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ABSTRACT

Revisiting the OxyContin Reformulation: The Role of Licit Substitutes

After the introduction of abuse-deterrent OxyContin in 2010, states with widespread extramedical OxyContin use experienced steep increases in heroin deaths, implying substitution from OxyContin to heroin. Leveraging cross-state variation in initial OxyContin utilization, we show the OxyContin reformulation also induced substitution to a similar prescription opioid product, Opana ER. States with high Opana ER utilization after the OxyContin reformulation experienced continued growth in prescription opioid deaths, and after Opana ER was reformulated 18 months later, an additional wave of substitution to heroin previously solely attributed to OxyContin. Our results highlight underappreciated substitution pathways throughout these pivotal years of the epidemic.

JEL Classification: I12, I18

Keywords: opioids, opioid epidemic, OxyContin, Opana ER, heroin

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1 Introduction

Consumption of opioids is associated with harms such as fatal overdose and opioid use disorder (OUD), a clinical diagnosis which describes compulsive or habitual opioid consumption to the extent of clinically significant impairment or distress [DSM-5, 2013]. When opioid-involved harms in a population diverge from a previously stable low equilibrium, an opioid epidemic is said to occur [Moore and Pacula, 2021]. The United States (US) is presently experiencing the most severe opioid epidemic on record, with 80,411 opioid-involved fatal overdoses in 2021 alone, up 889% from 8,050 in 1999.[1] Figure 1 illustrates that the types of opioids implicated in mortality throughout this period pivoted from predominantly prescription opioids to predominantly heroin and synthetic opioids, and that this pivot began sometime in 2010. Previous literature has identified extramedical[2] use of the prescription opioid product OxyContin as a key contributing factor to the initial rise in prescription opioid-involved mortality [Alpert et al., 2021] and, after the introduction of an abuse deterrent formulation of OxyContin in August 2010, the rise in heroin- and synthetic opioid-involved mortality thereafter [Alpert, Powell and Pacula, 2018, Evans, Leiber and Power, 2019, Powell and Pacula, 2021]. These studies, however, risk oversimplifying the role played by OxyContin by not adequately accounting for contemporaneous prescription opioid products which were close substitutes. In this study, we investigate the role of one such product marketed under the brand name Opana ER.

OxyContin had a profound potential for harm because it was a high-dose

[1] Figures count all drug-involved fatal overdoses involving Multiple Cause of Death codes T40.0 (Opium), T40.1 (Heroin), T40.2 (Other opioids), T40.3 (Methadone), T40.4 (Other synthetic narcotics), or T40.6 (Other and unspecified narcotics).

[2] Extramedical use is defined as any use of opioids outside the formal medical system or inconsistent with a doctor's prescription without excluding the possibility that the user may have medically-driven reasons for using the medication [Larance et al., 2011]. It includes, for example, extra dosing, chewing a pill to increase its bio-availability, or using the pill in conjunction with other drugs, for purposes which are medical, hedonic, or both.

extended-release (ER) formulation which delivered low concentrations of its active ingredient continuously over a prolonged period, as opposed to as-needed administration of lower-dose immediate-release (IR) products [Cicero and Ellis, 2017]. Tolerance, physical dependence, withdrawal, and symptoms of OUD can develop quickly in the context of such continuous use [CDC, 2016], and thus the product was associated with elevated risks of harm even under appropriate medical supervision. Furthermore, OxyContin's ER mechanism was easily bypassed and its whole dose – which was up to 24 times larger than a typical IR product[3] – could be accessed for immediate use. This design flaw enabled profound dose escalation, especially via changes in the route of administration,[4] thereby exposing people engaged in extramedical use to accelerated development of OUD-related symptoms and extreme harms such as fatal overdose. Yet, the drug's manufacturer aggressively and disingenuously marketed the product as a safe and effective treatment for a variety of diagnoses beyond the traditional confines of ER opioids [Van Zee, 2009, Alpert et al., 2021]. Such efforts had the effect of dramatically expanding OxyContin utilisation throughout the US, and as early as 2004, the product had become the most common pharmaceutical opioid used for extramedical purposes across the country [Cicero, Inciardi and Munoz, 2005, Alpert et al., 2021].

In August 2010, however, OxyContin was removed from the market and an abuse-deterrent formulation (ADF) which was resistant to tampering was introduced in its stead (hereafter the OxyContin reformulation). In the wake of the OxyContin reformulation, the population experiencing OUD-related symptoms as a result of extramedical OxyContin use, especially via the routes of administration the reformulation was designed to prevent, were forced to

[3]For example, 5mg hydrocodone or 30mg codeine pills contain roughly 5 milligram morphine equivalent (MME), whereas OxyContin was marketed in 7.5, 15, 22.5, 30, 45, 60, and 120 MME dosages.

[4]For example, by chewing the pill before swallowing it, crushing the pill and sniffing it, smoking the pill, or dissolving the pill and injecting it.

seek an alternative supply. Multiple studies across several disciplines indicate that a large portion of these individuals substituted to illicitly manufactured opioids such as heroin, initiating the large increases in heroin- and ultimately synthetic opioid-involved mortality evident in Figure 1 after 2010 [Cicero and Ellis, 2015, 2017, Alpert, Powell and Pacula, 2018, Evans, Leiber and Power, 2019, Powell and Pacula, 2021, Alpert et al., 2021].

Figure 1 also demonstrates that even though growth in prescription opioid-involved mortality slowed after the OxyContin reformulation, high levels persisted for several years afterwards. This suggests that substitute prescription opioid products, such as Opana ER, continued to play an important role after OxyContin was removed from the market. Similarly to OxyContin, Opana ER was also a high-dose ER formulation containing doses up to 24 times larger than a typical opioid product, and its ER mechanism could also be easily bypassed to access these doses for immediate use. Importantly, the active ingredient in Opana ER (oxymorphone) also carries a higher abuse liability than the active ingredient in OxyContin (oxycodone), suggesting potential scope for increased harms such as more rapid development of OUD [Babalonis et al., 2014].

While Opana ER made up only a small portion of the US prescription opioid market prior to 2010 (see, for example, Figure 2), Opana ER utilisation sharply increased immediately following the OxyContin reformulation, making up approximately 41% of the simultaneous decline in OxyContin utilisation by January 2012 on a national-level. Furthermore, in February 2012, Opana ER was also reformulated with abuse-deterrent properties, whereupon its utilisation sharply decreased. It is unknown the extent to which Opana ER acted as a pathway into OUD in itself, a substitute to OxyContin after the OxyContin reformulation, or as a pathway from prescription opioids to heroin after the Opana ER reformulation. In this study, we attempt to answer these questions by extending on research designs common in the OxyContin-related literature using large administrative data observing the

universe of prescription opioid shipments by brand name throughout the US.

Our results demonstrate that the increased use of Opana ER after the OxyContin reformulation and before the Opana ER reformulation (hereafter the between-reformulations period) occurred disproportionately in states with a high initial OxyContin utilisation, suggesting that the OxyContin reformulation not only drove substitution to illicit substitutes but also to licit substitutes. In fact, our estimates imply that substitution from OxyContin to Opana ER explains nearly all of the continued growth in prescription opioid-involved mortality beyond the OxyContin reformulation. Thus, the potential for the OxyContin reformulation to reduce prescription opioid-involved harms was muted by the continued presence of Opana ER on the market.

We also provide evidence that states with high versus low between- reformulations Opana ER utilisation experienced an additional wave of substitution to heroin after the Opana ER reformulation in 2012. These results enhance our understanding of these pivotal years of the epidemic by revealing that the substitution patterns from OxyContin to heroin identified in previous literature also include a pathway through Opana ER. Our estimates imply that if the Opana ER pathway were shut down at the time of the OxyContin reformulation, states with the same level of initial OxyContin utilisation would have experienced as much as 33% lower and growth in heroin-involved mortality and as much as 38% lower growth in synthetic opioid-involved mortality from 2009 to 2016.

Altogether, our results carry two important policy implications. Firstly, our results imply that population-level prescription opioid-involved harms throughout the US opioid epidemic were driven by a small class of products, specifically high-dose ER prescription opioids. Thus, in settings where these products are not yet widely utilised, policymakers can minimize harm by ensuring their use is carefully regulated from the outset. Secondly, our results imply that the potential for the OxyContin reformulation to reduce prescription opioid-involved harms was muted by substitution to licit sub-

stitutes, and the potential for the OxyContin and Opana ER reformulations to reduce overall opioid-involved harm by substitution to illicit substitutes. Thus, in settings characterized by widespread utilisation of high-dose ER products, policymakers should work in concert with companies seeking introduce ADFs to consider all possible substitution effects, and ensure that demand is channelled to the least harmful substitutes such as methadone and buprenorphine.

The remainder of the paper is structured as follows. In Section 2 we discuss the relevant literature concerning OxyContin and Opana ER. Section 3 introduces our data, including the unique administrative dataset we use to observe OxyContin and Opana ER utilization. Section 4 lays out our empirical methodology – continuous treatment event studies similarly to Alpert, Powell and Pacula [2018] and Powell and Pacula [2021], among others. Results are presented and discussed in Section 5. Finally, in Section 6 we discuss the implications of our findings for public policy throughout the US opioid epidemic.

2 Background

Introduced by Purdue Pharma in 1996, OxyContin was an ER oxycodone formulation designed to achieve a prolonged analgesic effect by delivering low concentrations of its active ingredient continuously over a sustained period. To achieve this, the drug was manufactured in doses of up to 120 oral milligram morphine equivalents (MMEs),[5] roughly equivalent to 24 IR pills containing a more typical 5 MME dose. Such high-dose ER formu-

[5]MME provides a standardized measure to compare potency across different opioid compounds when delivered orally. For example, the MME conversion factors for oxycodone (the active ingredient in OxyContin) and oxymorphone (the active ingredient in Opana ER) are 1.5 and 3 respectively, so one milligram of oxycodone is equivalent to 1.5/3=0.5 milligrams of oxymorphone. MME varies by a constant for non-oral delivery methods.

lations are advantageous where a prolonged analgesic effect is desired but difficult or burdensome to achieve with repeated use of IR pills. Continuous use of opioid-type drugs, however, can hasten the development of tolerance, physical dependence, and withdrawal symptoms relative to as-needed dosing [CDC, 2016]. Prior to OxyContin, ER opioid products were traditionally reserved for diagnoses where immediate quality of life concerns outweighed the medium- or long-term risks associated with physical dependence, such as in severe cancer-related pain or palliative care. Purdue, however, aggressively marketed the product as safe and efficacious for non-cancer related chronic pain where lower-dose IR products or non-opioid analgesics were previously preferred [Van Zee, 2009, Alpert et al., 2021]. These efforts resulted in rapid expansion in utilisation of the product, and as early as 2004, the product had become the most common pharmaceutical opioid used for extramedical purposes across the country [Cicero, Inciardi and Munoz, 2005, Alpert et al., 2021].

Furthermore, OxyContin's ER mechanism was easily dissolved to reveal a tablet of otherwise pure[6] oxycodone. Tampering with the pill in this manner enabled profound dose escalation by ingesting its whole dose all at once. It also enabled more efficient routes of administration (and thus even further dose escalation) such as chewing the pill before swallowing it, crushing the pill and sniffing it, smoking the pill, or dissolving the pill and injecting it [Quinones, 2016, McGreal, 2018]. Such high dose opioid consumption is associated with accelerated development of OUD and extreme side effects such as fatal opioid overdose [CDC, 2016].

Facing regulatory scrutiny around growing extramedical use and patent expiry, in 2010 Purdue sought approval for an abuse-deterrent formulation (ADF) which rendered these methods of tampering impossible. The FDA ap-

[6]Some opioid products are combined with, for example, acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), large or prolonged doses of which can induce liver toxicity before the onset of symptoms of OUD.

proved the new ADF OxyContin in August of the same year and almost immediately Purdue removed the original non-ADF OxyContin from the market. For people engaging in extramedical opioid use[7] by chewing, crushing or dissolving the pill, the reformulation did not reduce their demand for opioids. Rather, by forcing less efficient routes of administration, the reformulation made extramedical use of OxyContin less attractive relative to substitutes.

A large interdisciplinary literature demonstrates that one unintended consequence of the reformulation was to spur substitution to illicitly manufactured opioids such as heroin. Evans, Leiber and Power [2019], for example, shows that national-level heroin-involved mortality began diverging from a previously stable level in the exact month of the OxyContin reformulation. Alpert, Powell and Pacula [2018], furthermore, show that this divergence occurred disproportionately in states with high levels of pre-reformulation non-medical OxyContin use, and that such use explains as much as 80% of the growth in heroin-involved mortality evident in Figure 1 from 2010 to 2013. Beheshti [2019], Powell, Alpert and Pacula [2019], Powell and Pacula [2021], and Dennett and Gonsalves [2023], among others, have subsequently identified corroborating evidence of substitution to heroin across a broad range of outcomes, including intravenous drug use (IDU), the incidence of blood borne disease transmission, first time heroin-involved treatment admissions, elevated rates of synthetic opioid-involved mortality after the introduction of these drugs into the US heroin supply, and ultimately large increases in overall opioid-involved mortality.

Some people engaging in extramedical OxyContin use also likely substituted to other prescription opioid products such as IR oxycodone [Cicero and

[7]In the 2009 National Survey of Drug Use and Health an estimated 1.68 million Americans reported non-medical consumption of OxyContin in the past year, and 510 thousand in the past month [NSDUH, 2011]. Importantly, these estimates do not include individuals who had developed or were developing OUD in the course of medical treatment with OxyContin, or those engaging in non-advised use for medical purposes who would not classify their use as "non-medical" in a survey context.

