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The impact of the abuse-deterrent reformulation of extended-release OxyContin on prescription pain reliever misuse and heroin initiation

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HIGHLIGHTS

- Odds of prescription pain reliever misuse declined with abuse-deterrent OxyContin.
- Odds of heroin initiation declined with abuse-deterrent OxyContin.
- No evidence that the odds of heroin use changed due to the OxyContin reformulation.

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ABSTRACT

The introduction of abuse-deterrent OxyContin in 2010 was intended to reduce its misuse by making it more tamper resistant. However, some studies have suggested that this reformulation might have had unintended consequences, such as increases in heroin-related deaths. We used the 2005–2014 cross-sectional U.S. National Survey on Drug Use and Health to explore the impact of this reformulation on intermediate outcomes that precede heroin-related deaths for individuals with a history of OxyContin misuse. Our study sample consisted of adults who misused any prescription pain reliever prior to the reformulation of OxyContin (n = 81,400). Those who misused OxyContin prior to the reformulation were considered the exposed group and those who misused other prescription pain relievers prior to the reformulation were considered the unexposed group. We employed multivariate logistic regression under a difference-in-differences framework to examine the effect of the reformulation on five dichotomous outcomes: prescription pain reliever misuse; prescription pain reliever use disorder; heroin use; heroin use disorder; and heroin initiation. We found a net reduction in the odds of prescription pain reliever misuse (OR:0.791, $p < 0.001$) and heroin initiation (OR:0.422, $p = 0.011$) after the reformulation for the exposed group relative to the unexposed group. We found no statistically significant effects of the reformulation on prescription pain reliever use disorder (OR: 0.934, $p = 0.524$), heroin use (OR: 1.014p = 0.941), and heroin use disorder (OR: 1.063, $p = 0.804$). Thus, the reformulation of OxyContin appears to have reduced prescription pain reliever misuse without contributing to relatively greater new heroin use among those who misused OxyContin prior to the reformulation.

1. Introduction

Opioid misuse continues to be a significant public health concern in the United States. In 2015, approximately 12.5 million people had used prescription pain relievers non-medically (i.e., misused) in the past year, making it the second most misused class of drugs after marijuana (Hughes et al., 2016). This is concerning, as continued misuse of prescription pain relievers can lead to addiction, overdoses (including fatal overdoses), and experimentation with potent, illicit opioids, such as heroin (Alpert, Powell, & Pacula, 2018; Compton, Jones, & Baldwin, 2016; Jones, 2013). Government agencies have enacted several policies to curb prescription pain reliever misuse, including educational efforts

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about appropriate use (US Department of Health and Human Services, 2015); prescription drug monitoring programs (Ali, Dowd, Classen, Mutter, & Novak, 2017); opioid prescribing guidelines (Dowell, Haegerich, & Chou, 2016); and supporting abuse-deterrent formulations of prescription opioids (Cicero & Ellis, 2015; Cicero, Ellis, & Surratt, 2012).

Abuse-deterrent opioid formulations (Opioid Abuse Deterrence, Research, and Recovery Act of 2017, 2017) have received recent attention, particularly related to their impacts on prescription pain reliever misuse and associated outcomes. Abuse-deterrent formulations are intended to reduce abuse by making the drugs more tamper resistant. A notable example was the 2010 reformulation of OxyContin, which made that product more difficult to cut, crush, and dissolve (OXYCONTIN, 2017) This innovation has received substantial policy and research interest because of the original product's high market share and potential for abuse (Cicero & Ellis, 2015; Cicero et al., 2012; Butler et al., 2013; Coplan, Kale, Sandstrom, Landau, & Chilcoat, 2013; Havens, Leukefeld, DeVeaugh-Geiss, Coplan, & Chilcoat, 2014; Sessler et al., 2014; Severtson et al., 2016).

Previous studies examining the impact of the reformulation found that, as anticipated, it coincided with a significant reduction in OxyContin misuse (Cicero et al., 2012; Coplan et al., 2013; Havens et al., 2014; Jones, Muhuri, & Lurie, 2017; Opioid Abuse Deterrence, Research, and Recovery Act of, 2017; Sessler et al., 2014; Severtson et al., 2016). One notable exception to this is work by Jones and colleagues (Jones et al., 2017); which found no significant difference in the prevalence of OxyContin misuse before the reformulation from 2006 to 2009 and after the reformulation in 2013. Concerns have been raised, however, that the reformulation may have led to an unintended consequence: an increase in heroin use and deaths (Alpert et al., 2018; Cicero & Ellis, 2015; Dart et al., 2015; Evans, Lieber, & Power, 2019). Between 2010 and 2014, the number of heroin-related deaths tripled, (Center for Disease Control and Prevention NCfIPaC, Division of Unintentional Injury Prevention. Opioid Data Analysis. Accessed 5/21/, 2017) and some studies have concluded that the reformulation led to a substantial share of these deaths (Alpert et al., 2018; Evans et al., 2019). However, many of these studies did not test the intermediate steps necessary to link the reformulation to heroin deaths, such as heroin initiation and use; those that did seek to address this issue relied on small convenience samples which may not be generalizable to the broader population (Cicero & Ellis, 2015).

