ORIGINAL ARTICLE

Do abuse deterrent opioid formulations work?

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ABSTRACT

Objective: *We performed a systematic review to answer the question, "Does the introduction of an opioid analgesic with abuse deterrent properties result in reduced overall abuse of the drug in the community?"*

Design: *We included opioid analgesics with abuse deterrent properties (hydrocodone, morphine, oxycodone) with results restricted to the metasearch term "delayed onset," English language, use in humans, and publication years 2009-2016. All articles that contained data evaluating misuse, abuse, overdose, addiction, and death were included. The results were categorized using the Bradford-Hill criteria.*

Results: *We included 44 reports: hydrocodone (n = 7), morphine (n = 5), or oxycodone (n = 32) with Food and Drug Administration-approved Categories 1, 2, or 3 abuse deterrent labeling. The data currently available support the Hill criteria of strength (effect size), consistency (reproducibility), temporality, plausibility, and coherence. There was insufficient or no information available for the criteria of biological gradient, experiment, and analogy. We also assessed confounding factors and bias, which indicated that both were present and substantial in magnitude.*

Conclusions: *Our analysis found that only oxycodone extended release (ER) had information available to evaluate abuse deterrence in the community. In Australia, Canada, and the United States, reformulation of oxycodone ER was followed by marked reduction in measures of abuse. The precise extent of reduced abuse cannot be calculated because of heterogeneous data sets, but the reported reductions ranged from 10 to 90 percent depending on the measure and the duration of follow-up.*

INTRODUCTION

The toll of illness and death caused by epidemic prescription drug abuse in the United States is well documented, but effective approaches are widely debated. Among intervention strategies, there has been intense controversy surrounding the role of opioid analgesics with abuse deterrent properties.[1,2] Currently, these products have either a physical barrier that makes them difficult to crush or include opioid antagonists that are released when crushed thereby attenuating their effect after tampering. The United States Food and Drug Administration (FDA) has encouraged development of these products and has provided regulatory guidance.[3]

Although there are many different trajectories, opioid abuse often begins with excess ingestion of intact tablets followed by chewing. Manipulation of the tablet by chewing or crushing allows more rapid onset and increased intensity of intoxication. These behaviors are associated with increased risk of overdose, addiction, and death. In addition, intravenous abuse can cause infection and thrombotic complications.

Proponents view abuse deterrent opioids like seats belts: a difficult to abuse product that does not prevent abuse completely, but reduces harms from the medication by reducing chewing, nasal insufflation, and injection. This view is supported by research indicating the formulation of a drug can reduce its attractiveness for abuse.[4-23]

Opponents contend that the research available has not proven the effectiveness of these products, that abuse deterrent features can be overcome with enough effort and that an abuse deterrent formulation (ADF) might increase prescribing due to a false sense of security.[2,24,25] There is also concern about injection-related complications resulting from dangerous methods to overcome tamper-deterring properties as well as potentially "pushing" abusers to heroin.[26]

The FDA defines four categories of evidence for evaluating abuse deterrence from *in vitro* to population analysis: Laboratory Manipulation and Extraction Studies (Category 1), Pharmacokinetic studies (Category 2), Clinical Abuse Potential Studies (Category 3), and Postmarket Studies (Category 4).[3] The strength of the labeled claim of abuse deterrence increases with each category and culminates with Category 4 showing effectiveness under "real-world" conditions "in the community."[3] No opioid analgesic has Category 4 labeling.

We now have several years of postmarket experience with ADFs. The first opioid analgesic formulation with approved abuse deterrent labeling, reformulated OxyContin, was introduced in 2010 and was allowed labeling for Categories 1, 2, and 3. Several other products followed, with analogous labeling, but most have attained relatively low sales volume.

We performed a systematic review of the evidence available on products with abuse deterrent labeling in relation to Category 4. The question we assessed was "Does the introduction of an opioid with product labeling that fulfilled FDA Categories 1, 2, and 3 result in reduced overall abuse of the drug in the community?" We utilized the well-known Bradford-Hill "criteria" as a framework for analysis (Table 1). Bradford-Hill offered "… nine different viewpoints from all of which we should study association before we cry causation."[27] These dimensions do not prove causation, but provide a useful format for formulating assessment. In addition to the original criteria, we address the factors of confounding, bias, and competing interventions.[28,29]

METHODS

Search strategy

We performed a systematic review of the published literature to assess the body of evidence that addresses products with abuse deterrent properties, using the Ovid search engine (Ovid Technologies, New York, NY) on January 7, 2017. The search terms included each pharmaceutical ingredient available in an FDA approved category 1, 2, or 3 ADF (hydrocodone, morphine, oxycodone; Table 2), with search results restricted to the metasearch term "delayed onset," English language, use in humans, and publication years 2009 through 2016 (inclusive). Resulting citations and abstracts were hand searched by two investigators for any article that contained data evaluating misuse, abuse, overdose, addiction, and death as defined by FDA.[3] Full-text articles were then retrieved. We also contacted pharmaceutical manufacturers and researchers who had published data previously and reviewed the references of each article included.

Product selection

Identifying opioid analgesics with abuse-deterrent properties is difficult because these claims are dependent on formal submission to FDA abuse deterrent label claims; other opioid analgesics using similar drug delivery platforms may in effect be abuse deterrent, but were excluded from our analysis because they have not been approved by FDA for claims of deterrence. We included seven extended release (ER) products in our analysis: hydrocodone (Hysingla ER™), morphine (MorphaBond™, Arymo™), morphine plus naltrexone (Embeda®), oxycodone (OxyContin®, Xtampza ER™), oxycodone plus naloxone (Targiniq ER™), and oxycodone plus naltrexone (Troxyca ER™, Table 2). Drugs with older or other abuse-deterrent strategies without labeled claims were excluded: prodrugs (codeine), nonanalgesic opioids (Suboxone® [buprenorphine and naloxone]), Opana ER (extended-release oxymorphone), Zohydro (hydrocodone ER), Nucynta ER (tapentadol), and drugs in development.

