An Empirical Analysis of Policy Responses to the Opioid Epidemic

by

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INTRODUCTION

The United States is currently experiencing a drug overdose epidemic. More than 400,000 Americans have died from an opioid overdose between 1999 and 2017. The rate of opioid overdose deaths has more than doubled since the early 2000s. Policymakers, scholars, and the public at large are intensely interested in remedying this public health crisis. This dissertation studies the impact that state and federal policies have had on opioid overdoses and the relationship between opioid overdoses and worker injuries.

Chapter 1 analyzes the effect of state naloxone access laws on opioid overdose rates. Naloxone is a prescription drug that reverses the effects of an ongoing opioid overdose. From 2006 to 2016, most states enacted statutes expanding the ability of opioid users and others to access naloxone to administer to individuals experiencing an overdose. This chapter uses a richly detailed dataset to separately identify the effects of different naloxone access provisions on different subpopulations of opioid users. The results demonstrate that loosening naloxone prescription requirements saves thousands of lives annually, particularly among illegal drug users in urban areas.

Chapter 2 investigates the effect of the U.S. Food and Drug Administration's 2014 boxed warnings on opioid prescriptions. The FDA required manufacturers of opioids to place a boxed warning on the drug labels of all extended release opioid products in April 2014. Using the language of the warning, I explore how the warning affected opioid prescriptions among groups that the warning targeted. I find that the warning decreased prescriptions to repeat users of opioids by 30%. However, the substantial decrease in prescriptions to repeat users did not yield a decrease in opioid overdose fatalities.

Finally, chapter 3 studies the relationship between fatal occupational injuries and opioid overdoses. This chapter investigates whether increases in opioid abuse in a geographic area are associated with increases in occupational injuries. Because increases in worker injuries could increase opioid use just as well as increases in opioid abuse could increase worker injuries, this chapter uses instrumental variables estimation to identify the direction of causation. I find consistent evidence that opioid abuse significantly increased fatal worker injuries, while finding no evidence that dangerous working conditions increase fatal opioid overdoses.

CHAPTER 1: THE RIGHT PRESCRIPTION: AN EMPIRICAL STUDY OF NALOXONE ACCESS LAWS AND FATAL OPIOID OVERDOSES

I. Introduction

State and local governments are at the forefront of the battle against the ongoing drug overdose epidemic. In 2014 the average state's fatal opioid overdose rate increased by 13.5% over 2013 fatality rates.[1] Fatalities escalated even faster in 2015, with average rates growing by 15% relative to 2014 deaths, with individual state rates ranging from a 16% decrease to a 201% increase. Faced with rapidly escalating overdoses, state policymakers have adopted a variety of statutes and regulations to save lives (Davis and Carr 2015; Paulozzi, Kilbourne, and Desai 2011). Identifying optimal policy responses to the epidemic has become a priority of state governments nationwide.

This chapter evaluates the effect of legal changes that expanded access to naloxone. Naloxone is an opioid antagonist that works within a few minutes to treat an individual experiencing an opioid overdose (Lewanowitsch and Irvine 2002). Survival rates are extremely high if an individual experiencing an overdose receives sufficient naloxone quickly enough; one meta-analysis estimated a survival rate of 96% (McDonald and Strang 2016). Darke and Duflou (2016) presented evidence that naloxone administration within 20 to 30 minutes of use can reverse approximately half of opioid overdoses, while the remaining half could have been reversed by more rapid administration. While the United States Food and Drug Administration ("FDA") classifies naloxone as a prescription drug (Egan 2014), naloxone has no known recreational or therapeutic benefit other than to mitigate the effects of opioids that an individual has consumed (Chamberlain and Klein 1994). The side effects of naloxone administration tend to

[1] Year over year change calculated using the National Vital Statistics System's Multiple Cause of Death Restricted Access Files.

be mild. Naloxone has the added benefit of being simple to administer; the FDA has approved formulations of naloxone distributed via an autoinjector or nasal spray, allowing anyone in possession of the drug to easily treat someone experiencing an overdose (U.S. FDA 2018a, 2018b). The FDA has also developed consumer-friendly drug facts labels intended to convey the information a consumer would need in order to effectively administer naloxone in the case of an overdose (Staman 2018).