Our study fills an important gap in the literature by exploring whether the reformulation was associated with some of the intermediate outcomes necessary to explain the previously hypothesized connection to heroin deaths. We utilized data from the U.S. National Survey on Drug Use and Health (NSDUH) to measure the nationwide impacts of the reformulation on prescription pain reliever misuse, pain reliever use disorder, heroin intiation, heroin use, and heroin use disorder among individuals with a history of OxyContin misuse. To do this, we used a difference-in-differences methodology comparing two groups of individuals, each with a history of misuse: inidividuals who misused OxyContin prior to the reformulation and those who misused other prescription pain relievers prior to the reformulation. For the group with a history of OxyContin misuse, the drug they had misused became more difficult to use for non-medical purposes due to the reformulation; the group which misused other prescription pain relievers experienced no change in their ability to use their drugs non-medically.

2. Methods

2.1. Data

Our primary data source was the 2005–2014 National Survey on Drug Use and Health (NSDUH). The NSDUH is an annual cross-sectional survey at the individual-level conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) that provides detailed information about the substance use and mental health of the civilian, noninstitutionalized population age 12 and older in the United States. Data on self-reported substance use includes information on past month use, past year use, lifetime use, and age at first use. Item nonresponse in the survey is addressed using a model-based statistical imputation procedure (RTI International, 2015). More detailed information about NSDUH's design and data collection process can be found elsewhere (Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2015). We supplemented NSDUH with previously-published data on prescription drug monitoring programs (PDMPs) (Ali et al., 2017).

Our study sample was composed of individuals age 18 and above who reported engaging in non-medical use of any opioid or non-opioid prescription pain reliever (the vast majority of prescription pain relievers, however, are opioid-based) (Carpenter, McClellan, & Rees, 2017) prior to the introduction of the abuse-deterrent formulation of OxyContin (i.e., in 2010 or before) based on their reported year of first non-medical use (unadjusted n = 81,400). Non-medical use is defined in the NSDUH as taking a drug that was not prescribed for you or taking the drug only for the experience or feeling it caused.

2.2. Defining exposure

The intervention that we studied was the reformulation of OxyContin from non-abuse-deterrent to its abuse-deterrent formulation. We assume that individuals who misused non-abuse-deterrent OxyContin were exposed to the reformulation in that the product they had misused became more difficult to misuse. We defined exposure to the reformulation, therefore, as reported misuse of OxyContin in any year prior to the reformulation. To do this, we calculated the year of first misuse of OxyContin using the individual's current age and reported age at first misuse. Any individual whose calculated year of first misuse was prior to the reformulation was then assumed to be exposed to the reformulation. Based on this definition of exposure, we separated individuals into exposed and unexposed groups. The exposed group consisted of individuals who reported first misusing OxyContin in any year prior to and including 2010 (unadjusted n = 17,000). The unexposed group consisted of individuals who did not report misusing OxyContin prior to the reformulation but who did report their first misuse of other prescription pain relievers during this time (unadjusted n = 64,400). Because only non-abuse-deterrent OxyContin was available prior to the reformulation in 2010, our exposed group was comprised of individuals who misused non-abuse-deterrent OxyContin and our unexposed group was comprised of individuals who did not misuse OxyContin but did misuse other prescription pain relievers prior to the OxyContin reformulation. As such, the former group should be directly affected by OxyContin's reformulation while the latter group should not.

2.3. Outcomes

We considered five dichotomous outcomes in this study based on self-reported behavior in the twelve months prior to the interview (i.e.the past year): prescription pain reliever misuse, prescription pain reliever use disorder, heroin use, heroin use disorder, and heroin initiation. The outcomes measuring use disorder were derived from respondent answers to sets of survey questions corresponding to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (American Psychiatric Association, 1994; Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2015). The heroin initiation outcome equaled one if the respondent indicated using heroin for the first time in the past year and equaled zero if the respondent indicated never using heroin; respondents who reported using heroin more than one year prior to the survey year were excluded from this outcome measure.

Table 1
Mean Descriptive Characteristics of Adults in Sample, by Exposure and Time Period.

