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Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone

Stevan Geoffrey Severtson[a], Matthew S. Ellis[b], Steven P. Kurtz[c], Andrew Rosenblum[d], Theodore J. Cicero[b], Mark W. Parrino[d], Michael K. Gilbert[e], Mance E. Buttram[c], Nabarun Dasgupta[e], Becki BucherBartelson[a], Jody L. Green[a], Richard C. Dart[a,*]

[a] Rocky Mountain Poison and Drug Center, 777 Bannock Street, Mailcode 0180, Denver, CO, 80204, USA
[b] Department of Psychiatry, Washington University School of Medicine, Washington University School of Medicine, Box 8134, 660 S Euclid, St. Louis, MO, 63110, USA
[c] Center for Applied Research on Substance Use and Health Disparities, Department of Justice and Human Services, College of Humanities, Arts and Social Sciences, Nova Southeastern University, 7255 NE 4th Avenue, Suite 112, Miami, FL, 33138, USA
[d] American Association for the Treatment of Opioid Dependence, New York, NY, USA
[e] Epidemico, Inc., 50 Milk St., 20th floor, Boston, MA, 02109, USA

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ABSTRACT

Background: The development of abuse deterrent formulations is one strategy for reducing prescription opioid misuse and abuse. A putative abuse deterrent formulation of oxycodone extended release (OxyContin®) was introduced in 2010. Early reports demonstrated reduced abuse and diversion, however, an analysis of social media found 32 feasible methods to circumvent the abuse deterrent mechanism. We measured trends of diversion, abuse and street price of OxyContin to assess the durability of the initial reduction in abuse.

Methods: Data from the Poison Center Program, Drug Diversion Program, Opioid Treatment Program, Survey of Key Informant Patients Program and StreetRx program of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System were used. The average quarterly rates of abuse and diversion for OxyContin were compared from before reformulation to the rate in second quarter 2015. Rates were adjusted for population using US Census data and drug availability.

Results: OxyContin abuse and diversion declined significantly each quarter after reformulation and persisted for 5 years. The rate of abuse of other opioid analgesics increased initially and then decreased, but to lesser extent than OxyContin. Abuse through both oral and non-oral routes of self-administration declined following the reformulation. The geometric mean difference in the street price of reformulated OxyContin was 36% lower than the reformulated product in the year after reformulation.

Discussion: Despite methods to circumvent the abuse deterrent mechanism, abuse and diversion of OxyContin decreased promptly following the introduction of a crush- and solubility- resistant formulation and continued to decrease over the subsequent 5 years.

1. Introduction

Misuse and abuse of prescription analgesics is a major health problem. In 2014, there were 2.2 million current nonmedical users of prescription pain relievers in the United States (Center for Behavioral Health Statistics and Quality, 2015). More than 16,000 deaths were attributed to prescription pain relievers in 2013 (Hedegaard et al., 2015). In 2011, the Office of National Drug Control Policy issued a national strategy to combat prescription drug abuse (United States Office of National Drug Control Policy, 2011). The strategy included several components, including research into formulations with abuse deterrent properties. In 2015, the FDA released guidance regarding the development of abuse deterrent formulations (United States Food and Drug Administration, 2015). One specified property was physical-chemical barriers, which involves making a tablet difficult to crush; thereby inhibiting use through chewing, nasal insufflation, injection, or smoking.

* Corresponding author.
E-mail addresses: Geoff.Severtson@rmpdc.org (S.G. Severtson), ellism@psychiatry.wustl.edu (M.S. Ellis), Steven.kurtz@nova.edu (S.P. Kurtz), Rosenblum@ndri.org (A. Rosenblum), cicerot@psychiatry.wustl.edu (T.J. Cicero), Mark.Parrino@aatod.org (M.W. Parrino), michael@epidemico.com (M.K. Gilbert), mance.buttram@nova.edu (M.E. Buttram), nabarun@epidemico.com (N. Dasgupta), Becki.Bucher-Bartelson@rmpdc.org (B. BucherBartelson), Jody.Green@rmpdc.org (J.L. Green), rdart@rmpdc.org (R.C. Dart).

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OxyContin® is an extended release (ER) formulation of oxycodone that became a popular drug of abuse (United States Food and Drug Administration, 2001). In 2010, the manufacturer introduced a reformulated tablet that was difficult to crush and formed a viscous hydrogel to make snorting and injection difficult (Alexander et al., 2014). The FDA approved new labeling describing the abuse deterrent features and subsequently denied applications from other oxycodone ER formulations without abuse deterrent features (United States Food and Drug Administration, 2013). Reformulated OxyContin and its authorized generic products remain the only form of oxycodone ER marketed in the United States.