Ellis, 2015], though empirical evidence for these pathways is mixed [Hwang, Chang and Alexander, 2015, Nolan et al., 2020]. One close substitute to OxyContin which has received little attention in the economics literature was an ER oxymorphone product manufactured and marketed by Endo Health Solutions from 2006 to 2017 under the brand name Opana ER – the subject of this study.[8] Crucially, Opana ER possessed a similar or even more profound potential for harm to OxyContin. Opana ER also contained doses up to 24 times larger than a typical opioid product, and by tampering with the pill these doses could also be easily accessed for immediate use. The active ingredient in Opana ER (oxymorphone) carries a higher abuse liability at equipotent doses than the active ingredient in OxyContin (oxycodone), suggesting increased scope for development of OUD or overdose [Babalonis et al., 2014]. Endo also broadly mimicked many elements of Purdue's OxyContin marketing strategy, such as extensive use of prescriber profiling data to target sales calls at high-volume prescribers[9], and making deceptive claims about comparative efficacy and safety of the product [State of New York v. Endo Health Solutions, 2019, State of Tennessee v. Endo Health Solutions, 2019, State of West Virginia v. Endo Health Solutions, 2019]. The company also engaged in marketing strategies that Purdue generally avoided and which further escalated the risk of iatrogenic harm, such as encouraging providers to engage in long-term treatment with Opana ER and to increase dosage with Opana ER over time [State of West Virginia v. Endo Health Solutions, 2019, State of Tennessee v. Endo Health Solutions, 2019, State of New York

[8]Endo also marketed a lower dose IR oxymorphone pill, an oxymorphone injection, and a oxymorphone suppository all brand named Opana (sans ER) which are excluded from this discussion because they were either not ER products (and thus not substitutes to OxyContin) or not widely distributed.

[9]According to litigation against the compnay, such data was used to target high-volume OxyContin prescribers specifically [State of New York v. Endo Health Solutions, 2019, State of Tennessee v. Endo Health Solutions, 2019, State of West Virginia v. Endo Health Solutions, 2019]

v. Endo Health Solutions, 2019]. As a result, according to Figure 3, the company shipped a greater proportion of its highest dose products than even Purdue.

Figure 2 illustrates that despite these efforts Opana ER obtained a low market share relative to OxyContin in its first few years on the market. In the 18 months after the OxyContin reformulation, however, Opana ER utilisation roughly doubled, making up approximately 41% of the simultaneous decline in OxyContin on a national-level, with substantial heterogeneity across states.[10] Although not all of this substitution can be attributed to extramedical opioid use, we note that the major functional difference between the two products at this time was the abuse deterrent properties of the reformulated OxyContin. Indeed, Cassidy et al. [2014] and Cicero and Ellis [2015] report explicit evidence of people previously engaging in extramedical OxyContin use switching to oxymorphone after the OxyContin reformulation. A variety of contemporaneous public health alerts,[11] contemporaneous popular press reports,[12] and subsequent litigation against Endo for its role in propagating the US opioid epidemic[13] provide additional support for this hypothesis.

In late 2011, Endo itself publicly acknowledged that some people previously engaged in extramedical OxyContin use had switched to Opana ER after the OxyContin reformulation, and submitted an application for an ADF Opana ER which was resistant to crushing. The reformulated ADF Opana ER was approved in December 2011 based on its bioequivalence to the orig-

[10]For example, in Tennessee, West Virginia, and Michigan, increases in Opana ER utilisation met the reductions in OxyContin utilisation nearly one-for-one, whereas in New Hampshire, Maine, and Hawaii, increases Opana ER utilisation only made up about 3% of the reductions in OxyContin utilisation.

[11]For example Kasich and Hall [2009] and Mangano [2011].

[12]For example in USA Today, Reuters, NPR (twice) and McGreal [2018].

[13]For example in State of New York v. Endo Health Solutions [2019], State of Tennessee v. Endo Health Solutions [2019] and State of West Virginia v. Endo Health Solutions [2019].

inal Opana ER, however the Food and Drug Administration (FDA) rejected some of the proposed abuse-deterrent labelling because (unlike ADF OxyContin) the drug could still be dissolved in water and prepared for injection. The first ADF Opana ER were shipped in February 2012, and although Endo continued to market both ADF and non-ADF products for a short period, the Opana ER reformulation was accompanied by a 70% decline in non-ADF Opana ER supply by March 2012 and 99% by April. According to the several reports in the epidemiological and public health literature, the reformulated Opana ER pill may have been even more dangerous than the original Opana ER because its design flaws triggered a spike in IDU, ultimately contributing to a 2015 HIV outbreak in Indiana and isolated outbreaks of thrombotic thrombocytopenic purpura (TPP), a potentially fatal blood disorder associated with an ingredient in the reformulated pills crush-resistant (CR) coating [Marder et al., 2013, Conrad et al., 2015, Peters et al., 2016, Gonsalves and Crawford, 2018]. According to Figure 2, however, the reformulation of Opana ER was also accompanied by a sharp decline in overall Opana ER utilisation, back to the levels which prevailed prior to the OxyContin reformulation. Similarly to OxyContin, the mechanism of action was likely not reductions in the demand for opioids, but rather relative price increases in extramedical Opana ER use, including non-monetary costs such as the stigma associated with IDU. A previously unexplored implication of the Opana ER reformulation, thus, is an additional wave of substitution to illicitly manufactured opioids such as heroin.

As a first pass, Figure 4 plots US prescription opioid- and heroin-involved mortality for four groups of states – those with above and below pre- reformulations (from January 2006 to July 2010) OxyContin utilisation crossed by those with above or below between-reformulations (August 2010 to January 2012) Opana ER utilisation. The high OxyContin/low Opana ER group illustrates the narrative of the OxyContin literature to date: after the OxyContin reformulation, prescription opioid-involved mortality levels off and

decreases, whereas heroin involved mortality rapidly increases. However, in states with high between-reformulations Opana ER utilisation (both the high OxyContin/high Opana ER group and low OxyContin/high Opana ER group), prescription opioid-involved mortality continues to climb after the OxyContin reformulation, and high rates of substitution to heroin appear to be delayed until immediately following the Opana ER reformulation. These trends are suggestive of a substitution pattern from OxyContin to Opana ER to heroin or even Opana ER to heroin, as opposed to the OxyContin to heroin pathways explored in previous literature, and motivate our identification strategy outlined in Section 4.

After the Opana ER reformulation, Endo engaged in an illegal pay-to-delay scheme with generic oxymorphone manufacturers followed by several prolonged patent infringement suits through which ADF Opana ER remained the dominant oxymorphone product on the market. Those generics were removed by the FDA in 2015. Finally, in September 2017, the FDA voted to remove ADF Opana ER from the market entirely and Endo complied voluntarily.

3 Data

To estimate the impact of the OxyContin utilisation on subsequent Opana ER utilisation, and Opana ER utilisation on subsequent opioid-involved mortality, we bring together several data sources observing shipments of OxyContin, Opana ER, and other opioids; mortality rates involving prescription opioids, heroin, synthetic opioids and all opioids; and demographic and policy controls. Our sample runs from 2006-2016,[14] encompassing both the OxyContin and Opana ER reformulations, and our analysis is conducted at the state-level.

[14]The lower bound marking the introduction of Opana ER, and the upper bound the last full year when Opana ER was on the market.

3.1 OxyContin, Opana ER, and other opioid utilisation

Utilisation rates of Opana ER, OxyContin, and other opioids are derived from Automation of Reports and Consolidated Orders System (ARCOS) microdata, released in 2018 as a part of ongoing litigation against opioid manufacturers and maintained by The Washington Post as a part of their "Opioid Files" investigation [Washington Post, 2018]. The data capture all reported movements of 14 active ingredients between manufacturers and brick-and-mortar pharmacies, hospitals, and practitioners[15] from January 1, 2006 to December 31, 2014. Importantly, the data include National Drug Codes (NDCs) – unique product identifiers for all drugs in the US intended for human use – which permit identifying the universe of OxyContin and Opana ER shipments specifically, as opposed to shipments of oxycodone and oxymorphone in the ARCOS Retail Summary Reports used in previous literature. The MME dosage of each shipment is computed by multiplying the dose of the product, quantity of pills, and the MME conversion factor of the pill's active ingredient, all of which are also provided in the dataset. All outcomes are aggregated to state-level and measured as per capita rates using Surveillance, Epidemiology, and End Results (SEER) population estimates in the denominator.

It is important to note that because a shipment of pills went to a particular state does not mean that all those pills were used by people in that state. It is thus assumed throughout the remainder of the paper that any measurement error incurred by measuring state-level opioid utilisation with state-level opioid shipments is uncorrelated with the treatment variables discussed below. Given these limitations the data are complemented with Medicaid State Drug Utilisation Data, which capture the universe of opioid *prescrip-*

[15] Returns, destroyed stock, shipments between manufacturers, to non-retail distributors, and to mail-order pharmacies are excluded.

tions subsidized by state Medicaid agencies. These data also contain NDC numbers, allowing us to identify claims relating to both Opana ER and OxyContin specifically. We are unable to use rates of non-medical use per capita as in previous literature [for example Alpert, Powell and Pacula, 2018, Powell, Alpert and Pacula, 2019, Powell and Pacula, 2021, among others] because the National Survey on Drug use and Health (NSDUH) did not start tracking non-medical Opana ER use until 2015.

3.2 Opioid-involved mortality

We observe opioid-involved mortality via the National Center for Health Statistics (NCHS) Multiple Cause of Death (MCOD) data accessed via the Centres for Disease Control (CDC) Wide-ranging ONline Data for Epidemiologic Research (WONDER) system. These data observe the universe of recorded deaths in the US since the introduction of ICD-10 codes in 1999. We follow related literature [Alpert, Powell and Pacula, 2018, Evans, Leiber and Power, 2019, Powell and Pacula, 2021, for example] and categorize a death as a drug overdose using International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) external cause of injury codes X40-X44 (unintentional drug overdose), X60-X64 (suicidal drug overdose), X85 (homicidal drug overdose) and Y10-Y14 (undetermined intent drug overdose); and a drug overdose as opioid-involved using MCOD codes T40.1 (heroin), T.402 (semi-synthetic opioids), and T40.4 (synthetic narcotics). We study these MCOD codes seperately and in aggregate, where in aggregate we also include MCOD T40.3 (methadone). We note that because multiple MCOD codes may be listed on the same death certificate where more than one substance is involved, a death involving prescription opioids *and* heroin, for example, will be counted in both the prescription opioid and heroin outcomes but only counted once in the aggregate outcome. We also note that is is likely some deaths are misreported – for example, a small portion of heroin overdoses are coded as T.406 (unknown narcotics)

and so excluded from our analysis [Ruhm, 2018], and because heroin quickly metabolizes into morphine in the body, a small portion of heroin overdoses may also be coded as natural or semi-synthetic opioid overdoses [Stam et al., 2018]. Thus for the remainder of the paper we assume any measurement error in mortality is uncorrelated with treatment variables discussed below.

All mortality outcomes are measured as crude mortality rates per 100,000 population in a state and year using SEER population estimates in the denominator. For privacy reasons CDC WONDER system suppresses all data cells (for example state-year-MCOD) where there are less than 10 deaths. Thus we replace all cells falling below this threshold with 5 deaths and run sensitivity analyses on our estimates. Further discussion of missing data and these sensitivity analyses are presented in Appendix A.

As a complementary measure, we also consider substance use treatment admission rates from the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episodes Data Set (TEDS-A) datasets. TEDS-A records the universe of treatment admissions to publicly funded substance use treatment facilities throughout the US. Importantly, the TEDS-A data record up to three substances of abuse for each admission, and thus permit distinguishing admissions where the primary substance of abuse is prescription opioids from those where the primary substance of abuse is heroin. Similarly to above, these outcomes are measured as crude treatment admission rates per 100,000 population over 12 years of age in a state and year using SEER population estimates in the denominator. The supply of treatment programs in a given state also depends on many factors other than levels of opioid use – for example, the availability of public funds and public attitudes toward medications for OUD – and there are some concerns of inconsistent reporting in others [Powell and Pacula, 2021]. Thus we assume that any changes in reporting of admissions are not correlated with the treatment variables discussed below.

3.3 Other data

Several other data sources are used primarily to control for other factors that may influence opioid utilisation and opioid-involved mortality. One such factor is the state-based implementation of prescription drug monitoring programs (PDMPs). Controlling for PDMPs is non-trivial because the exact nature of each program changes state to state, and there is some debate in the literature over implementation dates [Horwitz et al., 2018]. PDMP operational dates are taken from Horwitz et al. [2018] who attempt to reconcile discrepancies in other data sources by defining an "operational" PDMP as one which all permitted practitioners can readily access. Furthermore, enactment dates for pill mill laws (PMLs) (state laws which regulate pain management clinics) are derived from Prescription Drug Abuse Policy System (PDAPS). We also collect population and demographic controls – for example age, race, ethnicity, and sex – from SEER population estimates.

4 Methodology

Our empirical approach proceeds in three steps. First, we estimate reduced form models measuring the impact of (non-ADF) OxyContin utilisation prior to the OxyContin reformulation on the subsequent utilisation of Opana ER other prescription opioid products, and opioid-involved mortality. We refer to these as "reduced form" impacts because they also include the flow on effects of later interventions such as the Opana ER reformulation. Second, we extend on the above approach by accounting for the presence of other prescription opioid products on the market after the OxyContin reformulation – particularly non-ADF Opana ER – with the aim of investigating how allowing for more flexible substitution patterns alters our understanding of the evolution of opioid-involved mortality throughout these pivotal years of the epidemic. Finally, we summarize our estimates by simulating the growth of opioid-involved mortality if the Opana ER pathway were shut down at the

time of the OxyContin reformulation.