	Pre-Reformulation (Survey Years 2005 – 2010)			Post-Reformulation (Survey Years 2011 – 2014)		
	Exposed Group (N = 10,200)	Unexposed Group (N = 42,000)	P-value	Exposed Group (N = 6,800)	Unexposed Group (N = 22,400)	P-value
Age	31.061 (13.075)	37.656 (13.219)	< 0.001	34.065 (12.567)	40.576 (12.807)	< 0.001
Male	0.627	0.549	< 0.001	0.637	0.553	< 0.001
White, non-Hispanic	0.859	0.751	< 0.001	0.845	0.714	< 0.001
Black, non-Hispanic	0.039	0.088	< 0.001	0.036	0.098	< 0.001
Other, non-Hispanic	0.036	0.044	< 0.001	0.041	0.053	< 0.001
Hispanic	0.065	0.118	< 0.001	0.078	0.135	< 0.001
Less than High School Degree	0.174	0.154	< 0.001	0.152	0.134	< 0.001
High School Degree	0.327	0.308	< 0.001	0.312	0.288	< 0.001
Some College/Assoc. Degree	0.332	0.294	< 0.001	0.338	0.307	< 0.001
College Degree	0.104	0.133	< 0.001	0.120	0.148	< 0.001
Graduate/Professional Degree	0.062	0.111	< 0.001	0.078	0.123	< 0.001
Percent of Federal Poverty Level	308.143 (266.879)	345.798 (233.557)	< 0.001	284.974 (221.188)	320.287 (203.802)	< 0.001
Lives in Urban County	0.846	0.851	0.483	0.836	0.858	0.003
State has no PDMP	0.475	0.484	0.001	0.144	0.114	< 0.001
State has Voluntary PDMP	0.497	0.499	0.001	0.614	0.668	< 0.001
State Requires Prescribers to Access PDMP	0.007	0.006	0.001	0.106	0.097	< 0.001
State Requires Prescribers to Enroll in PDMP	0.020	0.011	0.001	0.058	0.066	< 0.001
State Requires PDMP Access and Enrollment	0.000	0.000	–	0.079	0.055	< 0.001
Past Year Prescription Pain Reliever Misuse	0.558	0.297	< 0.001	0.419	0.238	< 0.001
Past Year Prescription Pain Reliever Use Disorder	0.154	0.030	< 0.001	0.146	0.030	< 0.001
Past Year Heroin Use	0.056	0.005	< 0.001	0.074	0.007	< 0.001
Past Year Heroin Use Disorder	0.036	0.003	< 0.001	0.057	0.004	< 0.001
Past Year Heroin Initiation	0.017	0.001	< 0.001	0.017	0.002	< 0.001

Means (SD in parentheses) adjusted for survey design and weights. Survey-adjusted F-tests for differences between groups. The exposed group consists of individuals who misused OxyContin prior to the reformulation. The unexposed group consists of individuals who did not misuse OxyContin, but did misuse other prescription pain relievers, prior to the reformulation. Each individual is observed in only one survey year.
SD – Standard Deviation.
PDMP – Prescription Drug Monitoring Program.

2.4. Covariates

We controled for demographic and socioeconomic characteristics, including age, gender, race/ethnicity, educational attainment, and income as a percentage of the federal poverty level. We also controled for the respondent's state of residence using state fixed effects and for whether the respondent lives in an urban or rural area as defined by the Census Bureau (United States Census Bureau, 2015). Finally, we controled for whether there was an active PDMP in the respondent's state of residence at the time of interview, as these programs have been shown to substantially affect opioid prescriptions and prescription pain reliever misuse (Ali et al., 2017). We categorized states as having no PDMP, a voluntary PDMP, or a PDMP with mandatory provisions requiring prescribers to enroll in and/or access it when prescribing (Ali et al., 2017).

2.5. Statistical analysis

To estimate the impact of OxyContin's reformulation on each of our five outcomes, we employed multivariate logistic regression under a difference-in-differences framework. The difference-in-differences framework compared changes in outcomes over time between the exposed group and the unexposed group. The difference in those changes is interpreted as the net impact of the intervention on the exposed group relative to the unexposed group.

To estimate the model, we regressed the individual's self-reported outcome (e.g. whether or not the individual used heroin in the 12 months prior to the survey interview) on our exposure indicator (i.e., OxyContin misuse prior to the reformulation), an indicator for the post-reformulation period (i.e., 2011–2014), and the interaction between those two indicators, controlling for the covariates discussed above. The estimated coefficient on the interaction term captured the net impact of OxyContin's reformulation for individuals who were exposed to the original, non-abuse-deterrent formulation of OxyContin relative to those who were not exposed to the original OxyContin but who did have a history of other prescription pain reliever misuse.

