Drug and Alcohol Dependence 150 (2015) 63–68

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program☆

Chris Delcher[a,*], Alexander C. Wagenaar[a], Bruce A. Goldberger[b], Robert L. Cook[c], Mildred M. Maldonado-Molina[a]

[a] Department of Health Outcomes and Policy and Institute for Child Health Policy, University of Florida, College of Medicine, Gainesville, FL 32610-0177, United States
[b] Departments of Pathology, Immunology and Laboratory Medicine and Psychiatry, University of Florida, College of Medicine, Gainesville, FL 32610-0177, United States
[c] Department of Epidemiology, University of Florida, College of Medicine, Gainesville, FL 32610-0177, United States

ARTICLE INFO

Article history:
Received 16 September 2014
Received in revised form 5 February 2015
Accepted 6 February 2015
Available online 19 February 2015

Keywords:
Prescription pain medication
Prescription drug monitoring
Drug-related mortality
Time series

ABSTRACT

Background: In Florida, oxycodone-caused deaths declined substantially in 2012. Multiple important law enforcement, pharmaceutical, policy, and public health actions occurred concurrently, including implementation of a statewide Prescription Drug Monitoring Program (PDMP). The effects of the PDMP on oxycodone-caused mortality in Florida were evaluated.
Methods: A time-series, quasi-experimental research design with autoregressive integrated moving average (ARIMA) statistical models, including internal and external covariates. Data included 120 repeated monthly observations. Monthly counts of oxycodone-caused deaths, obtained from the Florida Medical Examiners Commission (MEC) was the outcome variable. Models included market-entry of tamper-resistant oxycodone HC1 controlled release tablets (OxyContin®), enforcement crackdowns (Operation Pill Nation), and regulation by FL House Bill 7095, measured by the monthly count of Florida pain management clinics closed. Two approaches were used to test the PDMP's hypothesized effect: (1) a binary indicator variable (0 = pre-implementation, 1 = post-implementation), and (2) a continuous indicator consisting of the number of PDMP queries by health care providers.
Results: Oxycodone-caused mortality abruptly declined 25% the month after implementation of Florida's PDMP ($p = 0.008$). The effect remained after integrating other related historical events into the model. Results indicate that for a system-wide increase of one PDMP query per health care provider, oxycodone-caused deaths declined by 0.229 persons per month ($p = 0.002$).
Conclusions: This is the first study to demonstrate that the PDMP had a significant effect in reducing oxycodone-caused mortality in Florida. Results have implications for national efforts to address the prescription drug epidemic.

1. Introduction

In the United States, deaths from prescription drug abuse, especially from pain relievers such as oxycodone, have now reached epidemic proportions (Centers for Disease Control and Prevention, 2012; Jones et al., 2013; Levy et al., 2013; Paulozzi, 2012; White House, 2011). Florida has been a focal point in the national crisis, in part due to the well-publicized, proliferation of pain management clinics (i.e., "pill mills") and their corresponding role in the widespread distribution of oxycodone and other prescriptions and the resulting public health consequences (Johnson et al., 2014; Rigg et al., 2012; Sauber-Schatz et al., 2013; Surratt et al., 2014). From 2003 to 2009 in Florida, the rate per 100,000 population of oxycodone-caused mortality increased 265% (Goldberger et al., 2011). From 2007 to 2010, the rate per 100,000 population of oxycodone-caused deaths increased by 118.3% compared to only 16.3% for hydrocodone, −13.8% for methadone, −5.0% for fentanyl, 0.1% for morphine, −34.6% for propoxyphene, and 62.4% for hydromorphone (Lee et al., 2014). In South Florida, oxycodone was found to be a preferred prescription opioid among pill mill clients (Rigg et al., 2012). Yet, in 2014, a Centers for Disease

☆ Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering http://dx.doi.org/10.1016/j.drugalcdep.2015.02.010.

* Corresponding author. Tel.: +1 352 294 5976.
E-mail address: cdelcher@ufl.edu (C. Delcher).

http://dx.doi.org/10.1016/j.drugalcdep.2015.02.010
0376-8716/

Control and Prevention (CDC) study reported unprecedented, annual declines in oxycodone-caused mortality in Florida beginning after 2011 (Johnson et al., 2014). Declines in oxycodone deaths coincided with multiple law enforcement, pharmaceutical, and public health actions (Johnson et al., 2014).