Initial reports suggested that reformulation reduced the abuse and diversion of OxyContin (Severtson et al., 2013; Butler et al., 2013). However, a review of internet forums found 32 feasible recipes to overcome the tamper resistant properties (McNaughton et al., 2014). Previous research suggests that many abusers switch to other products, particularly immediate release oxycodone and hydromorphone (Cicero et al., 2012; Havens et al., 2014). If methods to circumvent abuse deterrent methods became widespread, abuse and diversion could return to high rates. OxyContin represents a sentinel opportunity to assess the durability of the strategy of physical-chemical abuse deterrent properties.

We analyzed rates of opioid analgesic abuse and diversion for the 5 years following reformulation to determine whether initial reductions in OxyContin abuse persisted despite the availability of methods to circumvent the abuse deterrent properties.

2. Methods

2.1. Data sources

The Researched, Abuse, Diversion, and Addiction Related Surveillance (RADARS®) System provides post-marketing surveillance of prescription medication abuse and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The System is comprised of multiple surveillance programs that independently gather data on prescription drug abuse from different perspectives. The RADARS System is owned and operated by the Denver Health and Hospital Authority, which operates the public hospital for the city and county of Denver. The system is supported by subscriptions from pharmaceutical companies that produce prescription opioids or stimulants, which use the data for risk management and postmarketing surveillance reporting to the Food and Drug Administration.

The Poison Center Program studies acute health events by recording the substances involved in poison center cases classified as intentional abuse. The Drug Diversion Program measures drug diversion by recording the drugs involved in cases opened by law enforcement drug diversion investigators. The Opioid Treatment Program and the Survey of Key Informants' Patients Program both query new patients entering substance-abuse treatment about medications that they have abused. The StreetRx Program utilizes a crowdsourcing website that gathers street price data for drugs using a publically-accessible website. Further information on each surveillance program has been published (Dart et al., 2015).

2.2. Definitions

In the Poison Center Program, a *case* involves an individual exposure contact in which the case was coded to the category of Intentional Abuse, which is defined as an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a euphoric or other psychotropic effect (American Association of Poison Control Centers, 2014). Poison Center Program *mentions* are the total number of active pharmaceutical ingredient (API) reports involved for all cases within a defined group. Mentions differ from cases in that an individual (case) may be exposed to more than one product (mention). There is an average of 1.04 opioid mentions per case.

In the Opioid Treatment and Survey of Key Informants' Patients programs, a case is defined as a survey respondent endorsing the abuse of a prescription opioid in the preceding 30 days. In these programs, *mentions* are the total number of endorsements. The average number of mentions per case is 1.68 for the Opioid Treatment Program and 1.83 for the Survey of Key Informant Patients Program.

In the Drug Diversion Program, a case is defined as an investigation, which can have one or more mentions (drugs involved in the case). Drug diversion officers submit data quarterly on the number of new cases involving prescription products within their jurisdiction. These cases arise from arrests, street buys and sales by law enforcement agents, and investigation of prescribers, among other reasons.

In StreetRx, users enter the price of drugs they paid or heard was paid from an extensive list of drugs provided on the website (http://streetrx.com). StreetRx submissions from the United States for OxyContin that included a price paid, dosage strength, and date were included.

Quarterly population rates were calculated by dividing the total number of cases by the sum of the population in the 3-digit ZIP codes covered by each program using 2010 US census results, thus allowing for each individual to contribute once to the numerator and once to the denominator within each drug group. In contrast, rates adjusted for prescriptions dispensed are calculated by dividing the sum of the mentions by the sum of the projected prescription volume in the 3-digit ZIP codes covered by each program. For mention based rates, such as prescription rates, a single individual may be counted multiple times in both the numerator and denominator. Quarterly prescription rates were calculated using the projected number of prescriptions dispensed as provided using a proprietary method by IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc. (Danbury, CT) for each drug. Due to preferences indicated by US FDA, we also calculated rates using the concept of "extended dosage units," which is defined as individual tablets or capsules dispensed at retail pharmacies (IMS Government Solutions, Danbury CT; Secora et al., 2014)

2.3. Analysis procedures

Generalized linear modeling was used to compare the difference in mean population intentional abuse and diversion rates in the year prior to the reformulation (Baseline period: July 2009 through June 2010) to the estimated rate for 2015 quarter (2Q, April 2015 through June 2015) based upon the trend (slope) of the post-reformulation rates. Changes in the OxyContin rate were compared to changes for the Other Opioid group (oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and immediate release oxycodone). The group was chosen because published evidence indicates that abusers switch to a variety of other prescription opioid analgesics, therefore, we combined the oral dosage unit formulation of those products into a single comparison group (Cicero et al., 2012; Havens et al., 2014). Oxymorphone data were only available from 2011 in the Drug Diversion program and from 2011 Q3 in the Opioid Treatment and Survey of Key Informants' Patients Programs. A Poisson regression analysis was used to calculate the expected rates and 95% confidence bands for each time period and drug group. A drug group specific dispersion parameter was included in the model to allow for unequal variances and overdispersion. The six month period encompassing the introduction of