While the difference-in-differences approach is often used with longitudinal data, its application to pooled cross-sectional data, such as the NSDUH, is well established in the literature 28-31 (Buckley & Shang, 2003; Chatterji et al., 2010; Hong, 2013; Rudasingwa, Soeters, & Basenya, 2017; Rudd, Aleshire, Zibbell, & Matthew, 2016). When using this approach with pooled cross-sectional data, one key assumption upon which the validity of difference-in-differences estimation relies is that neither the exposed nor the unexposed group may experience disproportional compositional changes in the sample over time. We examined the distributions of characteristics over time graphically and tested for compositional change by regressing individual characteristics on our policy variables and found no evidence of observable compositional changes that could bias our results. We also examined pre-reformulation trends to ensure that the parallel trends assumption was satisfied, conducted a falsification test using an alternative policy implementation date, estimated our models without controls, and estimated the models with clustered standard errors rather than survey-adjusted standard errors. Our results were robust to these alternative specifications. More details on the models and tests of their underlying assumptions may be found in the Supplementary Appendix.

We also estimated a set of event study models similar to the difference-in-differences model described above but replacing the single indicator for the post-reformulation period with a set of indicators representing each survey year in our data. In these event study models, the coefficient estimates on the interactions between our exposure indicator and the indicator for each survey year provide estimates of the impact of the OxyContin reformulation in each individual year.

We conducted all analyses in Stata 15 using the svy prefix to account for survey weights and sampling design (McClellan et al., 2018). The analysis weights in NSDUH were constructed through a multistage process and represent the inverse probability of selection at each sampling stage (i.e., household selection, respondent selection),

Table 2
Estimating the Effects of the OxyContin Reformulation: Odds Ratios from Models for Prescription Pain Reliver Misuse and Use Disorder and Heroin Use, Use Disorder, and Initiation Outcomes, Difference-in-Difference Framework.

Outcome Measures	Past Year Prescription Pain Reliever Misuse	Past Year Prescription Pain Reliever Use Disorder	Past Year Heroin Use	Past Year Heroin Use Disorder	Past Year Heroin Initiation,
Exposure	2.683***	5.349***	9.547***	11.536***	10.875***
	[2.479,2.905]	[4.705,6.081]	[7.159,12.733]	[8.117,16.394]	[7.083,16.696]
	(< 0.001)	(< 0.001)	(< 0.001)	(< 0.001)	(< 0.001)
Post-reformulation	0.808***	1.055	1.300	1.373	2.654***
	[0.753,0.868]	[0.896,1.243]	[0.923,1.832]	[0.883,2.137]	[1.502,4.690]
	(< 0.001)	(0.517)	(0.134)	(0.160)	(0.001)
Exposure × Post-reformulation	0.791***	0.934	1.014	1.063	0.422**
	[0.694,0.902]	[0.756,1.153]	[0.697,1.476]	[0.657,1.718]	[0.218,0.818]
	(< 0.001)	(0.524)	(0.941)	(0.804)	(0.011)
Observations	81,400	81,400	80,600	79,700	72,800

Survey-adjusted odds ratios from logit regressions with confidence intervals presented in brackets and P-values in parentheses. "Exposure" is an indicator for OxyContin misuse prior to the reformulation, and "Post-reformulation" is an indicator for individuals surveyed after the reformulation (i.e. 2011–2014 survey years). The reference group is made up of those individuals who did not misuse OxyContin prior to the reformulation.
Reformulation date set at 1/1/2011.
* P < 0.10, ** P < 0.05, *** P < 0.01.
x – Indicates interaction term.
All models control for age, age squared, gender, race/ethnicity, education, income, urbanicity, state PDMP policy, and state of residence (implemented as state-level fixed effects). See Supplementary Appendix for full results.

adjustments for nonresponse and extreme weights, and poststratification to known population data (i.e., from the U.S. Census) (RTI International. (2015), 2015). The use of these weights and accounting for the sampling design produced estimates that are nationally representative.

3. Results

The demographic and socioeconomic characteristics of our sample are shown in Table 1. The composition of our exposed and unexposed groups was generally stable over time, as were the differences between them. While the prevalence of PDMPs increased after the reformulation, similar changes occurred in both groups. We observed some differences between the groups within the two periods: individuals in our exposed group were younger and were more likely to be male, white, have no college degree, and to be poorer. We adjusted for these observed differences in the multivariate logistic regression.

The key results from our difference-in-differences framework are shown in Table 2. The full results and sensitivity analyses are shown in the Supplementary Appendix. We found that misuse of prescription pain relievers declined in both the exposed and the unexposed groups, but the decline was greater in the exposed group relative to the unexposed group. Specifically, the exposed group had 21 percent lower odds of misusing prescription pain relievers after the reformulation than the unexposed group (OR: 0.791, CI: 0.694–0.902, p < 0.001). Similarly, although heroin initiation increased in both groups, the increase was smaller in the exposed group than in the unexposed group. We found that the odds of heroin initiation in the exposed group were 58 percent lower than the unexposed group (OR: 0.422, CI: 0.218–0.818, p = 0.011). We found no statistically significant effect of the reformulation on the exposed group relative to the unexposed group for prescription pain reliever use disorder (OR: 0.934, CI: 0.756–1.153, p = 0.524), heroin use (OR: 1.014, CI: 0.697–1.476, p = 0.941), and heroin use disorder (OR: 1.063, CI: 0.657–1.718, p = 0.804). Our sensitivity analyses broadly confirm these results; details are provided in the Supplementary Appendix.

