87%	85%	62%	2.9	3.3	6.7
Prescription opioids	2.5	2.9	1.6	73%	79%	50%	7.3	4.9	12.6
Fentanyl	2.6	8.0	1.5	60%	77%	46%	33.1	18.7	50.0
5-15%									
Any Opioid	5.1	5.2	2.3	85%	86%	44%	15.9	13.7	18.4
Heroin	1.7	3.9	0.9	54%	73%	29%	9.5	6.6	21.7
Methadone	1.3	1.4	0.8	81%	89%	66%	2.6	1.8	4.6
Other and unspecified narcotics	1.3	1.4	1.0	86%	86%	78%	1.8	1.9	2.0
Prescription opioids	1.4	2.3	1.0	71%	80%	50%	5.6	4.6	8.8
Fentanyl	2.6	7.0	1.4	62%	76%	48%	24.1	15.5	38.8
15-25%									
Any Opioid	3.6	3.5	1.7	85%	87%	61%	9.4	8.6	17.4
Heroin	1.1	1.3	0.6	68%	71%	40%	3.5	4.0	9.8
Methadone	0.9	1.1	0.5	85%	89%	65%	1.5	1.4	2.9
Other and unspecified narcotics	0.5	0.7	0.4	89%	90%	86%	0.7	0.7	0.6
Prescription opioids	1.9	2.2	1.0	83%	83%	59%	3.2	3.4	6.6
Fentanyl	1.3	3.5	0.7	56%	71%	39%	17.5	11.0	23.9
>25%									
Any Opioid	2.3	4.5	1.5	72%	90%	54%	17.4	9.2	23.5
Heroin	1.2	2.9	0.8	59%	78%	40%	6.7	4.2	13.7
Methadone	0.9	1.3	0.6	82%	90%	68%	1.7	1.5	3.1
Other and unspecified narcotics	0.5	0.6	0.4	77%	84%	69%	1.0	0.8	1.3
Prescription opioids	1.1	2.0	0.8	65%	83%	50%	4.2	3.1	6.8
Fentanyl	1.9	5.6	1.0	60%	76%	46%	22.0	14.6	32.3

Chapter 5

Conclusion

United States (US) injury rates declined throughout much of the 20th century, largely due to decreasing rates of occupational injuries. However, injury rates began increasing near the beginning of the 21st century in association with the US opioid epidemic. The opioid epidemic has been characterized by several interconnect waves of overdose, each driven by specific drug types. The epidemic's temporally dynamic nature demonstrates the necessity of time series analysis for deeper understanding of the current US drug crisis and broader trends within historical injury data. Thus, this study aimed to explore the application of time series analysis to United States (US) injury data.

We began by examining trends in US occupational injuries treated in US emergency departments for 2012-2019. Findings from this first study, which used autoregressive integrated moving average (ARIMA) modeling, support peer-reviewed literature finding that US occupational injuries in the 21st century have continued their decades-long trend of decline. We then sought to elucidate the transition from prescription to illicit opioid overdoses in West Virginia (WV), which is often considered the opioid crisis' epicenter (Merino et al., 2019). This second study extended the first's use of ARIMA modeling to interrupted time series analysis (ITSA) in an effort to compare the impact of factors potentially influencing the transition between the opioid epidemic's first and subsequent waves. ITSA results indicate that patterns in opioid-involved overdose in WV changed near the point when hydrocodone and oxycodone tablet shipments (measured via dosage units) to the state began decreasing in late 2011. The contrasts previous literature supporting the hypothesis that the 2010 release of an abuse deterrent OxyContin formulation was a primary factor in initiating illicit opioid use in the US. In our third study, we compared the ability of three time series models to forecast US opioid-involved overdose rates. This study found that exponential smoothing (ETS) modeling accurately forecast US opioid-involved overdose death rates for 1999-2019. Notably, ETS models maintained a high degree of prediction interval precision relative to other approaches, including ARIMA modeling, both overall and stratified by individual drug involvement.

Separately, these studies use three common utilizations of time series analysis (trend analysis, ITSA, and time series forecasting) and apply them to injury data. They also use approaches less common in injury epidemiology, such as the use of locally estimated scatterplot smoothing (LOESS) to inform an ITSA study in study two and time series cross validation (TSCV) in study three. To the authors' knowledge, these methods have not been applied within these specific epidemiological contexts.

Time series analysis allows for the assessment of temporally collected injury data and is a useful method for studying injury trends. However, it is not without limitations. First, time series analysis is inherently an ecological study design as it assesses group-level data. This includes ITSA, which aims to assess the impact of temporally-defined events. However, ITSA is often the most robust study design available for assessing the impact of natural events in large groups. Moreover, assessing the impact of multiple potential intervention and comparing between them, as we did in study two, can strengthen conclusions. A limitation specific to forecasting is its inability to anticipate unexpected events (Naess et al., 2015). This was observed in our third study, where each method projected future opioid overdoses with relative accuracy until rates increased drastically beginning in 2014. In such scenarios, prediction interval assessment as can improve forecast validation as it measures how well a model adjusts to unanticipated events while maintaining relative precision (Kim et al., 2011) This approach allowed us to determine that ETS models produced optimal forecasts throughout the transition to the epidemic's fentanyl-

dominated third wave and, therefore, would have been most useful for planning future resource allocation (Christoffersen, 1998).

These studies demonstrate the utility of time series analysis in the field of injury epidemiology. Future studies should apply similar methods to injury-related topics beyond those explored here. One potential area of applicability is in the study of firearm injuries, one of the only sources of injuries (aside from overdoses) to increase significantly in recent years (Centers for Disease Control and Prevention, 2022). One exciting advancement from Schleimer et al. used TSCV-validated models to forecast rates of firearm violence during the COVID-19 pandemic (Schleimer et al., 2021). In addition to TSCV, studies of firearm injury forecasts should begin to incorporate assessments of prediction interval precision in order to describe the uncertainty associated with their forecasts. Similarly, there have been several methodological advancements that have made the application of time series analysis to epidemiological data more robust. These include the use of synthetic controls in ITSA studies (Bonander, 2018; Degli Esposti et al., 2020) and Gasparrini's case time series study design, which incorporates self-matching procedures within a longitudinal, time series framework (Gasparrini, 2021, 2022). To our knowledge, the case time series design has yet to be incorporated into the field of injury epidemiology. Future research should apply these and other unique time series methods to injury data to improve epidemiologists' current understanding of temporal trends in injuries and their associated exposures.

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