Our estimation strategy builds on the seminal work of [Alpert, Powell and Pacula, 2018] and [Powell and Pacula, 2021], among others. Similarly to these studies, we assume the extent of substitution from OxyContin to other opioids in each state depends on their level of extramedical OxyContin use prior to the reformulation – that is, we expect those states with greater extramedical use prior to the reformulation to see more substitution compared to those with relatively less extramedical use. While previous studies have interpreted this as "the effect of the OxyContin reformulation," we take more care in considering the counterfactual policy scenarios. Prior to the FDA approving ADF OxyContin, non-medical or extramedical use of OxyContin was still growing across most of the US, though to different degrees between states [Jones, Muhuri and Lurie, 2017]. Thus our models are likely silent on what would have happened had the FDA never approved ADF OxyContin. Instead, they are useful in considering the likely consequences had the OxyContin reformulation occurred earlier or later, when the level of extramedical use of OxyContin was lower or higher. Specifically, we estimate two-way fixed effects continuous treatment event studies of the form:

$$y_{st} = \alpha_s + \gamma_t + \delta_t^A OxyContin_s^{Pre} + x'_{st}\beta + \varepsilon_{st} \tag{1}$$

where y_{st} is the utilisation of OxyContin, Opana ER or other opioids in state s and quarter t, α_s and γ_t are state and quarter fixed effects respectively, x_{st} is a vector of controls,[16] and $OxyContin_s$ is the average OxyContin utilisation through the pre-reformulations period interacted with a full set of quarter

[16]Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), indicators for PDMPs and PMLs, and where indicated, the MME per capita supply of all other opioids in supply excluding OxyContin and Opana ER.

fixed effects δ_t^A. That is, $OxyContin_s^{Pre}$ is equal to:

$$OyxContin_s^{Pre} = \frac{1}{10} \sum_{q=2008q1}^{2010q2} \frac{MME\ OxyContin_{sq}}{Pop_{sq}} \tag{2}$$

We assume that states with high utilisation of closely track those with high rates of non-medical OxyContin use (similarly to Alpert, Powell and Pacula [2018] and Powell and Pacula [2021]) as well as those with high rates of iatrogenic harm arising from the course of legitimate medical treatment which might not otherwise be captured as non-medical use in the NSDUH survey data. The estimation sample runs from 2008q1 to 2014q4, the lower bound marking the end of the rapid expansion of OxyContin supply from 2006 to 2008 evident in Figure 2, and the upper bound marking the limit of the available ARCOS data. All estimates are weighted by state population and standard errors are clustered at the state-level. To motivate discussion, we also replicate the results of Alpert, Powell and Pacula [2018] and Powell and Pacula [2021] on state-year opioid-involved mortality outcomes by MCOD codes.[17] To do so, we estimate variations of Equation (1) defined at the state-year level.

The parameters of interest are the full set of coefficients δ_t^A, with the coefficient pertaining to the period prior to the reformulation normalized to zero. As above, estimates of these coefficients identify the differences in the outcome in each period across states with higher versus lower OxyContin utilisation in the period prior to reformulation. For the Opana ER utilisation outcome, for example, we expect to see a positive jump in δ_t^A after the OxyContin reformulation if high levels of initial OxyContin utilisation predict greater substitution toward Opana ER. Coefficient estimates are identified assuming a parallel trends-type assumption is met – specifically, that absent the reformulation, differences in the outcome across states would have

[17]Specifically, MCOD codes T40.1 (heroin), T.402 (semi-synthetic opioids), T40.4 (synthetic narcotics), and overall opioid-involved mortality, where we also include MCOD T40.3 (methadone).

continued unchanged for *every level of the treatment*. Preliminary evidence for this assumption can be discerned from Figure 4, where we observe that the distance between key comparison groups is largely constant prior to the reformulation and diverges only afterwards. Further evidence may be discerned from coefficient estimates prior to the reformulation, which should be approximately zero.

The aim of Equation (1) is to characterize a first stage-type relationship between initial OxyContin utilisation and the demand for Opana ER, the demand for other active ingredients such as morphine, codeine, hydrocodone, non-OxyContin oxycodone, and illicitly manufactured opioids such as heroin. The substitution patterns observed motivate our main model which extends on Equation (1) to evaluate the evolution of opioid-involved mortality allowing for more complex substitution patterns after the OxyContin reformulation. Similarly to above, the idea is to exploit variation in Opana ER utilisation across states between the OxyContin and Opana ER reformulations using continuous treatment event studies of the form:

$$y_{st} = \alpha_s + \gamma_t + \delta_t^B OxyContin_s^{Pre} + \theta_t^B OpanaER_s^{Btwn} + \eta_t^B OtherOpioids_s^{Btwn} + x'_{st}\beta + \varepsilon_{st} \tag{3}$$

where $OpanaER_s^{Btwn}$ and $OtherOpioids_s^{Btwn}$ are average MME Opana ER capita and average MME per capita of all other opioid products[18] through the between-reformulations period ($q = 2010q3, ..., 2012q1$) in state s, and all other variables are defined as above (except at the state-year level). We include $OtherOpioids_s^{Btwn}$ to isolate the Opana ER channel against all other opioids though find our results do not depend on its inclusion. As with Equation (1) we use MME per capita as our exposure variable to capture

[18]Specifically, we include all products containing codeine, dihydrocodeine, hydromorphone, hydrocodone, levorphanol, meperidine, morphine, opium, tapentadol and fentanyl. We exclude buprenorphine and methadone because they are commonly prescribed in the context of OUD treatment.

complications associated with both extramedical and medical Opana ER use. The estimation sample runs from 2006 to 2016, the lower bound marking the introduction of Opana ER, and the upper bound the last full year when Opana ER was on the market.

In this case, the main parameters of interest are the full set of θ_t^B. Similarly to above, these coefficients identify difference in the outcome across states with higher versus lower between-reformulations Opana ER utilisation relative to the period prior to the reformulation and conditional on having the same initial OxyContin utilisation. For heroin-involved mortality, for example, we expect to see an increase in θ_t^B after the Opana ER reformulation if high levels of between-reformulations Opana ER utilisation predict greater subsequent substitution toward heroin. Coefficient estimates are also identified by a parallel trends-type assumption – that absent the both reformulations, differences in the outcome across states would have continued along the same trends for every level of each treatment. Again, preliminary evidence for our identifying assumption can be discerned from Figure 4, and further evidence by estimates of the pre-reformulations coefficients. For all δ_t^A, θ_t^B and η_t^B, coefficients pertaining to the period prior to the OxyContin reformulation normalized to zero. As above, all estimates are weighted by state population and standard errors are clustered at the state-level.

Finally, we quantify the overall effect of Opana ER via a simulation exercise where we predict opioid-involved mortality in the absence of the Opana ER pathway. To do so, we use our event study estimates from Equation (3) to predict mortality were Opana ER utilisation to remain at its level prior to the OxyContin reformulation, and OxyContin and other opioid utilisation to its mean value in the sample. Thus, estimates represent estimated mortality were the Opana ER pathway shut down at the time of the OxyContin reformulation. We also estimate our models using alternative exposure variables in Appendix B, estimate trendbreak specifications similarly to Alpert, Powell and Pacula [2018], Evans, Leiber and Power [2019] and Powell and

Pacula [2021] except allowing for the Opana ER pathway in Appendix C, and estimate our models using treatment admissions outcomes in Appendix D.

5 Results

5.1 The OxyContin reformulation

We begin by demonstrating that states with high initial OxyContin utilisation prior to the OxyContin reformulation experienced greater absolute reductions in OxyContin utilisation afterwards. In addition to recovering the substitution pathways already discussed in the literature (for example, from OxyContin to heroin) we also show that these same states, on average, saw simultaneous and striking increases in the utilisation of Opana ER. Finally, we establish that the Opana ER reformulation induced large and immediate reductions in Opana ER utilisation, this latter relationship being necessary to leverage variation in between-reformulations Opana ER utilisation to identify the impact of the Opana ER reformulation on subsequent mortality in the next section. The analysis is conducted at the state-quarter level so as to highlight trends in the 18 months between the OxyContin and Opana ER reformulations. The sample runs from 2008q1 to 2014q4, two years prior to the OxyContin reformulation, the 18 months between the Opana and OxyContin reformulations, and the two years after the Opana ER formulation.

Figure 5 plots the full set of state-quarter coefficient estimates and their respective 95% confidence intervals from Equation (1) for OxyContin in Panel A and Opana ER in Panel B. Beginning with the OxyContin outcome, the coefficients pertaining to 2008q1 and 2008q2 indicate the post-2008 expansion of OxyContin utilisation evident in Figure 2 occurs primarily in high OxyContin states. Over the remaining quarters prior to the reformulation, coefficient estimates are close to zero but noisy and statistically insignificant, indicating similar pre-trends across states with high and low initial non-

ADF OxyContin in the 8 quarters prior to the OxyContin reformulation. Immediately following the OxyContin reformulation, however, there was a large decrease in OxyContin utilisation in states with high versus low initial OxyContin which grows throughout the remainder of the sample. From a pre-reformulation average of 25.16 MME OxyContin per capita (s.d. 10.03), an increase of 1 MME OxyContin per capita prior to the reformulation predicts a nearly 0.25 MME larger decrease in MME OxyContin per capita in the first full quarter afterwards, decreasing to 0.33 MME by the quarter of the Opana ER reformulation and 0.53 MME by the end of the sample. The large and immediate effects likely arose from a combination of both demand- and supply-side mechanisms discussed in Section 2. On the demand side, the reformulation increased the price of extramedical OxyContin use by forcing less efficient routes of administration and making substitutes relatively cheaper. On the supply side, the introduction of the ADF OxyContin may have signalled to prescribers that OxyContin was dangerous or that the pill was being targeted by regulators, and some may have responded by changing their prescribing behaviour. Results are consistent with existing literature concerning the effect of the OxyContin reformulation on outcomes such as non-medical OxyContin use [Alpert, Powell and Pacula, 2018, Cicero and Ellis, 2015] and oxycodone supply [Evans, Leiber and Power, 2019], but our outcome (OxyContin shipments per capita) is unique. We demonstrate a qualitatively similar pattern of coefficient estimates using OxyContin market share (as both the outcome and treatment) rather than OxyContin per capita in Appendix B.

We also show that our strategy of using OxyContin utilisation rather than non-medical OxyContin use recovers similar results on state-year opioid-involved mortality documented in previous studies [for example Alpert, Powell and Pacula, 2018, Evans, Leiber and Power, 2019, Powell and Pacula, 2021]. All mortality effects are presented in Figure 6. As previous literature estimate Equation (1) without controls, we also present our estimates with-

out controls in Figure E1. Altogether, our results indicate that reductions in OxyContin utilisation after the OxyContin reformulation were associated with large and statistically significant increases in heroin-involved mortality (Panel B), synthetic opioid-involved mortality after its introduction the US illicit opioid markets circa 2014 (Panel C), and overall opioid-involved mortality (Panel D). Substitution away from OxyContin toward illicitly manufactured opioids, however, suggests that states with high initial OxyContin utilisation should have also experienced reduction in the rate of prescription opioid-involved mortality after the OxyContin reformulation. Similarly to Alpert, Powell and Pacula [2018][19] and Powell and Pacula [2021],[20] however, our event study estimates in Panel A indicate that, simultaneous to substitution to heroin, high OxyContin states experienced a jump in the rate of prescription opioid-involved mortality in the year of the OxyContin reformulation which remained elevated throughout the remainder of the sample. We interpret these findings as an indication that mechanisms additional to substitution to heroin were also at play around the OxyContin reformulation.

One obvious explanation is substitution among prescription opioid products, particularly to products with a similar potential for harm to OxyContin. We thus turn to the state-quarter Opana ER outcome in Figure 5 Panel B. Estimated coefficients prior to the OxyContin reformulation exhibit an increasing pre-trend relative to the normalization, in part explained by Endo's extensive use of prescriber profiling data to target sales calls at high volume OxyContin prescribers specifically [State of New York v. Endo Health Solutions, 2019, State of Tennessee v. Endo Health Solutions, 2019, State of West Virginia v. Endo Health Solutions, 2019]. Immediately after the reformulation, states with high initial OxyContin utilisation, on average, experience large and immediate increases in Opana ER utilisation. The magnitude of this differential grows through the between-reformulations pe-

[19] See Alpert, Powell and Pacula [2018] Appendix Figure A.9 Panels A and B.
[20] See Powell and Pacula [2021] Figure 2 Panel C.

riod until it makes up for approximately 49.95% of the decrease in OxyContin evident in Panel A, although this figure is likely overestimated due to the pre-existing trend. As the large increase in Opana ER utilisation in the between-reformulations period coincides precisely with the post-reformulation decline in OxyContin utilisation and is concentrated among states with the highest levels of initial non-ADF OxyContin, we interpret these estimates as indicative of substitution between the two products. Although not all of this effect is likely attributable to risky prescription opioid use, we note that the major functional difference between Opana ER and OxyContin after the OxyContin reformulation was the abuse-deterrent properties of the reformulated OxyContin. Furthermore, after the Opana ER reformulation in February 2012, coefficient estimates almost immediately return to pre-OxyContin reformulation levels. The reduction in Opana ER utilisation after the Opana ER reformulation is likely mediated by similar demand- and supply-side factors which underpinned the reduction in OxyContin utilisation 18 months earlier. On the demand side, for example, individuals previously chewing, sniffing or smoking the original Opana ER were no longer able to. Those reticent to inject the ADF formulation would have seen substitutes such as IR oxycodone or heroin[21] as relatively more attractive. On the supply side, the introduction of the crush-resistant pill may have served as a signal to prescribers to change their prescribing behaviour. Results are consistent with existing literature outside economics concerning the effect of the OxyContin reformulation on smaller samples of individuals previously engaging in extramedical OxyContin use [Cassidy et al., 2014, Cicero and Ellis, 2015], but are the first to grapple with the extent of substitution from Opana ER to OxyContin across the US. Similarly to above, we also demonstrate a qualitatively similar pattern of coefficient estimates using market share as the treatment and outcome in Appendix B.

[21] At the time, the most common route of delivery for heroin in the US was sniffing [NSDUH, 2010].

Finally, we additionally estimate Equation (1) for other common active ingredients found in prescription opioids, namely hydrocodone, non-OxyContin oxycodone, codeine, and morphine. For brevity, coefficient estimates and their respective 95% confidence intervals are presented in Figure E2. In summary, there is no evident substitution effect from OxyContin to hydrocodone (Panel A), non-OxyContin oxycodone (Panel B), nor codeine (Panel C) with all coefficients prior to, between, and after the reformulations approximately equal to zero or negative. MME morphine per capita (Panel D) appears to increase after the OxyContin reformulation and again after the Opana ER reformulation, although the effects are neither clean nor large. Altogether, we interpret these results as indicative of a prominent pathway from OxyContin to Opana ER above and beyond other opioid products, although we will still control for other products in our models presented in the next section. Finally, similarly to Alpert, Powell and Pacula [2018] and Powell and Pacula [2021] we also investigate a trendbreak model which aims to estimate the overall effect of each reformulation conditional on controls. The model and results are presented in Appendix C. In summary, estimated magnitudes largely agree with above – initial OxyContin is associated with large and statistically significant reductions in MME OxyContin per capita, increases in MME Opana ER per capita (approximately 28% of the decline in OxyContin), and no effect on other opioid products through the between-reformulations period. After the Opana ER reformulation, OxyContin utilisation continues to decline, Opana ER returns to zero relative to the pre-period, and other opioids remain at a stable level.