In Fig. 1, we present odds ratios estimated from the event study models for the exposed group relative to the unexposed group for each outcome variable in each year. For the years after the reformulation, the results confirm our findings from our difference-in-differences framework and demonstrate that the impact of the reformulation on the exposed group appears to have grown over time for prescription pain reliever misuse while being steady over time for heroin initiation. For the other outcome measures, we continued to find that the reformulation had no statistically significant impact on the exposed group relative to the unexposed group.

4. Discussion

Mitigating the rise in prescription pain reliever misuse requires policies that can address the numerous paths leading to this behavior. Three possible outcomes that might justify a role for abuse-deterrent opioids include: (1) discouraging users of prescription pain relievers from misusing these products; (2) reducing the likelihood that existing prescription pain reliever misusers transition into use disorders; and, consequently (3) preventing the transition from prescription pain relievers to illicit opioids, such as heroin. Our analysis provides three findings that collectively suggest that the reformulation of OxyContin was associated with a reduction in the misuse of prescription pain relievers among those with a history of OxyContin misuse and that it was not associated with relatively greater increases in heroin initiation or the likelihood of heroin use among this group.

Our first major finding is that the reformulation of OxyContin was associated with a net reduction in the misuse of prescription pain relievers among those who misused OxyContin prior to the reformulation. While both the exposed and unexposed groups experienced a decline in prescription pain reliever misuse following the reformulation, that decline was greater for the exposed group. We estimate that individuals who had misused OxyContin prior to the reformulation experienced a cumulative 21 percent reduction in the odds of misuse over the first three years following the reformulation relative to the unexposed group, and this impact appears to have increased over time. These results suggest that some individuals no longer misused any prescription pain relievers once it became more difficult to tamper with OxyContin.

Our second major finding is that the reformulation appears not to be associated with a net change in the incidence of prescription pain reliever use disorder, heroin use disorder, or heroin use among those with a history of pre-reformulation OxyContin misuse. Although abuse-deterrent OxyContin is more difficult to cut, crush, and dissolve compared with the original extended-release product (OXYCONTIN, 2017), there are still ways for individuals to circumvent these properties (Cicero & Ellis, 2015). This result, combined with our first major finding, suggests that the reformulation may have discouraged some from misusing prescription pain relievers, but it may not have impacted the likelihood