In January, 2010, Florida required pain management clinics to register with the Florida Department of Health, which provided more regulatory oversight (Florida Department of Health, 2010). In August, 2010, a reformulated extended-release oxycodone (ERO) was introduced to the national market. In February 2011, the U.S. Drug Enforcement Agency (DEA) took action against illegitimate pain management clinics in an operation known as "Operation Pill Nation" (Alvarez, 2011) In July 2011, House Bill 7095 took effect which established or strengthened state regulation of activities by controlled substance dispensing physicians, pain management clinics, pharmacies and wholesale controlled substance distributors (*Florida House Bill 7095*, 2011). In October, 2011, Florida became the 37th state to implement a Prescription Drug Monitoring Program (PDMP; Alliance of States with Prescription Drug Monitoring Programs, 2013).

PDMPs are principally designed to detect abnormalities in the prescribing of controlled substances (e.g., higher-than-expected doses per unit time, questionable overlapping prescriptions, "doctor shopping" for multiple prescribers and dispensers). An effective PDMP could plausibly reduce oxycodone overdoses in the population by reducing the quantity of pills available from medical sources that could be abused (Green et al., 2011; Gugelmann and Perrone, 2011). Forty-eight states have operational PDMPs but there is an urgent need to rigorously evaluate these systems and understand the pharmaco-epidemiological consequences of implementing them (Gugelmann et al., 2012; Haffajee et al., 2015). Studies examining the effects of state PDMPs on deaths from opioids, such as oxycodone (DEA Schedule II), are limited. As of June 2014, a single study had examined the effect of PDMPs on opioid mortality and indicated no differences in states with operational PDMPs compared to those without (Davis et al., 2014; Paulozzi et al., 2011). Subsequently, researchers noted several important limitations of this work (Green et al., 2011). Recent work limited to annual mortality data lack the temporal resolution to properly examine this question (Johnson et al., 2014). Thus, the current study, using higher time resolution observations, is designed to test the hypothesis that the PDMP contributed to a reduction in oxycodone-caused mortality in Florida.

2. Methods

2.1. Research design

The research design was an interrupted time-series, quasi-experimental. The dependent variable consists of 120 repeated monthly counts of oxycodone-caused mortality (106 pre- and 14 post-PDMP implementation) from January, 2003 to December, 2012. A comparison time-series was included to account for the many internal (i.e., Florida-specific) and external factors (i.e., nationwide trends) that might reasonably contribute to or confound an observed effect. The quasi-experimental design with multiple comparisons obviates the need for reliable measures of each specific possible confounder; such measures are for the most part not available (Cook and Campbell, 1979).

2.2. Dependent variable: Oxycodone-caused mortality

Data for drug-related deaths was obtained from the Florida Medical Examiners Commission (MEC; Florida Medical Examiners Commission, 2013); reported to the MEC by district medical examiners who investigate all unnatural deaths in the state of Florida, including deaths due to accident, homicide and suicide. A death is considered "drug-related" if at least one drug was identified in the decedent. The MEC instructs district medical examiners to determine whether oxycodone was a cause of death (i.e., detected in lethal concentrations) or merely present (i.e., detected in non-lethal concentrations) at the time of death. Brand-names of drugs and medical conditions prior to death are not reported and no distinction is made for primary versus secondary cause of death when multiple drugs are found in lethal concentrations. Reports were received in electronic format beginning in January, 2010, which led to an increase in case reporting (Medical Examiner's Commission, 2008). To account for this change, an indicator variable (0 = pre-automation, 1 = post-automation) was included but not found to be significant.

The primary outcome consisted of monthly deaths determined by medical examiners to be caused by oxycodone not including deaths where oxycodone was merely present. Given the poly-drug nature of prescription drug abuse and recent concerns regarding opioid substitution effects (Cicero et al., 2012; Coplan et al., 2013; Jann et al., 2014), five additional drug-related time series models were tested, including mortality series consisting of (1) oxycodone-caused excluding alprazolam (2) benzodiazepine-caused, (3) alprazolam-caused excluding oxycodone, (4) any opioid-caused excluding oxycodone, and (5) heroin-caused.