Altogether, after the introduction of ADF OxyContin, OxyContin utilisation declined disproportionately in states with the highest initial utilisation. Additional to the substitution patterns explored in previous literature, our results also identify substantial substitution from OxyContin toward Opana ER in at least some of the same states at the same time. Finally, after Opana ER was reformulated in 2012, Opana ER utilisation quickly declined

to pre-reformulations levels, whereas the utilisation of other opioids remained stable. Considering the major functional difference between the two products prior to 2012 was the abuse deterrent properties of the reformulated OxyContin, this pattern of results strongly suggests that a population of people engaging in extramedical OxyContin use prior to the OxyContin reformulation migrated to Opana ER afterwards, and then elsewhere again after the Opana ER reformulation 18 months later.

5.2 The Opana ER reformulation

Next, we examine whether differences between states in Opana ER utilisation between the OxyContin and Opana ER reformulations, conditional on initial OxyContin utilisation and other substitution pathways, were associated with differential trends in opioid-involved mortality after the Opana ER reformulation. To do so, we estimate Equation (3) on outcomes observing prescription opioid-, heroin-, synthetic opioid-, and total opioid-involved mortality. Results are presented in Figure 7. Given data availability constraints on the public use MCOD data, the analysis is conducted at the state-year level. The sample runs from 2006 to 2016, the lower bound marking the introduction of Opana ER, and the upper bound the last full year Opana ER remained on the market. Notably the sample includes both the OxyContin reformulation in 2010, the Opana ER reformulation in 2012, and the introduction of synthetic opioids into US illicit opioid markets circa 2014.

Beginning with the prescription opioid-involved mortality outcome in Panel A, all three sets of coefficient estimates exhibit no significant pre-trend prior to the OxyContin reformulation. Contrary to previous literature and our replication in Figure 6 Panel A, coefficient estimates relating to initial OxyContin remain close to zero through the period of the OxyContin reformulation and throughout the remainder of the sample, indicating no differences in prescription opioid-involved mortality in high versus low initial OxyContin states. Estimated coefficients pertaining to other opioids

products are also flat or negative throughout the remainder of the sample. Estimated coefficients relating to Opana ER, on the other hand, jump in the year of the OxyContin reformulation, grow sharply through the between-reformulations period, and continue to grow after the Opana ER reformulation. Altogether, an additional 1 MME per capita per year in Opana ER through the between-reformulations period is associated with an increase of 0.06 prescription opioid-involved deaths per 100,000 population in 2012 compared to the baseline in 2009, growing to 0.10 by 2016. Notably, results are similar using alternative definitions of OxyContin and Opana ER utilisation such as using state Medicaid prescriptions and OxyContin and Opana ER market share (see Appendix B), alternative trendbreak specification (see Appendix C), and alternative outcomes measuring disease burden such as TEDS-A prescription opioid treatment admission outcomes (see Appendix D).

Thus, controlling for substitution pathways from OxyContin to other prescription opioid products eliminates the jump in prescription opioid-involved mortality attributable to initial OxyContin seen in previous literature and our replication in Figure 6 Panel A. Referring to descriptive evidence presented in Figure 4, it is likely these patterns do not represent an increase in overdose deaths but rather a continuation of the positive trend in prescription opioid-involved mortality in high Opana ER states while mortality in low Opana ER states levelled off after the OxyContin reformulation. Even so, they imply that the risks associated with extramedical Opana ER use were at least as substantial as OxyContin. Indeed, there is some evidence that oxymorphone carries a higher abuse liability than does oxycodone at equipotent doses [Babalonis et al., 2014]. Furthermore, Endo's marketing strategies encouraged long-term use and dose escalation above and beyond other products, implying some role for more severe OUD within the context of Opana ER use [State of New York v. Endo Health Solutions, 2019, State of Tennessee v. Endo Health Solutions, 2019, State of West Virginia v. Endo

Health Solutions, 2019]. The active ingredient in Opana ER (oxymorphone) is also twice as strong in MME and has approximately double the effective half-life than the active ingredient in OxyContin (oxycodone) [State of West Virginia v. Endo Health Solutions, 2019], and some individuals may have not adequately accounted for these differences when engaging in extramedical Opana ER use or when switching from OxyContin to Opana ER. After the introduction of ADF Opana ER in 2012, furthermore, the design flaws of the reformulated pill encouraged IDU, implying greater risks of fatal overdose via increases in the bio-availability of the drug, and greater risks of fatal complications such as TPP. Altogether, these results suggest the increases in prescription opioid-involved mortality in high OxyContin states demonstrated in in Figure 6 Panel A, Alpert, Powell and Pacula [2018] and Powell and Pacula [2021] are associated with between-reformulations Opana ER utilisation, rather than on the reformulated OxyContin or other opioids.

Panel B presents results using the heroin-involved mortality outcome. Consistent with previous literature and our replications in Figure 6 Panel B, coefficient estimates relating to initial OxyContin exhibit no significant pre-trend through the pre-reformulations period, indicating similar rates of heroin-involved mortality across high and low OxyContin states. Immediately after the OxyContin reformulation, however, heroin-involved mortality in high OxyContin states begins to diverge, although their estimated magnitude after the Opana ER reformulation is reduced by approximately 15-20% compared to Equation (1). Estimates relating to other opioid products also exhibit no pre-trend but decrease immediately after the OxyContin reformulation and throughout the remainder of the sample. Turning to the Opana ER coefficients, estimated coefficients are approximately zero through the pre- and between-reformulations period, indicating similar rates of heroin-involved mortality across both high and low Opana ER states through to 2012. Referring to Figure 4, these results do not imply there was no substitution from OxyContin to heroin after the OxyContin reformulation where

Opana ER was present, but rather that rates of heroin-involved mortality did not diverge in high versus low Opana ER states through this period. After the Opana ER reformulation, however, heroin-involved mortality increases sharply in high Opana ER states and continues to grow through the remainder of the sample, implying a second wave of substitution to heroin (the first following the OxyContin reformulation) in high Opana ER states occurring immediately after the Opana ER reformulation. Altogether, 1 MME per capita increase in between-reformulations Opana ER utilisation is associated with a 0.04 increase in heroin-involved mortality per 100,000 population in 2013 (the first full year after the Opana ER reformulation) and 0.1 by 2016 (the end of the sample). For comparison, a 1 MME increases in OxyContin per capita is associated with a 0.015 increase in heroin-involved mortality by 2013 and 0.037 by 2016. As above, results are consistent using alternative definitions of OxyContin and Opana ER utilisation (see Appendix B), an alternative trendbreak specification (see Appendix C), and TEDS-A heroin-involved treatment admission outcomes (see Appendix D).

Thus, our results suggest that the presence of Opana ER on the market delayed substitution to heroin in high Opana ER states, and that the reformulation of Opana ER 18 months later was followed by a wave of substitution additional to that which had already occurred as a result of the OxyContin reformulation. Such a pattern of results is consistent with ex-ante expectations arising from the OxyContin reformulation literature – that turning off the supply of a drug on which many people are dependent in the presence of substitutes will induce a degree of substitution. However, they indicate that some of the substitution from OxyContin to heroin identified in previous literature includes a pathway first through Opana ER. They also suggest that the increasing trend (rather than level shift) in heroin-involved mortality evident in other studies [for example Alpert, Powell and Pacula, 2018, Powell and Pacula, 2021] and in the descriptive evidence (for example Figure 1) represents additional populations of people substituting to heroin over time – at

the least, some who were previously using OxyContin after the OxyContin reformulation, and others who were previously using or substituted to Opana ER after the OxyContin reformulation.

Figure 7 Panel C presents results relating to synthetic opioid-involved mortality outcome. Once again, all three sets of coefficient estimates exhibit no significant pre-trend prior to the OxyContin reformulation. Estimates pertaining to other opioid products continue along this trajectory through the remainder of the sample, indicating no differences in mortality in high versus low states. Consistent with our replication in Figure 6 Panel C and previous literature [Powell and Pacula, 2021, for example], synthetic opioid-involved mortality in high OxyContin states diverges from low OxyContin states after the introduction of synthetic opioids into US illicit opioid markets circa 2014. Similar trends are evident in high versus low Opana ER states, suggesting that the expansion of illicit drug markets discussed in Powell and Pacula [2021] occurred in both high Opana and high OxyContin states simultaneously. Finally, Figure 7 Panel D presents results pertaining to overall opioid-involved mortality. Coefficients relating to other opioids are zero or negative throughout the entire sample. The OxyContin coefficients are flat prior to the Opana ER reformulation but increasing in the long-term, driven primarily by synthetic opioids [Powell and Pacula, 2021, similarly to]. The Opana ER coefficients, on the other hand, begin to increase after 2010 (owing to prescription opioid-involved mortality) and again after 2012 (owing to heroin- and synthetic opioid-involved mortality), ultimately suggesting large increases in overall opioid-involved mortality by 2016.

In summary, our results suggest that the presence of licit substitutes to OxyContin muted the efficacy of the OxyContin reformulation as a tool to reduce prescription opioid-involved harm. In fact, taken with the descriptive evidence presented in Figure 4, prescription opioid-involved mortality in states with high levels of substitution to Opana ER appears to have been unaffected by the OxyContin reformulation. These results highlight the dan-

gers of high-dose ER opioid products specifically throughout the US opioid epidemic, as opposed to lower dose IR products. Furthermore, while it is clear that the OxyContin reformulation induced large increases in the rate of substitution to heroin in states with a high OxyContin utilisation, our results show that states with high between-reformulations Opana ER utilisation experienced an additional, delayed wave of substitution to heroin after the Opana ER reformulation. It is possible, in fact, that the presence of Opana ER on the market after the OxyContin reformulation increased states exposure to subsequent interventions by enabling more individuals to engage in extramedical pharmaceutical opioid use or to develop more severe symptoms of OUD through Endo's intentional strategy of dose escalation.

5.3 Counterfactual growth in opioid-involved mortality

Finally, similarly to Alpert, Powell and Pacula [2018], Beheshti [2019] and Powell and Pacula [2021] for the OxyContin reformulation, we quantify the overall effect of substitution to Opana ER via a simulation exercise. Specifically, we use our estimates from Equation (3) to predict per capita mortality in a counterfactual scenario where, holding OxyContin and other opioids constant at their mean values in the data, no state experienced any additional substitution to Opana ER after the OxyContin reformulation. To do so, we substitute $OpanaER_s^{Btwn}$ for $OpanaER_s^{Pre}$ as defined by Equation (2). We thus investigate a scenario where the Opana ER pathway was shut down at the time of the OxyContin reformulation. Results are presented in Figure 8.

Beginning with the prescription opioid-involved mortality outcome in Panel B, our counterfactual predicts only slightly less prescription opioid-involved mortality in the pre-reformulations period but sharply diverges from observed mortality in the year of the OxyContin reformulation and continues to grow thereafter. From 2009 to 2016, actual prescription opioid-involved

mortality increased by 41%, whereas our predictions imply an increase of 3%. Thus, our estimates suggest that nearly all (92%) of the growth in prescription opioid-involved mortality after the OxyContin reformulation loads on Opana ER. Notably, most divergence between actual and predicted mortality occurs in the between-reformulations period, suggesting that the presence of Opana ER on the market entirely muted the efficacy of the OxyContin reformulation as a tool to reduce prescription opioid-involved harm.

Turning to the heroin-involved mortality in Panel B, actual and predicted mortality remain roughly equal in the pre- and between-reformulations periods, suggesting that heroin deaths were likely to have occurred after the OxyContin reformulation regardless of the availability of Opana ER. Immediately after Opana ER was reformulated in 2012, however, actual and predicted mortality diverge substantially, suggesting that the continued availability of Opana ER after the OxyContin reformulation either delayed some substitution from OxyContin to heroin which would have occurred otherwise, increased the population of individuals suffering from OUD-like symptoms and at risk of substituting to illicit substitutes, or both. From 2009 to 2016 actual heroin-involved mortality increased by 343%, whereas our predictions imply a 231% increase. Thus, our estimates suggest that in the absence of the Opana ER to heroin pathway, the growth of heroin-involved mortality would have been approximately 33% lower by 2016. Similarly for the synthetic opioid-involved mortality outcome in Panel C, our estimates imply a 38% reduction, almost all occurring after the introduction of synthetic opioids in the US heroin and counterfeit pill supply in circa 2014.

Finally, turning to overall opioid-involved mortality in Panel D, we estimate the total impact of substitution to Opana ER on opioid-involved mortality. Divergence between actual and predicted mortality begins in the year of the OxyContin reformulation, driven primarily by increasing prescription opioid-involved mortality. After the Opana ER reformulation, divergence continues to grow, now driven by prescription-, heroin- and synthetic opioid-

involved mortality. From 2009 to 2016 actual opioid-involved mortality increased by 111.5%, whereas our estimates imply an increase of 62%, suggesting an approximately 44% of overall opioid-involved mortality over this period loads on susbtitution to Opana ER.

6 Conclusion

In this study we have provided evidence that, in addition to substitution to heroin and synthetic opioids as identified in previous literature [Alpert, Powell and Pacula, 2018, Evans, Leiber and Power, 2019, Powell and Pacula, 2021], the OxyContin reformulation induced substitution among contemporaneous prescription opioid products with similar potential for harm. These substitution patterns explain the absence of substantial reductions in prescription opioid-involved mortality after the OxyContin reformulation. Furthermore, we have provided evidence that the February 2012 Opana ER reformulation was followed by a second wave of substitution to heroin previously solely attributed to OxyContin, suggesting the growing trend in heroin-involved mortality after 2010 was fed by several populations over time. This is not the first study to identify Opana ER as a major contributor to opioid-involved harm throughout the epidemic, but it is the first to grapple with the extent of extramedical Opana ER use across the country. Of course, the damage caused by Opana ER is not solely attributed to Endo. The continued prescription opioid-involved mortality after the OxyContin reformulation attributable to Opana ER, as well as elevated heroin- and synthetic opioid-involved mortality after the Opana ER reformulation, rest on the initial proliferation of OxyContin.