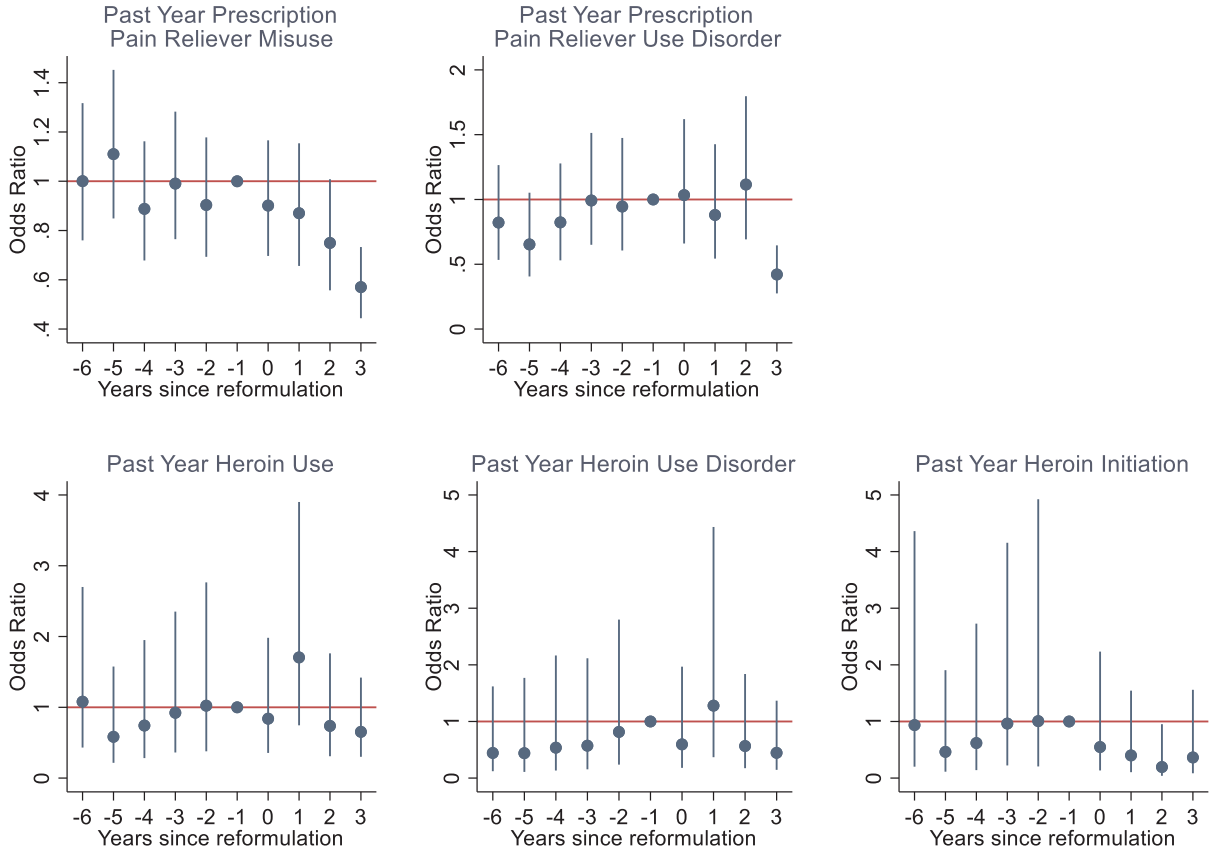

Fig. 1. Estimating Effects of the OxyContin Reformulation in Each Individual Year: Odds Ratios from Event Study Models for Prescription Pain Reliver Misuse and Use Disorder, and Heroin Use, Use Disorder and Initiation Outcomes. Survey-adjusted odds ratios with confidence interval bars for the interaction between exposure to the OxyContin reformulation and survey year. The year 2011 represents zero years since the reformulation. All models control for age, age squared, gender, race/ethnicity, education, income, urbanicity, state PDMP policy, and state of residence (implemented as state-level fixed effects).

of prescription pain reliever misuse or heroin use among those experiencing the more severe use disorders, at least in the first few years following the reformulation.

Our third major finding is that, while heroin initiation rose in both groups following the reformulation, the implementation of abuse-deterrent OxyContin appears to be associated with relatively lower heroin initiation for the exposed group; all else constant, the unexposed group experienced a larger increase in heroin initiation than did the exposed group. We estimate that individuals who had misused OxyContin prior to the reformulation experienced a 58 percent reduction in the odds that they initiated heroin after the reformulation compared to those who had misused other prescription pain relievers, with much of this impact occurring at least two years after the reformulation. This result suggests that the reformulation did not lead those who had previously misused OxyContin to more frequently begin using heroin relative to those who had misused other prescription pain relievers.

Combined, our results suggest that the reformulation did not increase the likelihood that OxyContin misusers would use heroin, either among new or existing heroin users. To the extent that misuse of prescription pain relievers may have led to heroin use prior to the OxyContin reformulation, the likelihood of that transition did not seem to increase because of the reformulation. While previous studies have suggested that the reformulation led to increases in heroin deaths (Alpert et al., 2018; Cicero & Ellis, 2015; Coplan et al., 2013; Dart et al., 2015), our results suggest that any increase that occurred was likely not due to individuals switching from OxyContin to heroin. If this had been the case, we would expect to observe increases in the odds of heroin initiation and heroin use. Our results, however, suggest the opposite: that the reformulation was associated with a relatively smaller increase in the odds of heroin initiation and no statistically significant change in the odds of heroin use or use disorder among those who misused OxyContin prior to the reformulation. Previous studies only analyzed trends in final outcomes, such as heroin deaths, and lacked the individual-level data to link OxyContin misuse with heroin-related deaths in any given individual. Other concurrent trends may have contributed to observed increases in heroin deaths during this time period; examples include the greater availability of heroin, lower heroin prices, changes in the quantity of heroin being used, and the increased potency of illicit opioids due to the expanded use of fentanyl and its analogues (Compton et al., 2016; Rudd et al., 2016). More research needs to be done to understand the relationship between these trends and the rising heroin death rate in the post-reformulation period.

We obtained our results by implementing a difference-in-differences approach which included a group that we hypothesize was not exposed to the reformulation. This method allowed us to remove the effects of factors that impacted both groups simultaneously or that were constant over time within each group. We also controled for PDMPs as well as unobserved factors that varied across states but were constant over time using the restricted NSDUH dataset with state identifiers.