2.3. Independent variables

PDMP: Two approaches to model the effect of the PDMP were used. First, a binary indicator variable (0 = pre-implementation, 1 = post-implementation). Second, the "health care provider query rate" was calculated as the number of queries divided by the number of registered health care provider per month from October, 2011 to December, 2012 (Florida's Prescription Drug Monitoring Program, 2012). A PDMP query is a single instance of an electronic request for a summary report of controlled prescription drugs filled by an individual patient. A health care provider is defined by the PDMP as prescribers and dispensers including advanced registered nurse practitioners, dentists, medical doctors, certified optometrists, osteopathic physicians, physician assistants, podiatric physicians or pharmacists. During the study period, the PDMP query rate ranged from 25 (October, 2011) to 216 (December, 2012) queries per health care provider per month.

Internal control series: The internal control series consisted of Florida's monthly counts of ethanol-caused mortality (excluding oxycodone deaths) to control for: (1) overall population change, (2) non-oxycodone mortality trends, (3) seasonal patterns, (4) unobserved trends in the drug-abusing population, and (5) random variation intrinsic to the MEC reporting system (e.g., budget changes, staffing levels) (Medical Examiner's Commission, 2008).

External control series: The external control series consisted of unintentional, monthly poisoning deaths involving oxycodone for New York City (NYC) from 2003 to 2012 (Paone et al., 2014). NYC was used as an external control series because: (1) the city's trend in opioid analgesic mortality was similar to Florida's (i.e., steady increase until 2011 with subsequent decline; Paone, 2013), (2) mandatory requirements for checking the NY PDMP became mandatory in August 2013 (after our study period) and (3) the population base of New York City is large and diverse, similar to Florida. Several attempts were made to obtain comparable drug-specific deaths from other states but most indicated that data was not available.

Covariates: Prior to estimating effects of the PDMP, the effects of ERO, Operation Pill Nation, and House Bill 7095 into the outcome series were integrated. ERO was expected to replace highly-abused forms over a 6-month period (Butler et al., 2012; Cicero et al., 2012; Dart et al., 2015). To reduce collinearity, the three effects were modeled using a single, continuous measure: the monthly number of pain management clinic closures calculated as the number of providers licensed with pain management clinics reported with an "inactive" license status by month (see [1] Supplementary materials). Analyses showed that this variable was highly correlated with all three events. To estimate rate of clinic closures, data was obtained from the Florida Division of Medical Quality Assurance (Division of Medical Quality Assurance (MQA) Services, 2014). Given the close timing of House Bill 7095 (July, 2011) and the start of the PDMP (October, 2011), for sensitivity analyses, 1-month, 2-month, and 3-month indicator variables for HB 7095 were tested separately using the same parameters as the final model.

2.4. Statistical analyses

The Box and Jenkins time-series analysis was used to model monthly counts (Y_t) of oxycodone-caused mortality from January, 2003 to December, 2012 (Box and Jenkins, 1976). The analyses was conducted in three phases: assessment of (1) mean, variance, and seasonality; (2) autocorrelation; and (3) autoregressive or moving average parameters. As expected, the analysis suggested a non-stationary mean [range: 25 to 126 deaths per month]. To detrend, first order differencing was used. To examine seasonality, a 6-month seasonal model of the form ARIMA$(0,1,1) \times (0,1,1)_6$ was tested.

As expected, the autocorrelation function (ACF) graph and partial autocorrelation function (PCF) graphs of $Y(t)$ was indicative of a strong linear trend, which the differencing procedure removed. The PCF showed that monthly counts were significantly correlated to lag(3) of the series (i.e., presence of a moving average parameter).

To test the autoregressive or moving average parameters, assessments for (1) statistical significance using maximum likelihood estimation and (2) serial dependence in the residuals using the Q-statistic (e.g., the likelihood that only random

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering http://dx.doi.org/10.1016/j.drugalcdep.2015.02.010.