Manual review and assessment

After forming the database, data relevant to the assessment of the benefits or harms associated with the drugs of interest were extracted by two authors (JLI, RCD) using a standardized form. Each article was examined for information regarding each of the original Bradford-Hill criteria as well as bias or confounding (Table 1).[27-29] The primary outcome for evaluation was abuse, but other secondary outcomes were also included.

Table 1. The Bradford-Hill and other evaluation criteria used for analysis[27]	
Factor	
Strength (effect size):	The larger the association, the more likely that it is causal.
Consistency (reproducibility):	"… consistency of the observed association. Has it been repeatedly observed by different persons, in different places, circumstances and times?"
Specificity	A causal relationship is supported if there is a very specific population at a specific site and disease with no other likely explanation.
Temporality	The effect has to occur after the cause. If appropriate, the effect must occur after expected delay.
Biological gradient	Greater exposure should generally lead to greater incidence of the effect.
Plausibility	A plausible mechanism between cause and effect is helpful but is limited by the state of current knowledge.
Coherence	Coherence between epidemiological and laboratory findings increases the likelihood of an effect.
Experiment	"… because of an observed association some preventive action is taken. Does it in fact prevent?"
Analogy	The effect of similar factors may be considered.
Additional criteria	
Confounding factors	The analysis should address alternative explanations for the observed associations and how well they are controlled for in analyses.
Bias	Systematic artifacts of data collection or study design that may obscure the association between intervention and outcome.

Table 2. Extended release opioid analgesics with abuse-deterrent label claims in the United States			
Product name manufacturer	**Active ingredient**	**Approval year**	**ADF mechanism**
Arymo™ Egalet	Morphine sulfate	2016	Physical-chemical
Embeda® Pfizer	Morphine sulfate + naltrexone hydrochloride	2009/2014	Agonist-antagonist
Hysingla® Purdue Pharma	Hydrocodone bitartrate	2014	Physical-chemical
MorphaBond™ Daiichi Sankyo	Morphine sulfate	2016	Physical-chemical
OxyContin® Purdue Pharma	Oxycodone hydrochloride	2010	Physical/chemical
Targiniq™ Purdue Pharma	Oxycodone hydrochloride + naloxone hydrochloride	2014	Agonist-antagonist
Troxyca® Pfizer	Oxycodone hydrochloride + naltrexone hydrochloride	2016	Agonist-antagonist
Xtampza® Collegium Pharmaceuticals	Oxycodone hydrochloride	2016	Physical-chemical
Abbreviation: ADF, Abuse Deterrent Formulation.			

Definitions

We used FDA definitions for misuse, abuse, and ADF. Misuse was defined as the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.[3] Abuse was defined as the intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.[3] An ADF is described as a product formulated

with properties shown to meaningfully deter abuse, even if they do not fully prevent abuse.[3]

RESULTS

We identified 45 reports that assessed formulations of hydrocodone (n = 7), morphine (n = 5), or oxycodone (n = 33) with approved ADF labeling. All but one article were published in peer-reviewed scientific journals. The majority of articles utilized postmarketing surveillance data. Sources of data included poison centers,[30-33] substance abuse treatment centers,[32-43] needle exchange programs,[39,41] law enforcement drug diversion investigators,[32,33,44] commercial prescription drug databases,[45-47] third-party claims databases,[46,48-50] fatalities reported to the manufacturer,[33,51] and other sources.[19,48,52] There were several clinical trials that assessed pharmacokinetics, efficacy, and or abuse liability.[4-18,21,53,54] Only oxycodone ER had analyses that addressed postmarketing measures of abuse. Reports originated from Australia,[39,41] Canada,[19,42,47] and the United States.[4-18,20,21,30-40,44-46,48-50,52-56] For oxycodone ER, product names varied by country but each formulation utilized the same drug delivery platform and have the same abuse-deterrent properties.

Strength of association (effect size)

The link between effect size and causation mandates that the greater the effect size after an intervention, the greater the likelihood of a causal relationship.[27] We defined effect size as the relative change in a measure of abuse before and after introduction of an abuse deterrent opioid formulation.

Poison center cases of abuse that involved oxycodone ER decreased after introduction of the reformulated product.[30-33] The largest and longest duration poison center analysis found that the population adjusted case rate for the category of "Intentional Abuse" decreased over the 5-year period following reformulation compared to the year preceding reformulation, ultimately reaching a 75 percent (95% CI: 78.4, 71.1) relative reduction (Figure 1a).[32] Similarly, the same data adjusted for market availability using number of prescriptions decreased 62.3 percent (95% CI: 67.9, 55.6) following reformulation.

Similar results were reported in several analyses of individuals reporting abuse of oxycodone ER.[31-40,43] In each report, the introduction of reformulated oxycodone ER was followed by a meaningful decrease in endorsement of that drug for recent (usually past month) abuse or for abuse intravenously. The results were qualitatively similar whether adjusted for population or for the number of prescriptions dispensed.

Three of these reports analyzed endorsement of opioid abuse in individual drug treatment programs.[34,40,42] Havens et al. used structured interviews of individuals in rural Appalachia that abused oxycodone ER. The past 30-day prevalence and frequency of abuse of the reformulated product through any route before reformulation was 74 percent and 13.4 d/mo, which decreased to 33 percent and 1.9 days/month after reformulation.[40] Sankey et al. found that endorsement of nonmedical use of oxycodone ER in Ontario, Canada, decreased from 94.4 to 34.2 percent postreformulation. The mean per-patient incidence of oxycodone-positive urine drug screens significantly decreased from pre- to post-transition.[42] Similarly, the Illicit Drug Injection Program (Sydney, Australia) reported that oxycodone ER had been used at least once by 36 percent of patients before reformulation compared to 8 percent of participants after reformulation.[39]