Our study has a few limitations. First, rather than measuring the same individuals over time, our data consist of repeated cross-sections containing different individuals in each year. While we did control for observed individual-level differences and found no evidence of observed differential changes in the sample composition, we were unable to account for unobserved individual-level differences or differential changes in sample composition that may have influenced the outcomes, including any triggered by the OxyContin reformulation. Second, the reformulation could have indirectly affected our unexposed group if it contributed to changes in, for example, the prices or insurance coverage of other prescription pain relievers, which could have either increased

or decreased our estimated impacts. Third, our approach made use of survey data that excluded people who were homeless or institutionalized and relied on self-reported measures of drug use. Both characteristics may have produced underestimates of heroin initiation and use, and our findings of the impact of the reformulation may not be generalizable to certain high-risk groups excluded from the NSDUH sampling frame. Finally, our study may not be generalizable to other abuse-deterrent opioids, particularly if they have lower market shares than OxyContin or are entering markets that are already partly saturated with other abuse-deterrent products.

Evidence indicates that abuse-deterrent formulations of prescription opioids are an important part of a broader public health strategy for addressing the opioid crisis. Additional efforts are needed to help the approximately two million people with existing opioid use disorders; interventions might include increasing the availability of naloxone and the utilization of medication-assisted treatment (MAT). Previous research has found that naloxone access laws and Good Samaritan laws are potentially associated with lower incidence of opioid-overdose mortality (McClellan et al., 2018). While MAT has been demonstrated to be effective at treating patients with opioid use disorder, it is underutilized from a clinical perspective (Naeger et al., 2016; Saloner & Barry, 2018). As additional approaches to addressing the opioid crisis are proposed, it will be important to subject them to similarly rigorous evaluation and to identify potential opportunities to implement them on a broader scale (Sharfstein, 2018).

This research is particularly timely for policymakers, who have been tasked with increasing the prevalence of abuse-deterrent opioids in the marketplace (Administration FaD, 2018) while they face scrutiny over whether these products are cost-effective and whether unintended risks might offset intended benefits (Becker and Fiellin, 2017). Our results suggest that expanding access to abuse-deterrent opioids might provide further contributions towards addressing prescription pain reliever misuse as part of a comprehensive strategy for combating the opioid crisis without contributing to new heroin use.

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Disclaimer

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Declarations of interest

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Contributors

All authors contributed to the design of the study, the statistical analysis, and the writing and editing of the manuscript. All authors have approved the final manuscript.

Conflict of interest

Carolyn Wolff, Lukas Glos, Matthew Rosenberg, and Andreas Schick are employees at the U.S. Food and Drug Administration. All other authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2019.106268.

References

Administration FaD. (2018). Healthy innovation, safer families: FDA's 2018 strategic policy roadmap. Silver Spring, MD.

Ali, M. M., Dowd, W. N., Classen, T., Mutter, R., & Novak, S. P. (2017). Prescription drug monitoring programs, nonmedical use of prescription drugs, and heroin use: Evidence from the National Survey of Drug Use and Health. *Addictive Behaviors, 69*, 65–77.

Alpert, A., Powell, D., & Pacula, R. L. (2018). Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids. *American Economic Journal: Economic Policy, 10*(4), 1–35.

Carpenter, C. S., McClellan, C. B., & Rees, D. I. (2017). Economic conditions, illicit drug use, and substance use disorders in the United States. *Journal of Health Economics, 52*, 63–73.

American Psychiatric Association. (1994). DSM-IV: Diagnostic and statistical manual. Washington, DC: American Psychiatric Association.

Becker, W. C., & Fiellin, D. A. (2017). Limited evidence, faulty reasoning, and potential for a global opioid crisis. *BMJ: British Medical Journal (Online),* 358.

Buckley, J., & Shang, Y. (2003). Estimating policy and program effects with observational data: The "differences-in-differences" estimator. *Practical Assessment, Research & Evaluation, 8*(24), 1–10.

Chatterji, M., Hutchinson, P., Buek, K., Murray, N., Mulenga, Y., & Ventimiglia, T. (2010). Evaluating the impact of community-based interventions on schooling outcomes among orphans and vulnerable children in Lusaka, Zambia. *Vulnerable Children and Youth Studies, 5*(2), 130–141.

Butler, S. F., Cassidy, T. A., Chilcoat, H., Black, R. A., Landau, C., Budman, S. H., & Coplan, P. M. (2013). Abuse rates and routes of administration of reformulated extended-release oxycodone: Initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. *The Journal of Pain, 14*(4), 351–358.

Dart, R. C., Surratt, H. L., Cicero, T. J., Parrino, M. W., Severtson, S. G., Bucher-Bartelson, B., & Green, J. L. (2015). Trends in opioid analgesic abuse and mortality in the United States. *New England Journal of Medicine, 372*(3), 241–248.

Center for Disease Control and Prevention NCfIPaC, Division of Unintentional Injury Prevention. Opioid Data Analysis. Accessed 5/21/2018, 2017.