Because naloxone has significant potential to decrease fatal opioid overdoses, state legislatures have expanded legal access to naloxone in recent years.[2] Expanded access has taken a variety of forms. Some states have extended criminal immunity or immunity from damages in any civil liability action to health care professionals that prescribe or dispense naloxone.[3] Other naloxone access statutes have focused on the individuals who administer naloxone, offering them civil or criminal immunity under certain circumstances.[4] Other provisions enable individuals who are friends or family members of opioid users to acquire naloxone to administer to an opioid user in the case of an overdose.[5] Still more states have allowed pharmacists to dispense naloxone without patients receiving a patient-specific prescription from a medical professional other than the pharmacist.[6] In 2006, only one state had adopted a naloxone access law, but by 2014 a majority of states had done so. Today, every single state has some form of a naloxone access law (Network for Public Health Law 2017).

Despite the dramatic uptake in naloxone access laws among states and the attention that naloxone availability has received in the federal government, relatively little empirical evidence

[2] *E.g.*, State v. W.S.B., 180 A.3d 1168, 1177 (N.J. App. Div. 2018) ("Encouraging the wider prescription and distribution of naloxone or similarly acting drugs to those at risk for an opioid overdose, or to members of their families or peers, would reduce the number of opioid overdose deaths and be in the best interests of the citizens of this State.") (quoting N.J. Stat. Ann. § 24:6J-2 (2018)).
[3] *E.g.*, Colo. Rev. Stat. § 13-21-108.7(4)(a) (2018).
[4] *E.g.*, Cal. Civ. Code §§ 1714.22(e)–(f) (2018).
[5] *E.g.*, N.J. Stat. § 24:6J-4(a)(1) (2018).
[6] *E.g.,* Ky. Rev. Stat. § 217.186 (2018).

exists demonstrating what effect these statutes have had on opioid overdose fatalities (Davis and Carr 2015). To date, three rigorous empirical studies have examined these laws (Doleac and Mukherjee 2018; McClellan et al. 2018; Rees et al. 2019). Daniel Rees and co-authors demonstrated that the adoption of naloxone access laws decreased fatal opioid overdoses by 9-11%. Shortly thereafter, Jennifer Doleac and Anita Mukherjee presented evidence that naloxone access laws had no effect on opioid overdose fatalities in urban areas but increased opioid-related crime and emergency room visits. Finally, Chandler McClellan and co-authors utilized a random effects model to demonstrate that naloxone access laws were associated with a 14% decrease in opioid mortality rates. These empirical studies focused on different aspects of the statutes, studied the laws at different geographic levels, and presented divergent results. Previous researchers have also evaluated the impact of individual naloxone access programs in localized areas and generally found that individuals participating in naloxone distribution programs successfully reversed overdoses (e.g., Doe-Simkins et al. 2009). The existing evidence does not provide a clear path forward for policymakers. The previous research provides insufficient evidence about which provisions of naloxone access laws are most beneficial and whether the benefits of naloxone only accrue to individuals in certain demographic groups or in certain areas. There is a pressing need for further information on what provisions to expand naloxone access work to reduce fatalities and in what circumstances.

In this chapter, I provide evidence that removing the need for a patient-specific prescription from a non-pharmacist practitioner decreases opioid overdose fatality rates. I do not find clear evidence that the other major provisions of naloxone access laws affect opioid overdose fatality rates. This empirical evidence is derived from the National Vital Statistics System's restricted access county-level mortality data, augmented with several other data sources which I present in detail in Part III. My data contain every single documented fatal opioid overdose in the United States from 2006–2016. I aggregate these data to construct monthly opioid overdose fatality rates for every single county in the United States. Using these richly detailed data, I estimate the individual effect of four naloxone access law provisions. I utilize a difference-in-differences empirical methodology, which is commonly used to identify the effects of state policies (McMichael et al. 2019). I present my methodology in detail in Section III.B.