Two policy implications emerge from our results. Firstly, the rising rates of extramedical prescription opioid use which characterized the initial stages of the US opioid epidemic was largely driven by a small class of products, specifically high-dose ER formulations. These products carry substantial

risks for harm even from legitimate medical treatment, and especially where non-ADF products enable extramedical use via rapid release of high doses intended to provide longer-duration pain relief. Thus, in settings where these products are not yet widely prescribed, harm can be minimized by ensuring their use is contained and carefully regulated from the outset. For example, policymakers need to ensure consumers and prescribers are aware of the risks associated with these drugs and product promotion is undertaken within strict guidelines [Lexchin and Kohler, 2011]. Policymakers should also ensure companies and prescribers develop plans to manage downstream harms should they arise [Lexchin and Kohler, 2011]. ADF products are likely to still play a role in these lower-use environments to prevent inadvertent rapid release or extramedical use.

Such prevention measures, however, are likely to be more effective in the early stages of a drug epidemic Winkler et al. [2004]. In this paper we have studied the situation where high-dose ER products had already proliferated widely. In this context, policymakers, including the FDA, faced three stark choices: not permit Purdue and Endo to reformulate their products and see OxyContin and Opana ER utilisation continue to rise across the US; permit Purdue and Endo to reformulate and see unbridled substitution effects among licit and illicit opioids; or permit Purdue and Endo to reformulate and simultaneously implement policies to channel substitution effects to the lowest risk alternatives. We largely observed the second scenario play out and, in this paper, we have documented that the devastating consequences. The first scenario was unlikely to have produced better outcomes – in fact, delaying the reformulations while utilisation continued to rise could have produced even more devastating consequences. This leaves only the third scenario. To minimize harm, there was a critical need to simultaneously deliver treatment options to individuals at risk of substituting among prescription opioid products or to illicit substitutes, for example to medications for OUD such as methadone and buprenorphine. Indeed, regulators and pharmaceutical

companies need to work in concert to identify at risk populations and ensure that evidence based care are accessible to them. Importantly, policymakers should only expect companies to be willing to pursue such strategies when they have clear incentives to do so, for example as a condition of market exclusivity rights or to avoid litigation.

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7 Figures

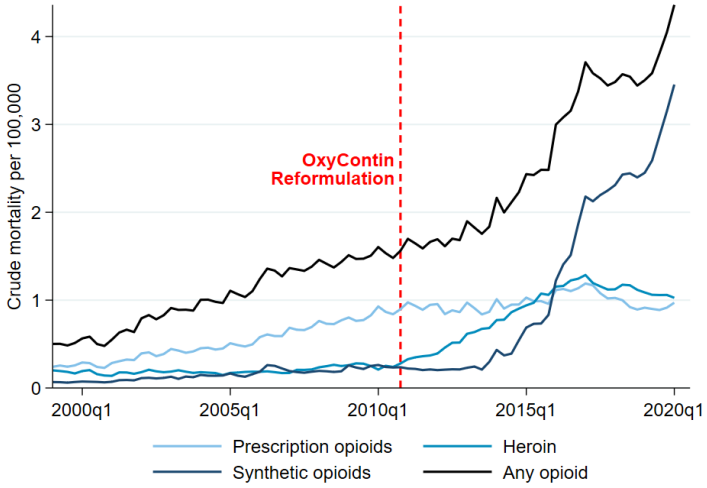
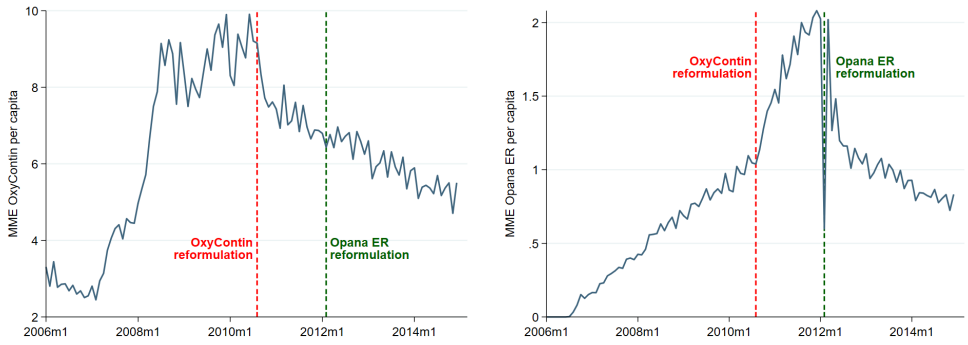


Figure 1. National trends in opioid-involved mortality.

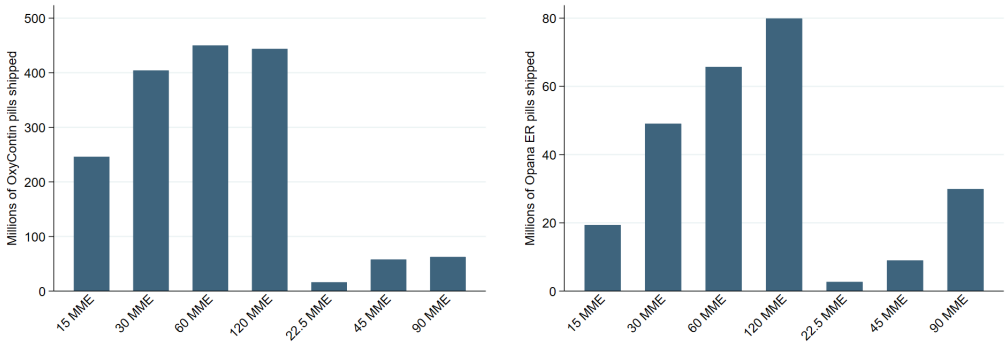
Note: Quarterly mortality per 100,000 population from the CDC National Vital Statistics System (NVSS). Opioid deaths are coded using ICD-10 external cause of injury codes X40-X44, X60-X64, X85 and Y10-Y14 and MCOD codes T40.1 (heroin), T.402 (semi-synthetic opioids, presented in the figure as prescription opioids), and T40.4 (synthetic narcotics, presented in the figure as synthetic opioids). For overall opioid-involved mortality we also include MCOD T40.3 (methadone).



Panel A. OxyContin Panel B. Opana ER

Figure 2. National trends in OxyContin and Opana ER shipments.

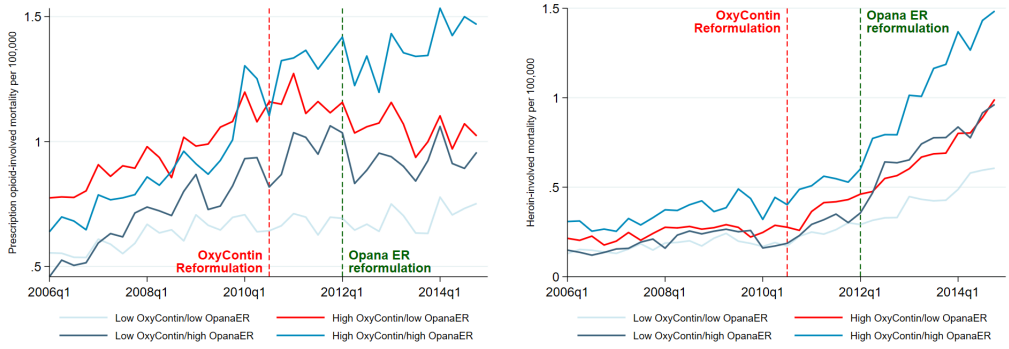
Note: Monthly shipments per capita of OxyContin and Opana ER from the Washington Post "Opioid Files" database [Washington Post, 2018]. OxyContin and Opana ER shipments are idenfied by NDCs pertaining to those products.



Panel A. OxyContin Panel B. Opana ER

Figure 3. OxyContin and Opana ER shipments by dose

Note: Millions of OxyContin and Opana ER pills shipped from 2006 to 2014 by product from the Washington Post "Opioid Files" database [Washington Post, 2018]. OxyContin and Opana ER products are identified by NDCs pertaining to those products. Note that each drug's manufacturer introduced 22.5, 45, and 90 MME doses after they introduced 15, 30, 60, 90 and 120 MME doses.

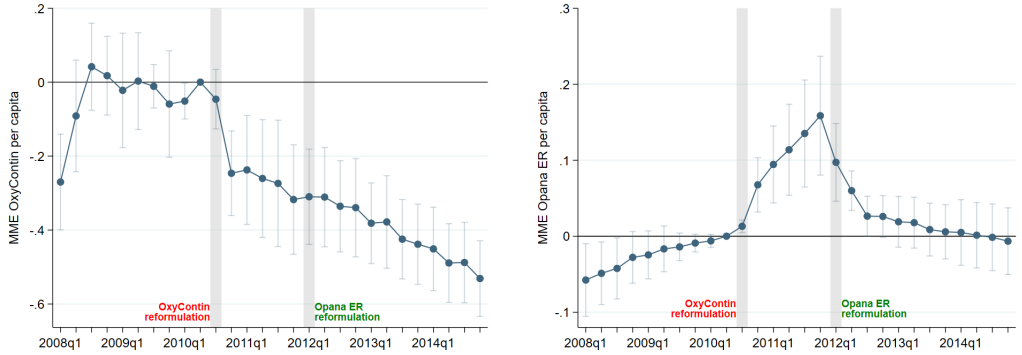


Panel A. Prescription opioid-involved mortality

Panel B. Heroin-involved mortality

Figure 4. Opioid mortality by OxyContin and Opana ER shipments.

Note: Prescription opioid- and heroin-involved mortality by states above and below average pre-reformulations ($q = 2006q1, ..., 2010q2$) OxyContin shipments per capita crossed with states above and below between-reformulations ($2010q3, ..., 2011q4$) Opana ER shipments per capita. Mortality data from the CDC NVSS, where opioid deaths are coded using ICD-10 external cause of injury codes X40-X44, X60-X64, X85 and Y10-Y14 and MCOD codes T40.1 (heroin), T.402 (semi-synthetic opioids, presented in the figure as prescription opioids). Shipments data are from the Washington Post "Opioid Files" database [Washington Post, 2018]. OxyContin and Opana ER shipments are identified by NDCs pertaining to those products.

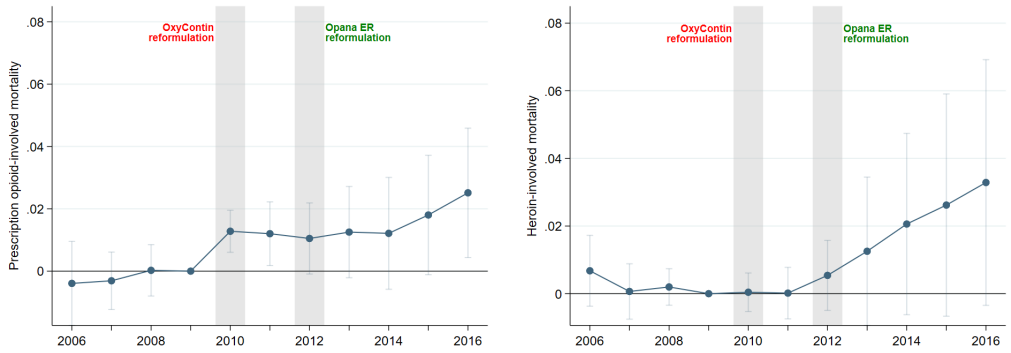


Panel A. OxyContin

Panel B. Opana ER

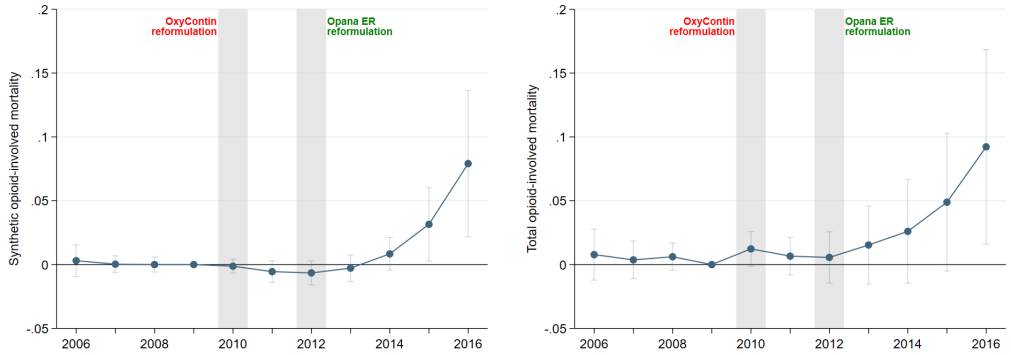
Figure 5. Effect of pre-reformulations OxyContin utilisation on subsequent OxyContin and Opana ER utilisation.

Note: Estimated coefficients and 95% confidence intervals from Equation (1) depicting the effect of pre-reformulations OxyContin utilisation on subsequent OxyContin utilisation in Panel A and subsequent Opana ER utilisation in Panel B. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), indicators for PDMPs and PMLs, and the MME per capita supply of all other opioids in supply excluding OxyContin and Opana ER. Estimates are weighted by state population and standard errors clustered at the state level.