Large multicenter surveillance programs of people entering treatment for substance abuse reported similar results (Figure 2). In the RADARS Opioid Treatment Program (OTP), the population adjusted rate of endorsement for oxycodone ER abuse decreased 82.6 percent (95% CI: 86.7, 77.1) over the 5 years following reformulation (Figure 1b).[32] The prescription adjusted oxycodone ER rate decreased similarly. The RADARS Survey of Key Informant Patients found that the population-adjusted rate for endorsement of oxycodone ER abuse decreased 53.9 percent (95% CI: 64.1, 40.7) during the 5-year period after reformulation (Figure 1c); the prescription adjusted rate decreased similarly.[32] Similar results showing decreased abuse of oxycodone ER after reformulation were reported by NAVIPPRO,[35,36] Cicero et al.,[37,38,43] and other programs that addressed overdose, doctor shopping, and opioid use disorder as well.[33]

In contrast, an analysis of nonmedical use in the United States using the general population-based National Survey of Drug Use and Health (NSDUH) and Client Treatment Study found no change in abuse or tampering of oxycodone ER after reformulation.[56] A limitation of the analysis is that the pre- and postperiods included only one calendar year. Therefore, it is likely that the postreformulation

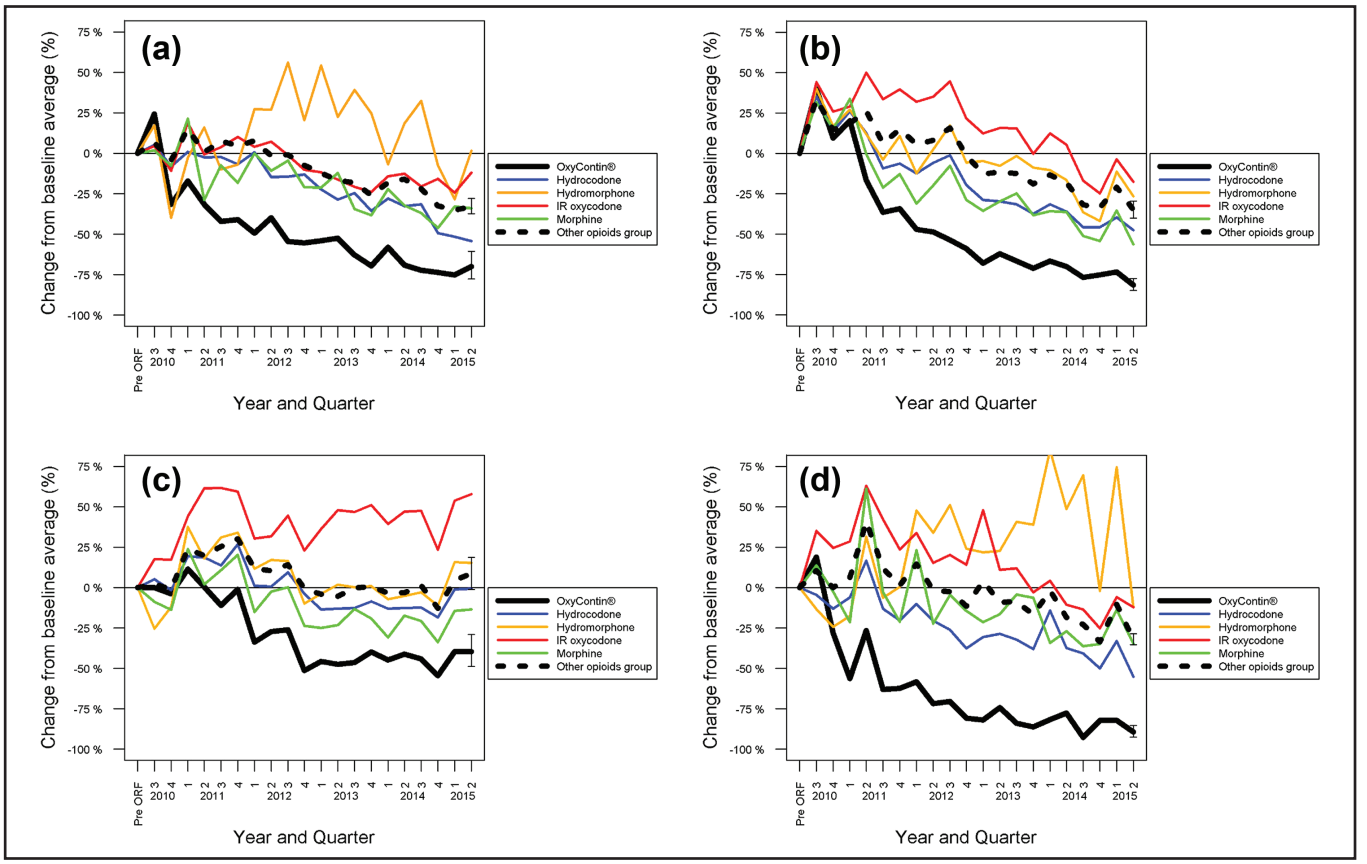

Figure 1. Trends of abuse measures after introduction of reformulated oxycodone ER Figure shows the trends in measures of abuse (modified from Severtson[32]). Each figure represents the trends adjusted for population of oxycodone ER compared to the group of Other Opioids, defined as all opioid analgesic oral dosage forms combined: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and immediate release oxycodone. The baseline average is the mean rate of the four calendar quarters preceding reformulation.[32] (a) RADARS Poison Center Program uses self-report of drug during case that involved intentional abuse. (b) RADARs Opioid Treatment Program and (c) survey of Key Informant patients records self-report of drugs abuse in the previous 30 days when entering a substance abuse treatment facility. (d) RADARS Drug Diversion Program records the drugs involved when a case of possible drug diversion is opened for investigation by law enforcement. ORF, OxyContin Reformulated.[57]

period was substantially contaminated by original formulation oxycodone ER that was still in circulation. A later report of nonmedical use using NSDUH, but including a longer follow-up period, reported a substantial decrease in nonmedical use of oxycodone ER from 0.7 to 0.5 percent, a 28 percent relative reduction.[55]

Measures of oxycodone ER diversion showed similar trends. The population-adjusted rate of diversion investigations involving oxycodone ER in the RADARS Drug Diversion Program decreased 89.4 percent (95% CI: 92.4, 85.2) over the 5-year period following reformulation (Figure 1d).[32] The geometric mean street price of oxycodone ER decreased 57 percent in the 5 years after reformulation.[32] Fatalities associated with oxycodone ER reported to the manufacturer decreased 82 percent following reformulation, but spontaneous adverse event data are not considered to be estimates of actual incidence.[51]

Overall, the effect size criterion demonstrated strong results favoring oxycodone ER across data sources. All analyses except one showed a substantial decrease in several measures of abuse and related outcomes.