Cicero, T. J., & Ellis, M. S. (2015). Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. *JAMA Psychiatry, 72*(5), 424–430.

Cicero, T. J., Ellis, M. S., & Surratt, H. L. (2012). Effect of abuse-deterrent formulation of OxyContin. *New England Journal of Medicine, 367*(2), 187–189.

Opioid Abuse Deterrence, Research, and Recovery Act of 2017 (2017).

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between nonmedical prescription-opioid use and heroin use. *The New England Journal of Medicine, 374*(2), 154–163.

Coplan, P. M., Kale, H., Sandstrom, L., Landau, C., & Chilcoat, H. D. (2013). Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiology and Drug Safety, 22*(12), 1274–1282.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA, 315*(15), 1624–1645.

Evans, W. N., Lieber, E., & Power, P. (2019). How the reformulation of oxycontin ignited the heroin epidemic. *Review of Economics and Statistics, 101*(1), 1–15.

Havens, J. R., Leukefeld, C. G., DeVeaugh-Geiss, A. M., Coplan, P., & Chilcoat, H. D. (2014). The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. *Drug and Alcohol Dependence, 139*, 9–17.

Hong, S. H. (2013). Measuring the effect of napster on recorded music sales: Difference-in-differences estimates under compositional changes. *Journal of Applied Econometrics, 28*(2), 297–324.

Hughes, A., Williams, M., Lipari, R., Bose, J., Copello, E., & Kroutil, L. (2016). Prescription drug use and misuse in the United States: Results from the 2015 National

Survey on Drug Use and Health. *NSDUH Data Review,* A1–A24.
Jones, C. M. (2013). Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers–United States, 2002–2004 and 2008–2010. *Drug and Alcohol Dependence, 132*(1), 95–100.
US Department of Health and Human Services (2015). Opioid abuse in the US and HHS actions to address opioid-drug related overdoses and deaths.
Jones, C. M., Muhuri, P. K., & Lurie, P. G. (2017). Trends in the nonmedical use of OxyContin, United States, 2006 to 2013. *The Clinical Journal of Pain, 33*(5), 452–461.
McClellan, C., Lambdin, B. H., Ali, M. M., Mutter, R., Davis, C. S., Wheeler, E., ... Kral, A. H. (2018). Opioid-overdose laws association with opioid use and overdose mortality. *Addictive Behaviors*.
Naeger, S., Ali, M. M., Mutter, R., Mark, T. L., & Hughey, L. (2016). Prescriptions filled following an opioid-related hospitalization. *Psychiatric Services, 67*(11), 1262–1264.
OXYCONTIN (oxycodone hydrochloride) extended-release tablet [package insert], Purdue Pharma L.P., Stamford, CT. 2017:28.
RTI International. (2015). 2014 National Survey on Drug Use and Health Methodological Summary and Definitions. Available at https://www.samhsa.gov/data/sites/default/files/NSDUH-MethodSummDefs2014/NSDUH-MethodSummDefs2014.htm.
Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available at http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.
Rudasingwa, M., Soeters, R., & Basenya, O. (2017). The effect of performance-based financing on maternal healthcare use in Burundi: A two-wave pooled cross-sectional analysis. *Global Health Action, 10*(1), 1327241.
Rudd, R. A., Aleshire, N., Zibbell, J. E., & Matthew, Gladden R. (2016). Increases in drug and opioid overdose deaths-United States, 2000–2014. *American Journal of Transplantation, 4*, 1323.
Saloner, B., & Barry, C. L. (2018). Ending the opioid epidemic requires a historic investment in medication-assisted treatmeNT. *Journal of Policy Analysis and Management, 37*(2), 431–438.
Sessler, N. E., Downing, J. M., Kale, H., Chilcoat, H. D., Baumgartner, T. F., & Coplan, P. M. (2014). Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. *Pharmacoepidemiology and Drug Safety, 23*(12), 1238–1246.
Severtson, S. G., Ellis, M. S., Kurtz, S. P., Rosenblum, A., Cicero, T. J., Parrino, M. W., ... BucherBartelson, B. (2016). Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone. *Drug and Alcohol Dependence, 168*, 219–229.
Sharfstein, J. M. (2018). A new year's wish on opioids. *JAMA. 319*(6), 537–538.
Stata Statistical Software: Release 14 [computer program]. (2015). Version. College Station, TX.
Substance Abuse and Mental Health Services Administration. (2016). Key substance use and mental health indicators in the United States: Results from the 2015 national survey on drug use and health. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available at https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf.
United States Census Bureau. (2015). 2010 Census Urban and Rural Classification and Urban Area Criteria. Available at https://www.census.gov/geo/reference/ua/urban-rural-2010.html.