Panel A. Prescription opioid-involved mortality

Panel B. Heroin-involved mortality

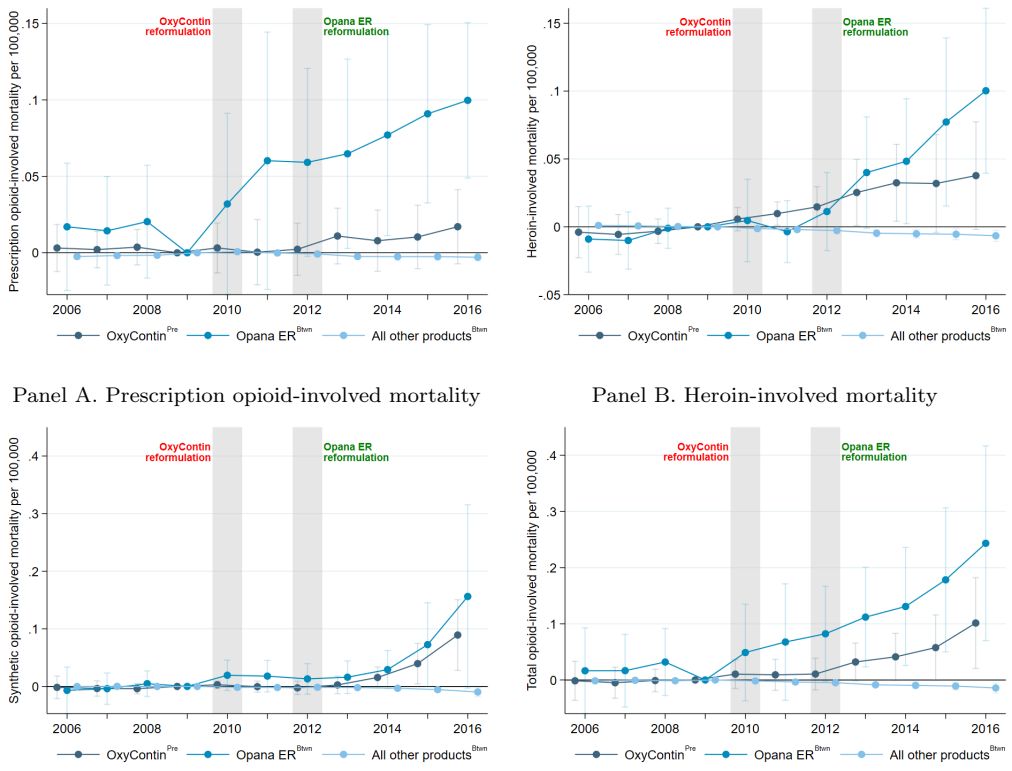


Panel C. Synthetic opioid-involved mortality

Panel D. Total opioid-involved mortality

Figure 6. Effect of pre-reformulations OxyContin utilisation on subsequent opioid-involved mortality.

Note: Estimated coefficients and 95% confidence intervals from our from Equation (1) depicting the effect of the OxyContin reformulation on the on prescription opioid-involved mortality in Panel B, heroin-involved mortality in Panel A, synthetic opioid-involved mortality in Panel C and total opioid-involved mortality in Panel D. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Estimates are weighted by state population and standard errors clustered at the state level.



Panel A. Prescription opioid-involved mortality

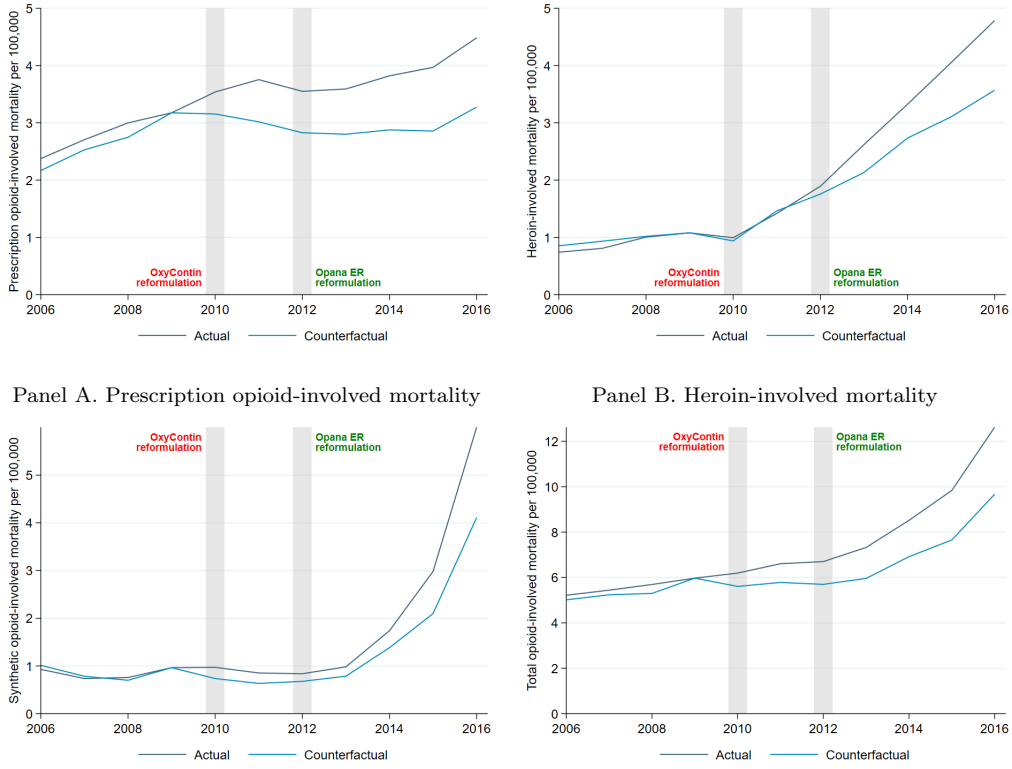
Panel B. Heroin-involved mortality

Panel C. Synthetic opioid-involved mortality

Panel D. Total opioid-involved mortality

Figure 7. Effect of between-reformulations Opana ER utilisation on subsequent opioid-involved mortality.

Note: Estimated coefficients and 95% confidence intervals from Equation (3) depicting the effect of initial OxyContin utilisation, between-reformulations Opana ER utilisation, and between-reformulation utilisation of other opioids on prescription opioid-involved mortality in Panel B, heroin-involved mortality in Panel A, synthetic opioid-involved mortality in Panel C and total opioid-involved mortality in Panel D. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Estimates are weighted by state population and standard errors clustered at the state level.



Panel A. Prescription opioid-involved mortality

Panel B. Heroin-involved mortality

Panel C. Synthetic opioid-involved mortality

Panel D. Total opioid-involved mortality

Figure 8. Simulation results.

Note: Simulation results using the event study estimates from Equation (3) to predict per capita mortality by year for each MCOD in the absence of substitution to Opana ER. In each plot, the black line represents actual mortality and the blue line represents predicted mortality if every state had the average level of Opana ER utilisation through the pre-reformulations period.

Appendix

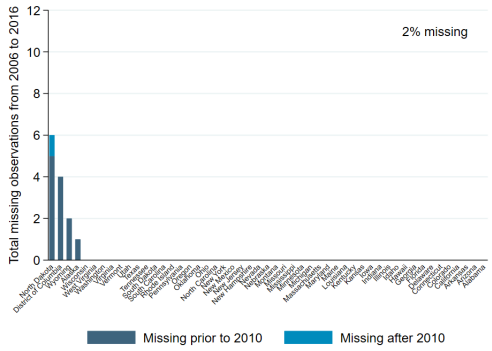
A Data suppression thresholds

Methodology and results

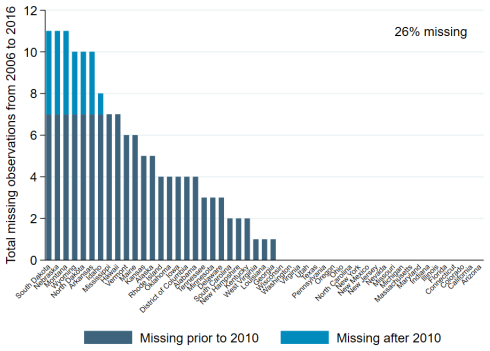
In the publicly available MCOD files, available through the CDC WONDER system, sub-national data cells – in this case, state-year-MCOD cells – representing fewer than ten persons (0-9) are suppressed to protect privacy. For the purposes of our analysis, these data restrictions particularly affect small states without severe mortality owing to a specific MCOD code, for example heroin-involved mortality in South Dakota prior to 2010. The count of missing state-year observations by state over 2006-2016 is represented in Figure A1, and ranges from 2% missing for semi-synthetic opioids (T40.2) to 26% missing for heroin (T40.1). For all codes, most data is missing prior to the OxyContin reformulation in 2010, meaning any bias arising from these missing data most severely affects estimates of the pre- rather than post-reformulations trends.

As may be discerned from Figure A1, this concern is especially relevant for heroin-involved deaths where up to 26% of observations are missing over the sample period. To check the sensitivity of our results to this potential source of bias, Figure A2 presents estimates from Equation (3) of coefficients δ_t^B (relating to $OxyContin_s^{Pre}$) in Panel A and θ_t^B (relating to $OpanaER_s^{Btwn}$) in Panel B using different replacement values for these missing observations on the heroin-involved mortality outcome. Especially for the Opana ER reformulation, pre-trends are more pronounced where data are outright excluded, potentially because many of the small states with high Opana ER supply (e.g. Tennessee, Kentucky, and West Virginia) are missing multiple observations prior to 2010. In general, however, pre-, between- and post-reformulations coefficient estimates do not vary over whether the missing observations are replaced with 0, 5, or 9.

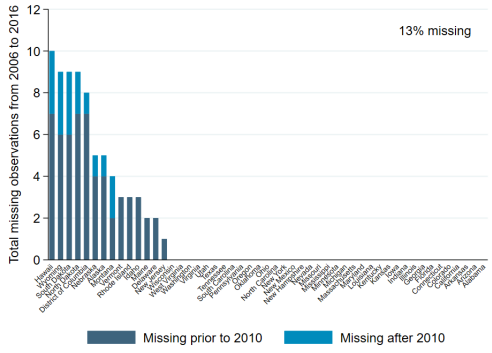
Figures



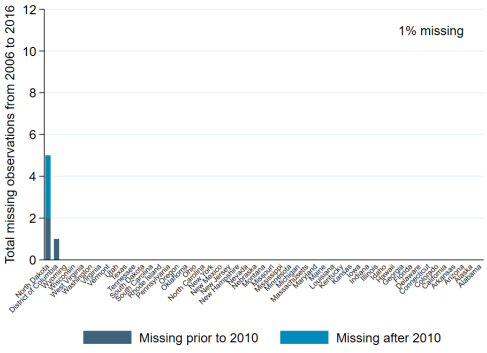
Panel A. Prescription opioids (T40.2)



Panel B. Heroin (T40.1)



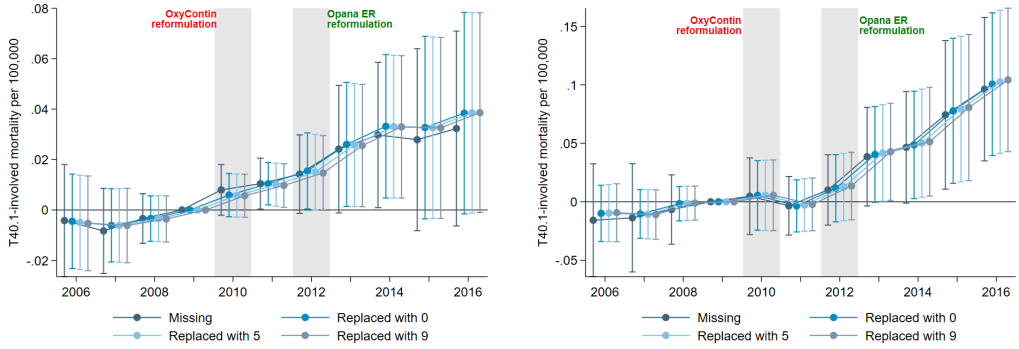
Panel C. Synthetic opioids (T40.4)



Panel D. Total opioids

Figure A1. Missing data by state and MCOD code.

Note: Bar graphs depicting the count of missing state-year observations for each MCOD code which fall below the data suppression thresholds of the CDC WONDER system.



Panel A. Estimates of δ_t^B (relating to $OxyContin_s^{Pre}$)

Panel B. Estimates of θ_t^B (relating to $OpanaER_s^{Btwn}$)

Figure A2. Robustness to missing data replacement

Note: Estimated coefficients from Equation (3) using heroin-involved mortality as the outcome and 0, 5, or 9 deaths to fill in suppressed data. Controls, weights, and standard errors are estimated equivalently to Figure 7.

B Medicaid and market share exposure variables

Methodology and results

We also estimate variations of our event studies in Equation (1) and Equation (3) where $OxyContin_s^{Pre}$ and $OpanaER_s^{Btwn}$ are measured as per capita rates using Medicaid data[22] and as market shares using ARCOS data.[23] We exclude $OtherOpioids_s^{Btwn}$ in these models to avoid perfect multicollinearity using the market share exposure variables and for brevity when using the Medicaid exposure variables.

Results for Equation (1) using OxyContin and Opana ER market shares as the outcome are presented in Figure B1.[24] Coefficient estimates exhibit similar patterns to the per capita outcome presented in Figure 5. OxyContin market share is flat prior to the reformulation and decreasing thereafter, whereas Opana ER market share exhibits a slight pre-trend, increases through the between-reformulations period, and returns to zero thereafter. Our estimates suggest that increases in Opana ER market share made up 27% of the decline in OxyContin by 2011 Q4, although again the figure is likely slightly overestimated due to the pre-existing trend.

Results for Equation (1) using the heroin- and prescription-opioid involved mortality outcomes are presented in Figure B2, for the Medicaid exposure in Panel A and Panel B and the market share exposure in Panel C and Panel D. For the prescription opioid-involved mortality outcome using the Medicaid exposure variable, there is a less pronounced jump in mortality in the year of the OxyContin reformulation compared to our main results in Figure 6 and existing literature [Alpert, Powell and Pacula, 2018, Powell and Pacula, 2021]. Using the market share

[22] We omit South Dakota and Washington due to these states being large outliers in their reported Medicaid-subsidised OxyContin prescriptions.

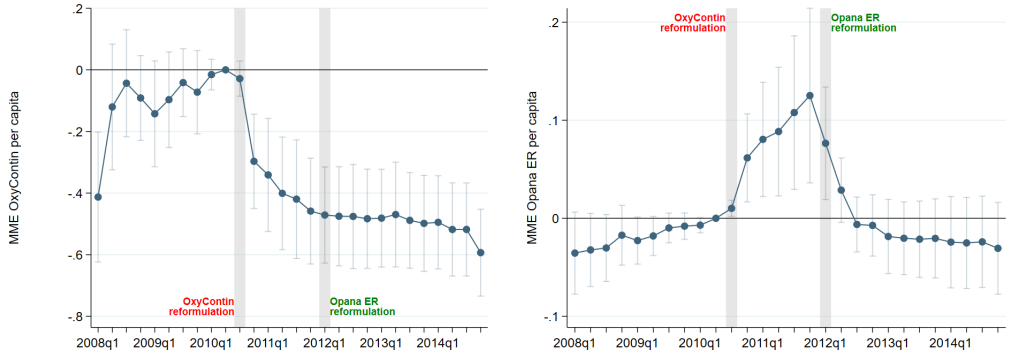
[23] Market share is defined similarly to Equation (2) except using $TotalMME_{st}$ in the denominator, namely total shipments of all active ingredients in the dataset except methadone and buprenorphine.