Replication of findings (consistency)

The concept of reproducibility is supported if findings observed from different source populations, sampling strategies, and geographic locations show similar directional effects. There should be few, if any, studies showing opposite or null results.[27]

In terms of source population, poison center data have the widest coverage geographically and

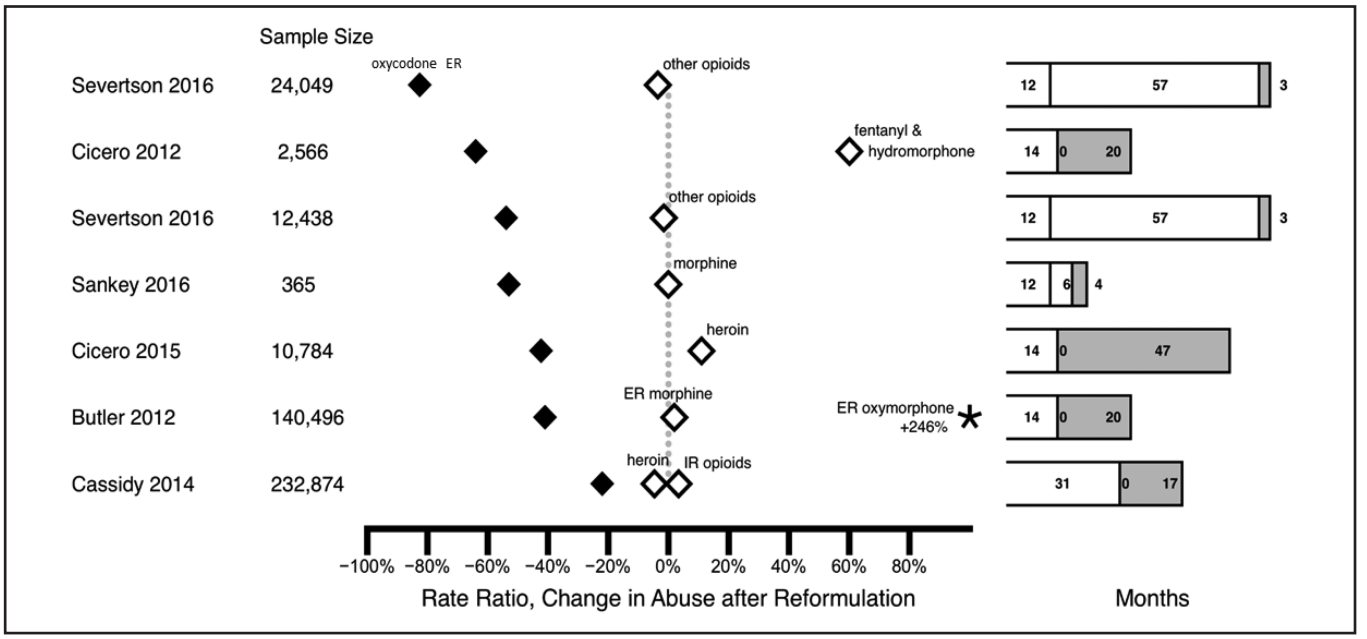

Figure 2. Reported change in measures of abuse after reformulation of oxycodone ER. The figure reports the change in rate ratio for oxycodone ER and comparators from studies involving individuals entering substance abuse treatment programs. The right side of figure provides duration of study with shaded evaluation period compared at baseline. IR, immediate release formulation; ER, extended release formulation.

represent the collective experience of a wide spectrum of ages and drug use backgrounds, from novice to long-term dependent. All four analyses involving poison centers showed marked decreases in poison center cases involving oxycodone ER immediately after reformulation.[30-33]

Active prospective surveillance of enrollees in substance abuse treatment centers sample those whose drug use has become problematic enough to warrant medical attention. All analyses showed a decrease in events involving oxycodone ER after reformulation while comparator drugs remained unchanged or increased [32,33,35-43], and each study that examined route of abuse also indicated the intravenous use decreased.[32,35,39-41] Similar results were reported for opioid use disorder[33], drug diversion and doctor shopping[32,33,44,47], overdose,[33] fatalities,[33,51] and street price.[32] Similar trends were reported from Australia, Canada, and the United States.[39,42]

On the other hand, one study,[56] which used a large nationwide household sample in the United States with weighted extrapolation for generalizability, found that nonmedical use of oxycodone ER did not decrease in the year following reformulation compared to one year before. This is likely an underpowered estimate of an early time point because the rate of nonmedical use of oxycodone ER decreased in subsequent years, ultimately becoming a 28 percent relative decrease (2013 compared to 2010).[55] Furthermore, even among individuals endorsing nonmedical use of painkillers in the previous year, the proportion endorsing oxycodone ER decreased from 15.4 percent in 2010 to 13.0 percent in 2013.[55]

Three reports documented changes in prescribing behavior for oxycodone ER. The introduction of reformulated oxycodone ER was followed promptly by a decrease in the number of prescriptions dispensed for oxycodone ER.[32,33,39,45,46] In contrast, prescription trends for other opioid analgesics were flat or even increasing during the period immediately after reformulation. The decrease in prescribing could represent a secular trend that led directly to a decrease in oxycodone ER abuse outcomes (eg, by limiting diverted supply), since the positive relation between abuse and the amount of opioid prescribed has been documented.[58] The counterfactual in this scenario is that there would have been declines in oxycodone ER prescribing and outcomes even without reformulation. We could find no evidence of events of regional or national scope that could explain the sudden decrease in prescribing of oxycodone ER alone, or of abuse outcomes; the increased influx of heroin appeared after the reductions in oxycodone ER outcome rates were initially observed.

