



# The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers



Jennifer R. Havens<sup>a,\*</sup>, Carl G. Leukefeld<sup>a</sup>, Angela M. DeVaugh-Geiss<sup>b</sup>,  
Paul Coplan<sup>b</sup>, Howard D. Chilcoat<sup>b</sup>

<sup>a</sup> Department of Behavioral Science, University of Kentucky College of Medicine, 333 Waller Avenue, Suite 480, Lexington, KY 40504, USA

<sup>b</sup> Risk Management and Epidemiology, Purdue Pharma L.P., One Stamford Forum, Stamford, CT 06901, USA

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## ABSTRACT

**Background:** Prescription opioid abuse is a significant public health concern that requires strategies to reduce its impact, including development of abuse deterrent formulations. OxyContin<sup>®</sup>, an extended-release oxycodone (ERO) formulation, has been widely abused. This study assessed the effects of reformulated ERO, designed to be more difficult to manipulate for purposes of intranasal and intravenous abuse, on patterns of opioid abuse among a sample of individuals from rural Appalachia with a history of ERO abuse.

**Methods:** Structured interviews assessing opioid abuse (past 30-day abuse and retrospectively reported abuse prior to the reformulation in August 2010) were completed by 189 individuals between December 2010 and September 2011.

**Results:** The past 30-day prevalence and frequency of reformulated ERO abuse through any route (33%, 1.9 days/month), snorting (5%, 0.2 days/month), and injecting (0.5%, <0.1 days/month) were low and infrequent compared to that of IR oxycodone (any route: 96%, 19.5 days/month; snorting: 70%, 10.3 days/month; injecting: 51%, 10.5 days/month) and retrospectively reported abuse of original ERO in August 2010 (any route: 74%, 13.4 days/month; snorting: 39%, 6.0 days/month; injecting: 41%, 8.6 days/month). After the reformulation, the prevalence of original ERO abuse significantly declined while abuse of reformulated ERO remained steadily low. Heroin abuse was rare in this sample.

**Conclusions:** In this sample, abuse of reformulated ERO was low, and lower than abuse of original ERO retrospectively and IR oxycodone concurrently, particularly through injecting and snorting routes of administration. There was no evidence to suggest that reformulated ERO became a substitute for original ERO.

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## 1. Introduction

While there is a demonstrated therapeutic benefit of prescription opioids to pain patients, abuse continues to be a significant public health concern in the United States (US; Compton and Volkow, 2006; Zacny et al., 2003) and an emerging problem globally (Degenhardt et al., 2005; Fountain et al., 2000; Tang et al., 2006; Kumar and Agrawal, 2012). The persistence of prescription opioid abuse has spurred the development of strategies to reduce its impact (Office of National Drug Control Policy, 2012a). One

strategy is the development of formulations that are more difficult to manipulate for purposes of abuse. Some opioids have recently been reformulated (Embeda package insert, 2012; Opana package insert, 2011; OxyContin package insert, 2013), and there is laboratory-based and clinical pharmacological evidence (Cone et al., 2013; Sellers et al., 2013; Perrino et al., 2013) as well as emerging evidence in national surveillance systems (Butler et al., 2013; Severtson et al., 2013; Cicero et al., 2012) on their impact. However, existing surveillance systems utilize cross-sectional averages and do not provide detailed measures of abuse or within-individual changes in abuse patterns. Therefore, additional research is warranted that examines patterns of abuse of reformulated opioids, particularly in populations that were abusing original formulations of these drugs.

Although many individuals abuse opioids orally and most new opioid users initiate through oral routes (Katz et al., 2011), there is

\* Corresponding author at: Center on Drug and Alcohol Research, Department of Behavioral Science, University of Kentucky College of Medicine, 333 Waller Avenue, Suite 480, Lexington, KY 40504, USA. Tel.: +1 859 323 6553; fax: +1 859 3236553.