[24] We note that Opana ER was listed on Medicaid in most states in 2009, and OxyContin delisted in most states after the OxyContin reformulation, and so omit results using these as outcomes.

exposure, prescription opioid-involved mortality does not jump but rather appears diverge in high versus low OxyContin states throughout the the sample. Turning to the heroin-involved mortality outcomes, there are few qualitative differences in the pattern of coefficient estimates compared to our main results in Figure 6. Both models appear to exhibit relatively flat pre-trends, and after the OxyContin reformulation states heroin-involved mortality begins to diverge in high versus low initial OxyContin states, leading to increasing coefficient estimates throughout the remainder of the sample.

Finally, results for Equation (3) using the heroin- and prescription-opioid involved mortality outcomes are presented in Figure B3, for the the Medicaid exposure in Panel A and Panel B and market share exposure in Panel C and Panel D. There are again few qualitative differences in the pattern of coefficient estimates compared to our main results in Figure 7. For the prescription opioid-involved mortality outcome, high versus low OxyContin states follow similar trends in the pre-, between-, and post-reformulations periods. In high versus low Opana ER states, on the other hand, trends in prescription opioid-involved mortality are approximately equal in low versus high Opana ER states before the OxyContin reformulation but diverge thereafter. For the heroin-involved mortality outcome, both high OxyContin and Opana ER states exhibit no difference in mortality compared to their low counterparts prior to the OxyContin reformulation. High OxyContin states diverge after the OxyContin reformulation (although decline after 2014 using the Medicaid exposure), whereas high Opana states continue on the same trajectory through the between-reformulations period and diverge only after the Opana ER reformulation. We interpret these findings as consistent with our main results in Figure 7.

Figures

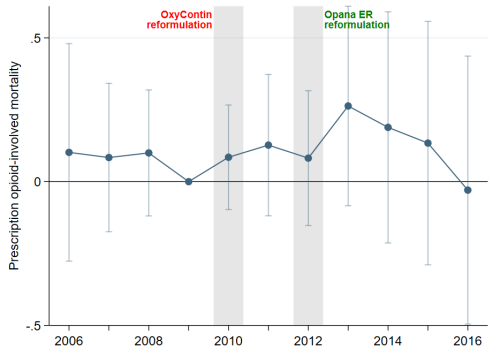


Panel A. OxyContin Medicaid prescriptions

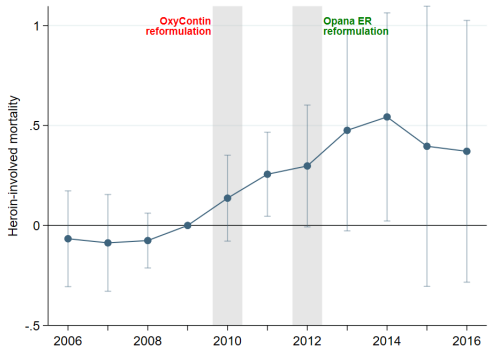
Panel B. Opana ER Medicaid prescriptions

Figure B1. The effect of pre-reformulation OxyContin market share on subsequent OxyContin and Opana ER market share.

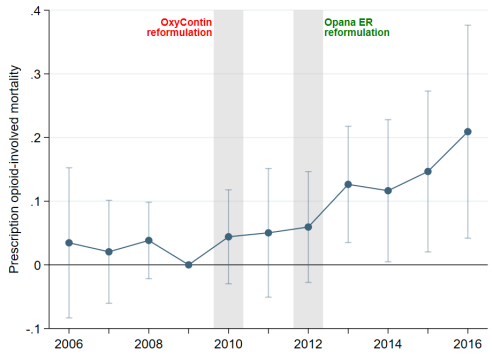
Note: Estimated coefficients and 95% confidence intervals from Equation (3) using market share exposure variable on OxyContin market share in Panel A and Opana ER market share in Panel B. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, ≥ 60), indicators for PDMPs and PMLs, and the MME per capita supply of all other opioids in supply excluding OxyContin and Opana ER. Standard errors are clustered at the state level and estimates weighted by state population.



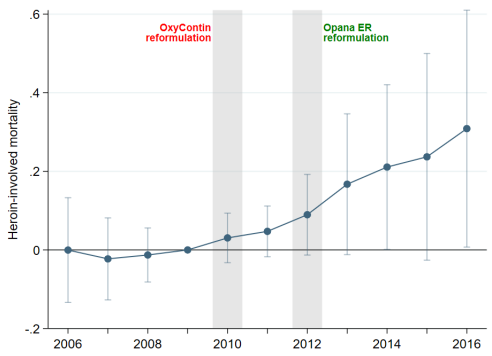
Panel A. Prescription opioid-involved mortality, Medicaid exposure



Panel B. Heroin-involved mortality, Medicaid exposure



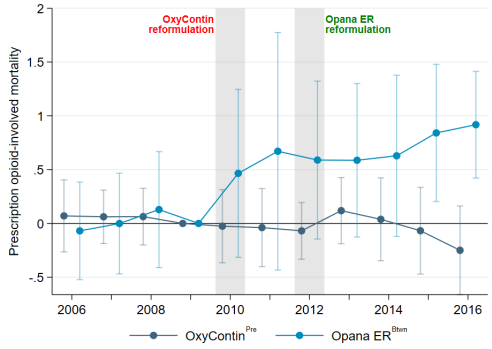
Panel C. Prescription opioid-involved mortality, market share exposure



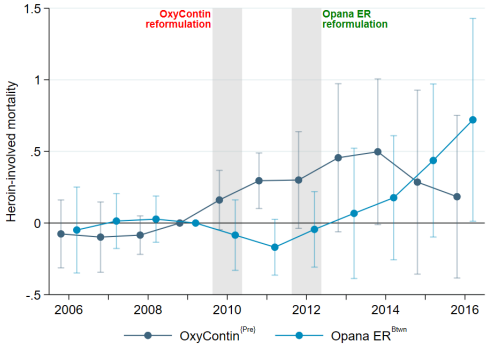
Panel D. Heroin-involved mortality, market share exposure

Figure B2. The effect of alternative OxyContin exposure variables on subsequent opioid-involved mortality.

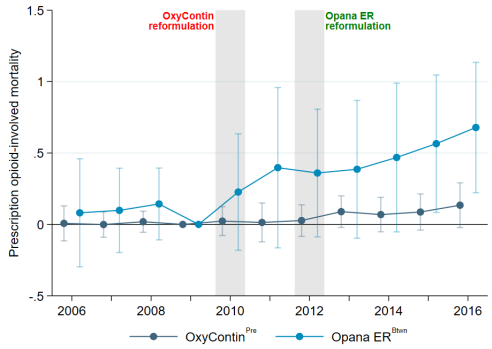
Note: Estimated coefficients and 95% confidence intervals from Equation (1) using Medicaid exposure variable in Panel A and Panel B and the market share exposure variable in Panel C and Panel D. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Standard errors are clustered at the state level and estimates weighted by state population.



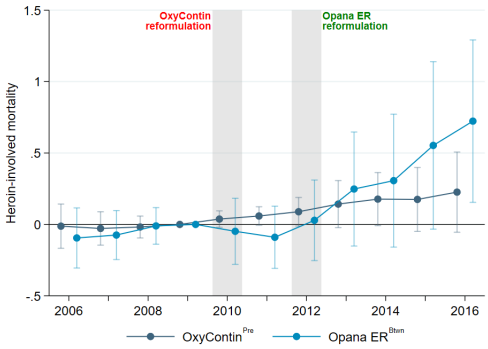
Panel A. Prescription opioid-involved mortality, Medicaid exposure



Panel B. Heroin-involved mortality, Medicaid exposure



Panel C. Prescription opioid-involved mortality, market share exposure



Panel D. Heroin-involved mortality, market share exposure

Figure B3. The effect of alternative OxyContin and Opana ER exposure variables on subsequent opioid-involved mortality

Note: Estimated coefficients and 95% confidence intervals from Equation (3) using Medicaid exposure variable in Panel A and Panel B and the market share exposure variable in Panel C and Panel D. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Standard errors are clustered at the state level and estimates weighted by state population.

C Trendbreak specifications

Methodology and results

We also estimate trendbreak specifications similarly to Alpert, Powell and Pacula [2018], Evans, Leiber and Power [2019] and Powell and Pacula [2021] accounting for the Opana ER pathway. Our specifications Equation (4) and Equation (5) are less flexible versions of Equation (3) but provide easier to interpret magnitudes. For the state-quarter outcomes, we estimate the model:

$$y_{st} = \alpha_s + \gamma_t + \sum_{A \in \mathcal{A}} \Big(\rho_1^A [A \times t] + \rho_2^A [A \times Btwn_t] + \rho_3^A [A \times Btwn_t \times t_{OxyContin}] + \rho_4^A [A \times Post_t] + \rho_5^A [A \times Post_t \times t_{OpanaER}] \Big) + x'_{st}\beta + \varepsilon_{st} \tag{4}$$

where $\mathcal{A} = \{OxyContin_s^{Pre}, OpanaER_s^{Btwn}, OtherOpioids_s^{Btwn}\}$, $Btwn_t$ is an indicator for the between-reformulations period, $Post_t$ is an indicator for the post-reformulations period, $t_{OxyContin}$ and $t_{OpanaER}$ are event-time variables pertaining to each reformulation,[25] t is a linear time trend, and x_{st} is a vector of demographic controls. This specification controls for pre-existing trends $A \times t$ while allowing for both a level shift $A \times Btwn_t$ and trend break $A \times Btwn_t \times t_{OxyContin}$ in the outcome in the between-reformulations period, and a level shift $A \times Post_t$ and trend break $A \times Post_t \times t^{OpanaER}$ in the post-reformulations period. On the state-year mortality outcomes, we estimate a variation of this model which does not account for the between-reformulations period. In particular:

$$y_{st} = \alpha_s + \gamma_t + \sum_{A \in \mathcal{A}} \Big(\rho_1^A [A \times t] + \rho_2^A [A \times Post_t^A] + \rho_3^A [A \times Post_t^A \times t_A] \Big) + x'_{st}\beta + \varepsilon_{st} \tag{5}$$

where all variables are defined as above, except now $Post_t^A$ and t_A pertain to A.[26]

Table C1 presents estimates of Equation (4). Similar to previous literature, all estimates presented are linear combinations of level shift and trend break co-

[25] Specifically, $t_{OxyContin} = t - 2010q3$ and $t_{OpanaER} = t - 2012q1$.

[26] Specifically, $Post_t^A = \mathbb{1}(year \geq 2010)$ and $t_A = t - 2010$ for $OxyContin_s^{Pre}$, and $Post_t^A = \mathbb{1}(year \geq 2012)$ and $t_A = t - 2012$ for $OpanaER_s^{Btwn}$ and $OtherOpioids_s^{Btwn}$.

efficients (for example $\rho_2^A + (2012q1 - 2010q3) \times \rho_3^A$ for the effect through the between-reformulations period). Results are consistent with our event studies presented in Section 4 and discussed in Section 5. In sum, a 1 MME increase in initial OxyContin is associated with 0.45 reduction in MME OxyContin per capita and 0.12 increase in MME Opana ER per capita (approximately 28% of the decline in OxyContin) through the between-reformulations period, both significant at 1%. After the Opana ER reformulation, OxyContin utilisation continues to decline whereas Opana ER returns to zero relative to the pre-period. Also similarly to above, the effect of the reformulation on the supply of other opioids is insignificant for each active ingredient. In sum, results are consistent with our main findings presented in Figure 5 and Figure E2.

Table C2 presents estimates from for our trendbreak specification Equation (5) on heroin-, prescription opioid-, synthetic opioid-, and total opioid-involved mortality. Again, we report estimates of the level shift coefficient plus trend break coefficients multiplied by the remaining periods in the sample (for example, $\rho_2^A + \rho_3^A(2016 - 2010)$ for OxyContin and $\rho_2^A + (2016 - 2012)\rho_3^A$ for Opana ER). To investigate how accounting for the Opana ER pathway alters our understanding of the relationship between OxyContin and subsequent opioid-involved mortality, the first column presents estimates using only initial OxyContin utilisation, the second for OxyContin and other opioids (excluding Opana ER), and the third OxyContin, other opioids and Opana ER. Starting with the first column, the effect of initial OxyContin utilisation on subsequent heroin-, synthetic opioid- and overall opioid-involved mortality is positive and statistically significant (the lattermost at 10%). Consistent with previous literature [Alpert, Powell and Pacula, 2018, Powell and Pacula, 2021], accounting for other opioids (second column) accentuates these estimates, particularly for prescription opioid-involved mortality. Including the Opana ER pathway, however, substantially decreases the influence of OxyContin across all outcomes, by 41% for prescription opioid-involved mortality, 29% for heroin-involved mortality, 17% for synthetic opioid-involved mortality, and 26% for overall opioid-involved mortality. In sum, results are consistent with the estimates presented in Figure 7, and further suggest that a large portion of the relationship between initial OxyContin utilisation and subsequent opioid-involved

mortality measured in previous literature owes to substitution from OxyContin to Opana ER.

Tables

	OxyContin	Opana ER	Hydrocodone	Oxycodone	Codeine	Morphine
Btwn-reforms.	-.4483***	.1239***	-.1238	-.2662	-.0015	-.0261
	(.1046)	(.0424)	(.1923)	(.8988)	(.0146)	(.0324)
Post-reforms.	-.7107***	-.0866	-.3136	-1.1309	-.0259	-.1206*
	(.1058)	(.0678)	(.4438)	(1.75)	(.0269)	(.0643)
N	1,428	1,428	1,428	1,428	1,428	1,428
TWFE	✓	✓	✓	✓	✓	✓
Controls	✓	✓	✓	✓	✓	✓

Table C1. Trendbreak specification results for utilisation by product and active ingredient.