In summary, the reformulation of oxycodone ER was consistently followed by decreases in various measures of abuse and across several types of abusers, data sources, periods of analysis, and across cultures.

Specificity of association

The link between specificity and causation is supported if rates of ADF abuse decrease while abuse rates of non ADF opioids show substantially lesser or no effect.

All data systems showed marked decreases in rates of ER oxycodone abuse, while other opioids were unchanged or less affected after reformulation. In fact, some programs showed an increase in the abuse of other opioids after ER oxycodone reformulation.[31,32,36]

Severtson et al. showed that the population-adjusted rate of poison center intentional abuse cases decreased by 75 percent from the mean rate before reformulation while other opioids combined only decreased by 32.8 percent.[32] Similar trends also occurred in the National Poison Data System abuse exposures reported to United States poison centers showing decreased rates of oxycodone ER abuse while other single ingredient oxycodone increased.[30]

The population-adjusted rate of ER oxycodone abuse reported by patients in treatment programs decreased by 82.6 percent in RADARS OTP and by 53.9 percent for the Survey of Key Informants Program, while the rates for other opioids decreased by 32 and 34.8 percent, respectively.[32] Trends were similar for rates adjusted for drug availability. Using a shorter postreformulation period through the end of 2011 in the United States, Cassidy et al. also showed a 22 percent decrease in the percent respondents in substance abuse treatment who endorsed abuse of oxycodone ER products after reformulation.[36] During the same time, the percent respondents endorsing oxymorphone ER abuse increased by 2.91 times, buprenorphine increased by 1.85 times, oxycodone immediate release (IR) increased slightly, and morphine ER remained unchanged. Data from Ontario methadone clinics also showed decreased endorsement of oxycodone ER nonmedical use and decreased positive urine drug screens after reformulation while morphine urine drug screens remained unchanged, and rates of opioid-dependent patients reporting oxycodone ER as their primary drug of abuse decreased while those reporting other opioids increased.[30,38,42]

In Australia, oxycodone ER was abused by those in the illicit drug reporting system before reformulation at a rate of 36 percent, with 31 percent reporting injection use, while after reformulation the rates dropped to 8 and 5 percent, respectively.[39] After reformulation, the rates of abuse and injection of reformulated oxycodone ER were the lowest of all drugs examined, while rates of other drugs including morphine, heroin, and other forms of oxycodone increased.

Data for other related endpoints also showed similar declines specific to oxycodone ER. Prescription sales for oxycodone ER after reformulation in the United States decreased by 23.8 percent in the year after reformulation, while other ER and IR opioids had no statistically significant changes, and health insurance claims data showed a similar decrease in oxycodone ER prescribing by 11.3 mg morphine equivalents per member per quarter while other ER opioids increased by 3.26 morphine equivalents.[45,46] In Australia, similar trends were seen with a 24 percent reduction in sales of abuse deterrent oxycodone ER while sales of other forms of oxycodone increased, and other opioids showed no change or small increases in sales.[39]

Diversion of oxycodone ER after reformulation decreased more than other opioids as well, with a decrease in population-adjusted rate by 89.4 and 26.8 percent, respectively.[32] The proportion of individuals who received prescriptions for oxycodone ER who met criteria for doctor-shopping decreased 50 percent after reformulation, while it increased 66 percent for ER oxymorphone and 5 percent for IR oxycodone.[33] Deaths reported spontaneously to the manufacturer decreased 82 percent after reformulation while there was no change in nonfatal adverse events reported or morphine ER deaths reported.[51]

Overall, the specificity criterion showed that changes in oxycodone ER abuse and other related outcomes after reformulation were divergent or disproportionately lower for the ADF product. While there were secular trends leading to decreases in abuse rates of other prescription opioids during the same time frame, the decreases seen for oxycodone ER occurred earlier and were much larger than those of other opioids.

Temporality

In the case of an existing and frequently abused used product like oxycodone ER, temporality is

supported if abuse decreases substantially and abruptly at an appropriate time after introduction of the ADF. Some delay between product launch and decrease in abuse is expected because of a transition period during which existing supplies held by patients, pharmacies, wholesalers, and drug dealers are depleted. This period is expected to be measurable in months for opioid analgesics. The decrease in abuse would be expected to intensify initially and eventually plateau as the original formulation is depleted. Oxycodone ER reformulation launch dates were April 2014 in Australia, March 2012 in Canada, and August 2010 in the United States. Within 3-6 months, more than 90 percent of oxycodone ER dispensed in the United States was the reformulated product as the manufacturer stopped shipping the original formulation.[33,45,46]

Epidemiologic studies generally used an interrupted time-series approach. Temporal resolution was typically either 3-month calendar quarter or calendar year, including some reports with multiyear averages reported for pre- and postreformulation. The latter approach increased statistical power but reduced the temporal resolution.

Trend analysis of poison center cases involving the case type Intentional Abuse decreased promptly after introduction of reformulated oxycodone ER.[30-33] The largest analysis with the longest observation period found that population-adjusted rates decreased within 3 months after reformulation, continued to decrease for another 42 months and then plateaued for the remaining 18 months of observation (Figure 1a). Dispensing-adjusted rates showed the same temporal pattern.[32]

Similar results were reported in analyses of individuals entering treatment for substance abuse. Decreases in endorsement for prior-month abuse and injection of oxycodone ER were evident following product launch (examples in Figure 1b and 1c).[32-41,43]

Havens et al. interviewed residents of rural Appalachia (December 2010 through September 2011) with a history of oxycodone ER abuse, measuring endorsement for prior-month abuse and injection of oxycodone ER in two time frames. Self-reported drug use was compared for this period with retrospective reports during the 30 days prior to reformulation. The past 30-day prevalence and frequency of oxycodone ER abuse through any route before reformulation was 74 percent and 13.4 d/mo, which decreased to 33 percent and 1.9 d/mo after reformulation.[40] However, the long recruitment period and retrospective self-report of preformulation drug use limit temporal resolution.