E-mail address: [jennifer.havens@uky.edu](mailto:jennifer.havens@uky.edu) (J.R. Havens).

often progression to non-oral routes (Hays, 2004; Katz et al., 2011), and a longer duration of abuse is associated with snorting or injecting (Butler et al., 2010; Hays, 2004). Additionally, opioid abuse, is particularly prevalent in many rural areas of the US (Havens et al., 2007a, 2007b; Young and Havens, 2012; Leukefeld et al., 2002; Cicero et al., 2007): three studies found high rates of injection drug use (frequently OxyContin® [oxycodone HCl controlled release tablets], an extended-release oxycodone [ERO] formulation manufactured by Purdue Pharma L.P.) among prescription opioid users in rural cohorts (Havens et al., 2007a, 2007b; Young and Havens, 2012), including those where there was little use before the prescription drug epidemic (Leukefeld et al., 2002). Furthermore, Young and Havens (2012) reported that almost half of injection drug users reported initiating injecting with ERO. Recent data also suggest high rates of hepatitis C among rural prescription opioid users, which is largely attributed to injection drug use, particularly prescription opioids (Havens et al., 2013). Crushing and snorting prescription opioids have also been reported among rural drug users (Young et al., 2010). Given the adverse medical outcomes associated with non-oral abuse, it is important to understand the impact of abuse deterrent formulations on abuse, particularly in areas with high rates of opioid abuse through non-oral routes of administration.

In April, 2010, the Food and Drug Administration (FDA) approved a reformulation of ERO (OxyContin®, manufactured by Purdue Pharma L.P.), that is bioequivalent to the original formulation when taken as directed, but has physicochemical properties designed to make it more difficult to manipulate for abuse. In August 2010, manufacturer shipments of original ERO ceased and shipments of reformulated ERO began. By December 2010 and December 2011, 90% and 99%, respectively, of the ERO dispensed in the US was reformulated ERO, with a similar distribution in Kentucky (82% and 99% in the same time periods, respectively; IMS Health NPA), although there was evidence of continued availability of original ERO for abuse despite limited availability through legitimate channels (Butler et al., 2013). Therefore, the primary objective of this study was to describe the extent to which reformulated ERO was abused relative to other opioids, particularly other oxycodone products such as original ERO and immediate-release (IR) oxycodone, in a sample of individuals in rural Kentucky with an established history of ERO abuse. Other opioids, including IR oxycodone, were included to differentiate temporal or secular trends from ERO-specific changes, as well as to explore patterns of possible substitution from one opioid to another. Additionally, we compared abuse of ERO and IR oxycodone to retrospective reports of use prior to the reformulation (August, 2010).

This study complements an epidemiologic study program using several large national surveillance systems to evaluate the effects of the introduction of reformulated ERO on patterns of opioid abuse (Butler et al., 2013; Severtson et al., 2013) by assessing effects among a cohort of individuals with an established history of ERO abuse prior to the ERO reformulation in rural Appalachia, one of the regions of the country most impacted by prescription opioid abuse.

## 2. Methods

Individuals who abused ERO before the reformulation in August 2010 were recruited from rural Perry County, Kentucky, using a purposive sampling technique. Flyers were posted in the study office and areas around Perry County that have been utilized for prior studies (Havens et al., 2008) to recruit initial seed participants, who were in turn asked to recruit up to 3 peers. Individuals were eligible if they were at least 18 years of age and had abused ERO in the 6 months preceding the introduction of reformulated ERO in August, 2010. Consenting participants were interviewed privately at the study office by a single trained interviewer. Participants were compensated \$50 for their time and up to \$30 (total) for recruitment of additional participants. The Institutional Review Board from the University of Kentucky approved the study protocol.

An interviewer-administered questionnaire was used to assess history of substance use/abuse in addition to demographics, employment, medical history, and psychiatric history. The questionnaire was a modified version of Addiction Severity Index (McLellan et al., 1992), including additional drugs and information about routes of administration. Use of prescription opioids, alcohol, and illegal drugs were assessed.