Part IV presents the results of my estimates. Provisions that allow patients to purchase naloxone without a patient-specific prescription from a doctor[7] cause a statistically significant decrease in the rate of fatal opioid overdoses. Subsequent analyses demonstrate that the decreased fatalities are concentrated among 35 to 44-year-old white men in urban areas[8] and in heroin overdose fatalities. Removing the need for a patient-specific prescription by a doctor enables individuals to acquire naloxone at significantly lower cost. If every state permitted naloxone to be prescribed by standing order[9] or permitted pharmacists to prescribe naloxone, or if the FDA permitted naloxone to be purchased over the counter nationwide, I estimate that approximately 3,000 lives would be saved every year, an 11% reduction relative to the mean number of fatalities between 2006 and 2016. My data also suggest that extending legal immunity to administrators may increase opioid overdoses, though the results are inconclusive.

Part V discusses the broader implications of my results, including what additional steps federal, state, and local governments can take to further expand naloxone access. I propose that the Food and Drug Administration promulgate regulations to make naloxone available over the counter nationwide. The measure would yield even more benefits than state efforts to relax prescription requirements. In addition, state and local governments can expand efforts to ensure that naloxone is actually, rather than merely legally, accessible to opioid users.

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[7] *E.g.*, Ky. Rev. Stat. § 217.186 (2018); N.J. Stat. 24:6J-4 (2018).
[8] *See also* chapter 2, Table 2, indicating that this population is less likely to consume prescription opioids.
[9] A standing order is a prescription to dispense a drug to anyone meeting certain prescriber-specified criteria (Davis and Carr 2015).

II. The Naloxone Access Law Movement

In 2000, no state had passed a statute to make it easier for opioid users or their friends and family members to acquire naloxone (Prescription Drug Policy Abuse System 2018). Only 17 years later, every state had passed a statute that expanded naloxone access (Prescription Drug Policy Abuse System 2018). This Part traces the evolution of the naloxone legal landscape over the intervening time period. Section A presents the timeline of naloxone access law adoption and discusses the major relevant provisions of the different statutes. Section B discusses the various mechanisms by which naloxone access laws may affect opioid overdose fatalities.

A. History of Naloxone Access Law Adoption

The FDA approved naloxone for use to treat an individual experiencing an opioid overdose in 1971 (Yardley 2013). Local governments and hospitals rapidly outfitted hospitals and ambulances with the new drug; by 1991, naloxone was one of the most commonly administered drugs by emergency medical services (Seidel 1991). As opioid overdoses have increased, emergency medical service providers have administered increasing amounts of naloxone (Faul et al. 2015). But naloxone use by first responders has not been sufficient to prevent opioid overdose fatalities. Overdose fatalities grew in many states in the late 1990s and early 2000s (Centers for Disease Control and Prevention 2018), spurring action from state and local governments.

The earliest efforts to expand access to naloxone occurred through targeted programs in specific communities suffering above-average heroin overdose rates (Wheeler et al. 2015). Pilot programs in Boston, New York City, Baltimore, San Francisco, and Chicago provided active users and other individuals with naloxone, resulting in hundreds of overdose reversals (Doe-Simkins et al. 2009; Galea et al. 2006; Maxwell et al. 2006; Seal et al. 2005; Tobin et al. 2009).

In Chicago, the introduction of the program coincided with a substantial reversal in the rate of opioid overdose fatalities; whereas overdoses in Cook County (where Chicago is located) doubled from 1996 to 2000, they decreased by approximately 25% following the establishment of the naloxone distribution program (Maxwell et al. 2006). In each program, individuals who received naloxone were provided with training that told them risk factors for overdoses generally, instructions on how to intravenously inject naloxone,[10] and the importance of continued monitoring post-administration. Such programs also generally provided naloxone to participants free of charge.