Other abuse-related studies showed changes soon after oxycodone ER reformulation. Degenhardt et al. noted that injection of oxycodone ER in Sydney, Australia, decreased dramatically following reformulation of oxycodone ER.[39] Gomes showed that prescribing of crushable oxycodone ER in Windsor, Ontario, increased at the same time as the reformulation of oxycodone ER was instituted. The authors postulated this was due to diversion of drug through the Detroit-Windsor tunnel.[47] McNaughton evaluated the sentiment of web posts before and after reformulation of oxycodone ER. The ratio of posts with positive sentiment for abuse of oxycodone ER vs. negative sentiment (discouraging abuse) was 0.43, indicating that posts after reformulation discouraged abuse of reformulated oxycodone ER compared to the period before reformulation. The number of diversion investigations involving oxycodone ER opened by drug diversion investigators in the United States decreased 89.4 percent (95% CI: 92.4, 85.2) over 5 years after reformulation compared to the year before reformulation (Figure 1d).[32] The street price of oxycodone ER decreased 36 percent in the year following reformulation.[32]

Trends in nonmedical use from NSDUH showed no reduction in oxycodone ER endorsement in the year immediately following reformulation,[56] but a subsequent analysis through 2013 showed steady reductions in general population use of oxycodone ER, even though the survey instrument did not distinguish pre- and postformulations specifically.[55] Nonmedical use of oxycodone ER in the past 12 months peaked in 2010 at 0.7 percent of the United States population and then decreased progressively through 2013 to 0.5 percent, a 28 percent relative reduction.[55]

In summary, the temporal relation between introduction of reformulated oxycodone ER and indicators of decreased abuse was striking. Within months of launch, several abuse and related indicators declined rapidly, with steady, albeit slower, declines over the following 3-4 years eventually reaching a new stable rate.

Biological gradient

As originally stated, higher exposure to a causative agent should lead to increased likelihood of the

outcome.[27] In the case of abuse deterrent properties, however, we would not predict a dose-response relationship. Exposure to an abuse deterrent opioid more frequently or in larger volumes would not be expected to cause decreased abuse for an individual. Consequently, we considered the criterion of biological gradient not applicable to our analysis.

Plausibility

Hill suggested "[i]t will be helpful if the causation we suspect is biologically plausible."[27] The FDA guidance acknowledges a plausible link between premarketing studies and the likelihood of decreased postmarket abuse and defines three categories of premarket studies that would be expected to correlate with changes in postmarket abuse.[3]

Coherence

The relationship between laboratory and epidemiologic evidence is termed coherence. Accordingly, we defined coherence as alignment of Category 1 through 3 data with postmarketing epidemiologic data. While premarketing data are available for hydrocodone, morphine, and oxymorphone with abuse deterrent properties, the only opioid with published Category 4 data is oxycodone ER.

Premarket experimental data for abuse deterrent opioid analgesics show significant changes in pharmacokinetic parameters of manipulated drug compared to unprotected formulations. Several studies show the maximum serum concentration (C_{max}) is decreased for both the crushed and intact forms of reformulated oxycodone compared to original formulation when taken orally or intranasally.[15,16,20,53,59,60] Time to maximum serum concentration (T_{max}) was prolonged for ADFs compared to unprotected formulations for crushed, chewed, and intact ingestion, while T_{max} was found to be bioequivalent between crushed and intact ADFs.[15,16,59,60] Similarly, T_{max} was delayed for intranasal reformulated oxycodone compared to the original formulation.[53] These studies also showed decreased drug liking and other pharmacodynamic effects for chewed, crushed, and intranasal abuse deterrent oxycodone.

Postmarketing data for reformulated oxycodone ER shows decreases in abuse and related outcomes that are consistent and coherent with the experimental premarketing findings.

Experimental evidence

The replacement of original oxycodone ER with a reformulated version in Australia, Canada, and the United States constitutes a major natural experiment. As all of the epidemiologic data for ADF opioids involve this drug and is covered in earlier sections, no further analysis was conducted for this criterion.

Reasoning by analogy

Hill allowed for consideration of similar factors. For example, we could examine if abuse changed similarly for products with similar mechanisms of abuse deterrence (Table 2). However, these products have not yet been on the market long enough or garnered sufficient market share for analysis.

Confounding

The opioid crisis has spawned interventions to reduce prescribing, overdose, abuse, addiction, and diversion.[33] To be a true confounder within the epidemiologic counterfactual framework, a variable must simultaneously influence ADF prescribing (exposure) and abuse (outcome). Whether other interventions constitute a traditional confounder relationship between ADF exposure and abuse outcomes is unclear because most of the interventions routinely cited did not intend to influence ADF prescribing directly, but were efforts to reduce abuse and diversion in general. Quantitative adjustment for confounding was notably absent in the epidemiologic studies, except Cassidy et al.[36] Outcome rates were adjusted for population and/or dispensing, and rates were generally stratified by formulation, but these do not constitute a full accounting of possible confounders, collectively a major weakness of the observational studies.

Unfortunately, it is unknown what leads to changes in ADF prescribing levels in a geographically bounded area. At least for oxycodone ER, the switch from original to ADF was made *en masse*, relatively quickly, and without prescriber choice, reducing the potential for confounding from patient selection. This would not be the case if both non-ADF and ADF formulations of a drug were available.

Two specific interventions bear further consideration. First is the widespread uptake of prescription monitoring programs in the United States (state-level electronic patient registries of controlled

substance dispensing history) consulted during a clinical encounter. Second, multifaceted legislation in Florida, enacted June 2011, was designed to eliminate "pill mills" (medical practices suspected of irresponsibly prescribing opioid analgesics for dubious health benefit) and are hypothesized to have had an effect beyond Florida due to interstate diversion. How these interventions would directly influence ADF prescribing is unclear; however, both could reduce the supply of diverted opioids.