To measure substance abuse, participants were asked about abuse (defined as use of substances to get high), including routes of administration, during: (1) lifetime; (2) the 30 days prior to the release of the reformulation (August, 2010); and (3) in the 30 days prior to interview in the post-reformulation period (conducted December, 2010 through September, 2011). To anchor questions about drug abuse in August, 2010, participants were asked about their abuse before the Black Gold festival, a well-known event in the area that coincided with the initial shipments of reformulated ERO. Anchoring is a common technique used to improve the accuracy of recall (Barsky, 2002).

The Mini Neuropsychiatric Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; Sheehan et al., 1998) was used to measure psychiatric diagnoses common in substance-using and chronic pain populations at the time of the interview (i.e., current major depressive disorder or generalized anxiety disorder, and lifetime history of opioid dependence).

The prevalence of abuse was based on the number of participants reporting  $\geq 1$  day of abuse (any route, snorting, injecting, oral-swallowing). The frequency of abuse (days/month) was calculated as the mean days of abuse overall and via each route; participants who did not report abuse were included as 0 days/month. While the primary focus of this report is non-oral routes of administration, abuse via any route provides an overall measure of abuse encompassing both oral and non-oral routes; the prevalence and frequency of oral abuse are also shown in the figures to provide an overall picture of the abuse of reformulated ERO within this community.

In order to evaluate changes in abuse over time, past 30-day abuse is described both for the entire sample ( $n=189$ ) and divided into 4 mutually exclusive subgroups based on date of interview (period 1 [T1]: December, 2010 through February, 2011,  $n=51$ ; period 2 [T2]: March, 2011 through April, 2011,  $n=64$ ; period 3 [T3]: May, 2011 through June, 2011,  $n=43$ ; period 4 [T4]: July, 2011 through September, 2011,  $n=31$ ). While these subgroups were not defined a priori, they were selected to provide approximately equal time windows over the course of the post-reformulation interview period.

Regression models with Generalized Estimated Equations (GEE), which account for assessment of correlated outcomes within the same respondent, were used to explore abuse (both changes in the same drug across time periods or across drugs within a time period) (Liang and Zeger, 1986; Zeger and Liang, 1986). Poisson regression models with GEE were used for prevalence of abuse data. Negative binomial regression models (estimating rate ratios) with GEE were used for models with drug abuse frequency as the outcome. All models were run separately for each route of administration (any route, snorting, injecting). The models included indicator variables for drug (original ERO, reformulated ERO, any ERO, IR oxycodone) and time, as well as the time  $\times$  drug interaction terms. IR oxycodone was the referent when comparing across drugs within a time period; time period 1 (T1) was the referent when comparing within drugs across time periods. Pre- vs. post-reformulation comparisons were also based on Poisson models with GEE (prevalence) or negative binomial models with GEE (frequency) and were run separately for ERO and IR oxycodone, both overall, and stratified by interview period. Post-reformulation trends were tested using the Cochran–Armitage test for trend (prevalence) and the regression model including categorized date of interview as a continuous variable (frequency).

All analyses were conducted in SAS version 9.2.

## 3. Results

### 3.1. Demographics and drug abuse history

Overall, 365 individuals were screened and 194 were eligible (171 had no ERO abuse in the 6 months prior to the reformulation in August 2010). Of these, 192 were interviewed, and 189 were included in the analysis (3 participants were excluded: one with no substance abuse history, one with no lifetime abuse of ERO, and one who was discontinued from the study after threatening the study staff).

Of the 189 participants, 54.5% were male and nearly all were white (97.9%) (Table 1). All participants reported ever abusing IR oxycodone formulations, 51.3% reported ever abusing reformulated ERO, and nearly all (>90%) reported lifetime abuse of hydrocodone, methadone, benzodiazepines, cocaine, alcohol, and marijuana. Most had a history of injection drug abuse (81.5%), and among those, nearly all (96.1%) had injected prescription opioids. Almost all participants had a history of opioid dependence (96.3%).

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