Note: Estimates from Equation (4) of the effect of the OxyContin reformulation on between- and post-reformulations utilisation of OxyContin, Opana ER, hydrocodone, non-OxyContin oxycodone, codeine and morphine. All models are estimated at the state-quarter level from 2008q1 to 2014q4 ($N = 1,428$). Reported estimates represent a combination of level-shift and trendbreak coefficients multiplied through the period in question. Standard errors are in parenthesis. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), indicators for PDMPs and PMLs, and the MME per capita supply of all other opioids in supply excluding OxyContin and Opana ER. Standard errors are clustered at the state level and estimates weighted by state population. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

	OxyContin only	OxyContin and other opioids	OxyContin, other opioids, and Opana ER
Prescription opioids			
OxyContin	.0398	.1505**	.0886*
	(.0573)	(.0589)	(.0515)
Opana ER	.	.	.2572**
	.	.	(.1)
Other Opioids	.	-.0188**	-.0212***
	.	(.0086)	(.0058)
Heroin			
OxyContin	.1814**	.232**	.1639*
	(.0853)	(.0977)	(.0845)
Opana ER	.	.	.3178**
	.	.	(.1271)
Other Opioids	.	-.0135	-.017*
	.	(.0099)	(.0087)
Synthetic opioids			
OxyContin	.2523***	.3461***	.287***
	(.0773)	(.1079)	(.0985)
Opana ER	.	.	.3524
	.	.	(.2394)
Other Opioids	.	-.0213	-.0259**
	.	(.0131)	(.014)
Total opioids			
OxyContin	.2652*	.5097**	.3752***
	(.1568)	(.1801)	(.1557)
Opana ER	.	.	.6139**
	.	.	(.2694)
Other Opioids	.	-.0495**	-.0559***
	.	(.02)	(.017)
N	918	918	918
TWFE	✓	✓	✓
Controls	✓	✓	✓

Table C2. Trendbreak specification results for opioid-involved mortality.

Note: Estimates from Equation (5) of the effect of the OxyContin and Opana ER reformulations on prescription opioid-, heroin-, synthetic opioid- and total opioid-involved mortality. All models are estimated at the state-year level from 1999 to 2016. Reported estimates represent a combination of level-shift and trendbreak coefficients through the end of the sample. Standard errors are in parenthesis. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Standard errors are clustered at the state level and estimates weighted by state population. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

D Treatment admissions outcome

Methodology and results

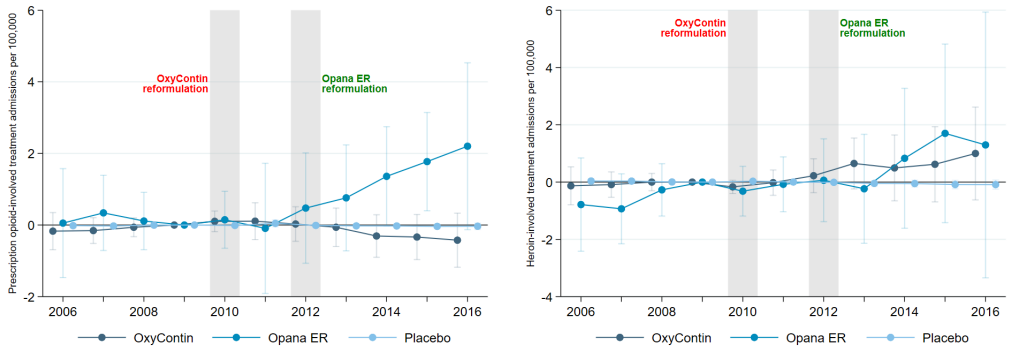
We also offer evidence that opioid-involved treatment admissions increased in the wake of the Opana ER reformulation. To do so, we estimate Equation (3) using prescription opioid- and heroin-involved treatment admissions per 100,000 population over 12 years of age as the outcome.[27] We consider a prescription opioid-involved treatment admission one where heroin is listed as the primary, secondary or tertiary substance of abuse on admission, and similarly for heroin-involved admissions. We note that due to changes in reporting over time, TEDS-A data are incomplete for some states (including high Opana ER states such as Tennessee) over the 2006 to 2016 period. For our main results we drop these states leaving $N = 43$ states and $NT = 473$ observations, though we find that our results do not depend on this sample restriction.

Overall, the qualitative pattern of coefficient estimates is similar to the mortality outcomes presented in Figure 7. For prescription opioid-involved admissions, we see no increase in prescription opioid-involved admissions in high versus low OxyContin or high versus low other opioid states at any point in the sample. We also see no increase in admissions in high versus low Opana ER states through the between-reformulations period, although high Opana ER states diverge rapidly thereafter. Trends in heroin-involved treatment admissions are similarly delayed by one to two years for both high OxyContin states after the OxyContin reformulation and high Opana ER states after the Opana ER reformulation. We note that the supply of treatment programs in a given state depends on factors other than the disease burden, for example the availability of public funds and physical capital. Furthermore, there is significant heterogeneity over the types of treatment available in each state – for example, some states focus on non-intensive outpatient care whereas others focus more on inpatient care. Thus the delays evident in all effects relative to the mortality outcomes may represent states responding to increased need under fiscal or other healthcare constraints. Altogether, we interpret our findings as lending credibility to the notion of increased demand for

[27] TEDS-A records treatment admissions for individuals over 12 years of age.

prescription opioid-involved admissions specifically after the Opana ER reformulation, and to a lesser extent, substitution to heroin after the OxyContin and Opana ER reformulations.

Figures



Panel A. Prescription opioids

Panel B. Heroin

Figure D1. Effect of between-reformulations Opana ER utilisation on subsequent opioid-involved treatment admissions.

Note: Estimated coefficients and 95% confidence intervals from Equation (3) depicting the effect of initial OxyContin utilisation, between-reformulations Opana ER utilisation, and between-reformulation utilisation of other opioids on prescription opioid-involved treatment admissions in Panel A and heroin-involved treatment admissions in Panel B. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Standard errors are clustered at the state level and estimates weighted by state population over 12 years of age.

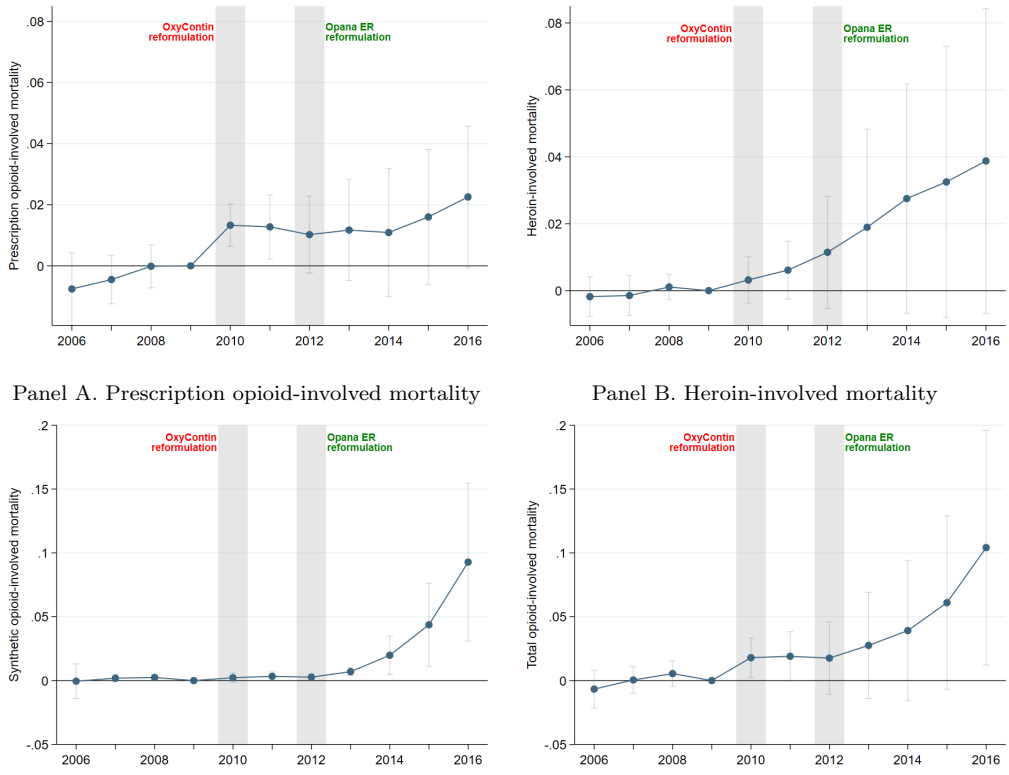
E OxyContin reformulation additional results

Methodology and results

In this section we verify that our strategy of using OxyContin utilisation rather than non-medical OxyContin use recovers similar mortality effects in models without control variables, similar to previous studies [for example Alpert, Powell and Pacula, 2018, Evans, Leiber and Power, 2019, Powell and Pacula, 2021]. We also isolate the OxyContin to Opana ER pathway by demonstrating that initial OxyContin utilisation does not predict substitution to other prescription opioid products by estimating variations of Equation (1) on per capita rates of hydrocodone, non-OxyContin oxycodone, codeine, and morphine.

Results are discussed in full in Section 5. In summary, for the mortality outcomes presented in Figure E1, models using no control variables recover qualitatively similar patterns of coefficient estimates to our main results and to previous studies. In particular, states with high initial OxyContin experienced differential heroin-involved mortality in the years after the OxyContin reformulation (Panel B), and increased synthetic opioid-involved and total opioid-involved mortality after the introduction of synthetic opioids in 2014 (Panel C and Panel D). Notably different is the 2011 coefficient in the heroin-involved mortality outcome, which is approximately 0 with controls but positive without. Similarly to Alpert, Powell and Pacula [2018] and Powell and Pacula [2021], we also see that prescription opioid-involved mortality in high OxyContin states increases immediately after the OxyContin reformulation and remains elevated through the remainder of the sample (Panel A), even though we see little evidence of substitution from OxyContin to other prescription opioid products (Figure E2).

Figures



Panel A. Prescription opioid-involved mortality

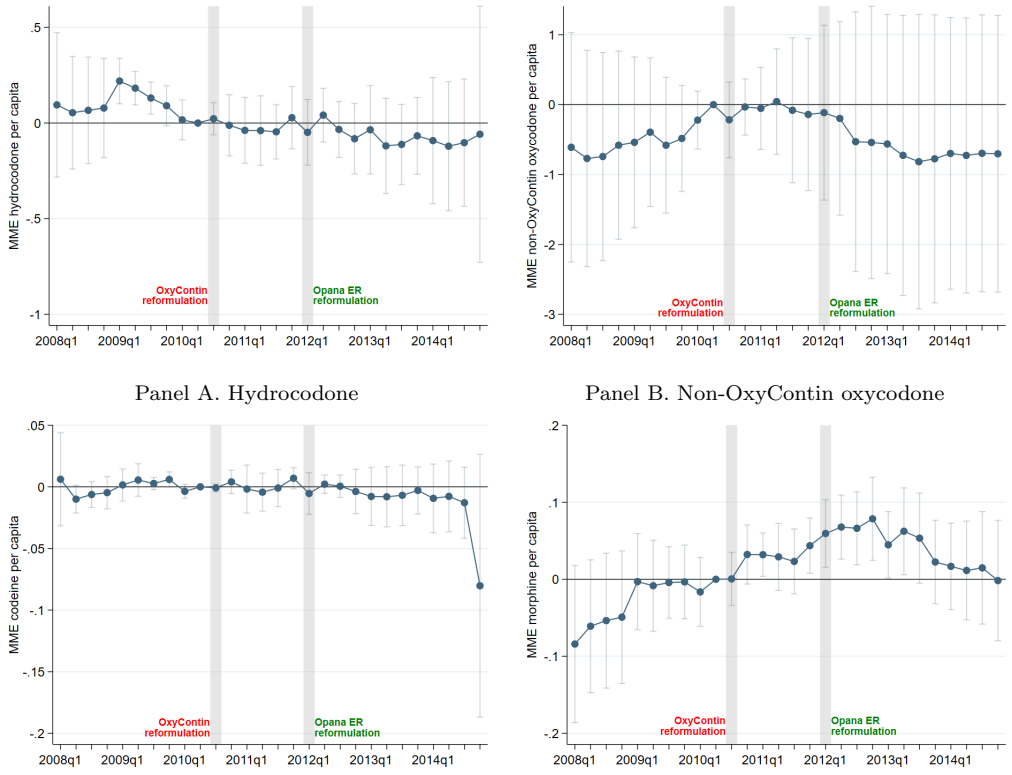
Panel B. Heroin-involved mortality

Panel C. Synthetic opioid-involved mortality

Panel D. Total opioid-involved mortality

Figure E1. Effect of pre-reformulations OxyContin utilisation on subsequent opioid-involved mortality.

Note: Estimated coefficients and 95% confidence intervals from our from Equation (1) depicting the effect of the OxyContin reformulation on the on prescription opioid-involved mortality in Panel B, heroin-involved mortality in Panel A, synthetic opioid-involved mortality in Panel C and total opioid-involved mortality in Panel D. To exactly replicate methodologies employed in previous literature, we omit controls. Estimates are weighted by state population and standard errors clustered at the state level.



Panel A. Hydrocodone

Panel B. Non-OxyContin oxycodone

Panel C. Codeine

Panel D. Morphine

Figure E2. Effect of pre-reformulations OxyContin utilisation on subsequent utilisation of substitute compounds.

Note: Estimated coefficients and 95% confidence intervals from Equation (1) depicting the effect of the OxyContin reformulation on the utilisation of most commonly supplied opioids at the active ingredient level, namely hydrocodone in Panel A, non-OxyContin oxycodone in Panel B, codeine in Panel C, and morphine in Panel D. Controls include the percentage of the population who identify as white, identify as Hispanic, identify as male, the percentage of population who fall in 20-year age bins (20-39, 40-59, $\geq$ 60), and indicators for PDMPs and PMLs. Standard errors are clustered at the state level and estimates weighted by state population.

1