One approach is to focus on the effect of the ER oxycodone reformulation between September 2010 and late 2011, before interdiction occurred in Florida. Most of the observed separation between ADF oxycodone ER and comparators occurred rapidly during this time window and remained fairly constant in the ensuing years (Figures 1a-1d). By definition, confounders must predate exposure, and therefore the Florida legislative efforts do not appear to be the single alternative explanation to the observed changes in abuse rates. However, increased use of prescription monitoring programs could hypothetically be a form of residual time-varying confounding. There is no known source for national prescription drug monitoring plan (PDMP) utilization rates. However, the information available suggests that utilization by opioid prescribers was consistently low during observation periods in the reported studies.[61]

Bias

There are several sources of potential bias. Misclassification bias was uniformly not considered for self-reported drug use in treatment center studies, but putatively mitigated through visual drug identification cues (paper and digital) although none of the studies made explicit mention of product identification assessment or handling of ambiguous and potentially misclassified responses.

Most of the studies used convenience samples of patients entering drug treatment, callers to poison centers, overdose decedents, retrospective interviews with community-dwelling drug users, drug users recruited from syringe service programs and a supervised injection facility, and spontaneous pharmacovigilance reports. Sampling from these sources is not expected to be representative of the drug using population as a whole, which creates selection bias. In substance abuse treatment centers, the large majority of individuals chose to participate; however, for other sources the relation between the reporter (eg, poison center callers) and the true incidence in the population is unknown. However, these data sources have long been essential to drug abuse research and these limitations are well characterized; most authors were careful not to overstate the findings. Only two studies used samples drawn from the general population. The absence of studies within pain patients is notable. Interlevel bias (also known as crosslevel bias or "ecological fallacy") is a concern for dispensing-adjusted rates calculated in aggregated geographies, which assume that each individual in a given geographic unit had the same likelihood of ADF exposure. Population adjusted rates mitigate this somewhat.

With treatment center and general population studies, not accounting for diverted supply could be a novel form of bias when comparing ADF to non-ADF opioids. If an individual had differential access to diverted non-ADFs over ADFs, endorsement counts could be a function of diverted supply instead of a fundamental property of the drug, akin to immune or immortal person-time bias. This could lead to inflated effect size reductions in biological outcomes (like abuse or overdose) for ADFs when compared to non-ADFs, but could simultaneously represent an important public health indicator.

While each study's sampling and design may be subject to a variety of biases, the totality of findings observed across studies are consistent. Many of the data collection systems were in place before the oxycodone ER reformulation; if the biases have not changed substantially, the consistency, temporality, effect size, and coherence of the observed time trends suggest that specific sources of bias alone are unlikely to explain the findings.

DISCUSSION

Our analysis found that only oxycodone ER (OxyContin in the United States and Australia, OxyNeo in Canada) had information available to evaluate abuse deterrence in the community. In each country, reformulation was followed by marked reduction in measures of abuse for oxycodone ER. The extent of reduced abuse cannot be calculated because of heterogeneous data sets, but the range of decreases were from 10 to 90 percent depending on the measure and the duration of follow-up. One study found no effect on nonmedical use although a subsequent analysis of the same data set for a longer period found that nonmedical use had decreased substantially.

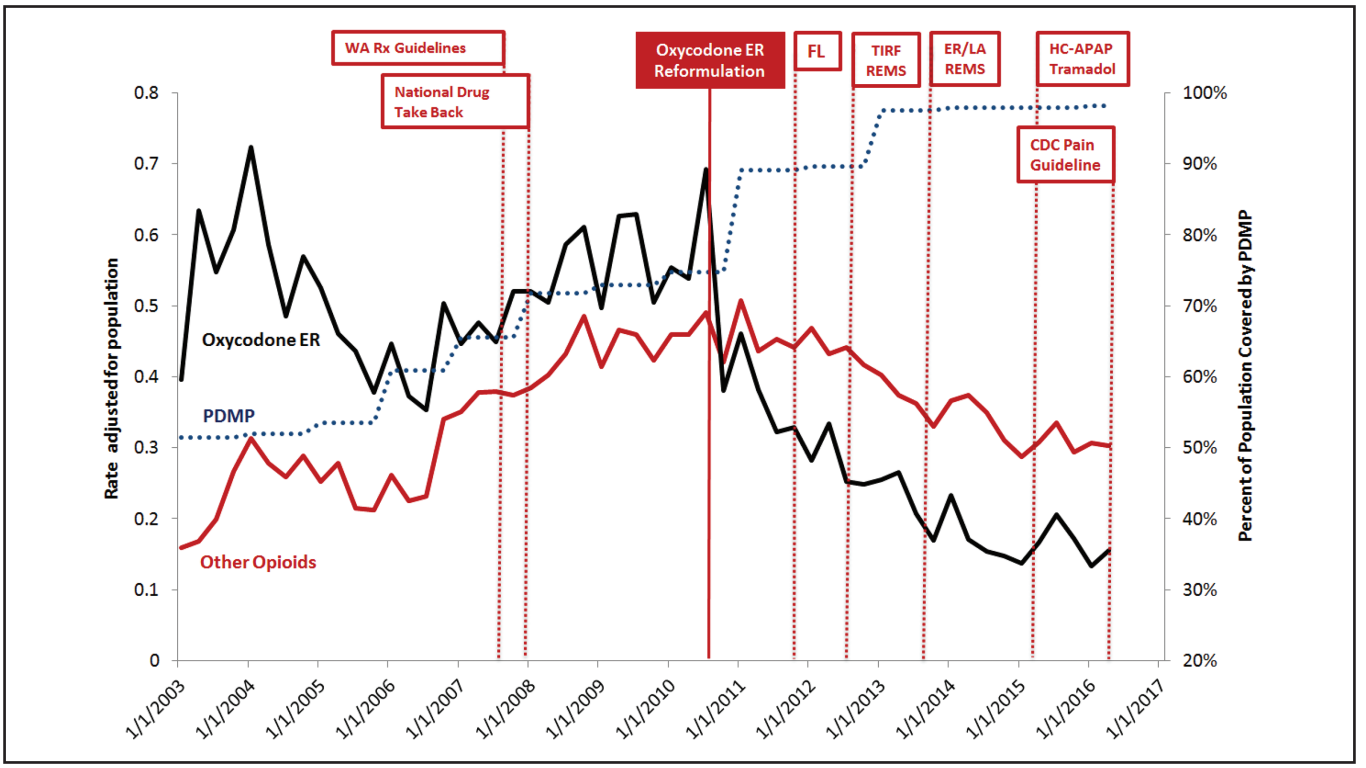

Figure 3. Temporal relation of RADARS poison Center Intentional Abuse case rate and interventions to reduce prescription drug abuse. Rates of intentional abuse in the RADARS System Poison Center Program adjusted for population are compared for oxycodone ER (black solid line) and all opioid analgesic oral dosage forms combined (hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and immediate release oxycodone). The proportion of states with an active Prescription Monitoring Program is provided in blue. The vertical intersects represent the initiation of a variety of interventions intended to reduce prescription opioid abuse. CDC, Centers for Disease Control and Prevention; WA, Washington; ER, extended release; FL, Florida; TIRF REMS, transmucosal immediate release fentanyl risk evaluation and mitigation strategy; ER/LA REMS, extended release/Long-acting risk evaluation and mitigation strategy; HC/APAP, rescheduling of hydrocodone-acetaminophen combination products from Schedule III to Schedule II; Tramadol, tramadol becomes a Schedule IV controlled substance.

The main threat to the validity of our results is confounding and competing interventions to address the opioid epidemic in the United States (Figure 3). Some other factor or combination of factors could potentially produce the same changes in opioid abuse. The most commonly mentioned factors are enhanced law enforcement, drug take-back days, prescription drug monitoring programs and changes in prescribing behavior. Unfortunately, measures of the impact of these interventions are either poor or do not exist.

The most convincing data are those addressing changes in oxycodone ER abuse in the 1-2 years following reformulation. This time period is crucial because it limits the potential effect of confounders and competing interventions. For example, a group of interventions in Florida occurred about 1 year after reformulation of oxycodone ER. Several other inventions occurred not long after reformulation, but not in the first 1-2 years after reformulation. Risk Evaluation and Mitigation Strategies (REMS) and several other interventions all occurred well after reformulation. Other interventions, like PDMPs have been progressively implemented over many years. No large PDMP became active at the time oxycodone ER abuse decreased and the effect of PDMPs seems to be modest.[62]

One factor not often considered as a cause of decreased abuse is decreased prescribing. It is clear that prescribing for oxycodone ER decreased starting at the time of reformulation even as the prescribing of all other opioids continued to increase.[30,32,39] The decrease in prescribing of oxycodone ER in the United States for the first year was about 15-20 percent.[32,33,45,46] The decrease in abuse measures was generally much larger than the decrease in prescribing.[31-33] However, if the decreased prescribing disproportionately affected oxycodone ER prescriptions

ultimately destined for abuse, relatively modest changes could have a disproportionate effect on measures of abuse. The question becomes one of demand and supply. Did decreased desirability of oxycodone ER for the purpose of abuse cause it to be prescribed less? Or did decreasing prescribing by knowledgeable prescribers, perhaps stimulated by their PDMP, mean there was less drug available for abuse? In the former, decreased demand led to decreased abuse and decreased prescribing. In the latter scenario, decreased supply through decreased prescribing led to decreased abuse.

Ultimately, we do not have the data needed to answer this question definitively. However, there are several indications that it was decreased illicit demand that caused the decrease in both prescriptions and abuse. Illicit demand for a drug is comprised primarily of three sources, (1) convincing a prescriber to write a prescription (doctor shopping), (2) simply purchasing the drug through a fraudulent physician-patient relationship (pill mill), or, (3) borrowing or stealing drug from acquaintances or family members. An ADF would be expected to decrease at least the first two types of illicit demand. Doctor shopping would change because abusers could simply manipulate the process to have a different drug prescribed. Similarly, a pill mill doctor, many of whom wrote prescriptions for millions of high dosage opioid analgesics would not prescribe a drug that their "patient" did not desire.

A large intervention to address doctor shopping and pill mills occurred in Florida in 2011. Effectively, it occurred about a year after reformulation of oxycodone ER. Even then, one would expect its impact to occur a few months later. The Florida program had an impact although the reported decreases suggest the effect was modest.[61]

The price of oxycodone ER in the illicit street market can help inform this analysis. If decreased supply of oxycodone ER due to decreased prescribing led to decreased abuse, economic theory predicts that the price would rise as abusers were willing to pay more for the remaining desirable product. However, the data indicate the opposite—the price of oxycodone ER decreased 36 percent promptly even though the drug was in lower supply.[32] This market response would be expected if the drug were actually less desirable for abuse. Substantial evidence supports that the desirability of oxycodone ER had decreased.[34,38,40,52] One concern expressed is that abusers would learn how to circumvent the abuse deterrent features of an ADFs and thus abuse measure would rebound after their initial decline. However, studies extending 5 years after reformulation have not found this to be the case.[32]

Since the data suggest that interventions like PDMPs have had some effect, it is likely that the effect, if any, of the oxycodone ER reformulation has been obscured. Inspection of the trends for oxycodone ER and other drug shows that the separation in trends for oxycodone ER and other products occurred in the first 1-2 years after reformulation (Figures 1a-1d and 3). After that time, the abuse of both groups have decreased and plateaued. Perhaps the initial separation is the formulation specific effect of oxycodone ER initially followed by a secular trend that affected all opioid analgesics.

In this article, we present evidence that the strategy of opioid analgesics with abuse deterrent properties does reduce abuse of the product involved. Although there is continued debate on the effectiveness of ADF products, the data for oxycodone ER document a substantial reduction in abuse and diversion that occurred following reformulation. Numerous studies show that the observation is robust with consistent, specific, and coherent results that demonstrate unique temporality. Prescription drug abuse is a complex phenomenon that requires multiple forms of interventions. However, if there is evidence that one approach, ADFs, is able to make an incremental change, this should not be overlooked.

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