During the same time period, New Mexico was experiencing higher-than-average opioid overdose rates statewide (CDC 2018a). Observing the successes of community-based programs elsewhere, New Mexico adopted the country's first broadly applicable statute expanding the authority of health care providers to distribute naloxone.[11] Citing an emergency need to protect public safety, New Mexico decriminalized possession of naloxone without a prescription, authorized doctors to prescribe naloxone via standing order, authorized prescriptions to individuals who intended to use naloxone on a third party, and immunized individuals who dispense or administer naloxone to another from damages in a civil suit or criminal prosecution in any action arising out of such distribution or use of naloxone as long as the individual acted with reasonable care.[12] Two years later, Connecticut became the second state to expand naloxone access,[13] with legislators citing the success of the Chicago naloxone administration program (measured in decreased fatal overdoses) as evidence of the benefit of providing broad access.[14]

[10] At the time of the Chicago program, the FDA had yet to approve the nasal spray or autoinjector naloxone formulations.
[11] 2001 N.M. Laws Ch. 228 (H.B. 813).
[12] 2001 N.M. Laws Ch. 228 (H.B. 813).
[13] 2003 Conn. Acts 159 (Reg. Sess.).
[14] Conn. H.R. Tran., May 29, 2003.

In 2007, California followed suit and broadened naloxone access in seven of its largest counties.[15]

The rate of naloxone access statute adoption has since accelerated. Figure 1 presents a series of state maps showing the evolution of naloxone access laws from 2006 to 2015. Other early adopters of naloxone access laws included Illinois,[16] New York,[17] Massachusetts,[18] Rhode Island,[19] and Washington.[20] Then in 2014 and 2015, 33 states and Washington, D.C. adopted naloxone access laws, dramatically shifting the balance of states that had expanded naloxone access (Prescription Drug Abuse Policy System 2018). By the end of 2016, only three states had not enacted any naloxone access law. By 2018, every state had some form of naloxone access law.

As with most state legal interventions, the particular statutory scheme that each state adopted varied from state to state. In this chapter, I focus on the effects of four naloxone access law provisions: (1) provider civil or criminal immunity provisions,[21] (2) lay administrator civil or criminal immunity provisions,[22] (3) third party provisions,[23] and (4) provisions authorizing prescription by standing order (or other non-patient specific prescription) or authorizing pharmacists to directly prescribe naloxone.[24] For brevity, I will generally refer to civil or criminal immunity provisions as "legal" immunity. Likewise, I refer to provisions which permit

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[15] 2007 Cal. Legis. Serv. Ch. 477 (West). California's access law applied only in Alameda, Fresno, Humboldt, Los Angeles, Mendocino, San Francisco, and Santa Cruz counties until 2014. *Compare* 2007 Cal. Legis. Serv. Ch. 477 (West). *to* Cal. Civ. Code § 1714.22 (2018) (applying to all of California). No other state passed a naloxone access law which only applied to particular counties.
[16] 20 Ill. Comp. St. § 301/5-23 (2018).
[17] N.Y. Pub. Health Law § 3309 (2018).
[18] Mass. Gen. Laws ch. 94c, §§ 19(d), 94c (2018).
[19] R.I. Gen. Laws § 31-2-9 (2018).
[20] Wash. Rev. Code § 69-50-315 (2018).
[21] *E.g.*, Colo. Rev. Stat. § 13-21-108.7(4)(a) (2018); 20 Ill. Stat. § 301/5-23(d)(1) (2018); Cal. Civ. Code §§ 1714.22(e)–(f) (2018).
[22] *E.g.*, Colo. Rev. Stat. § 13-21-108.7(3) (2018); Cal. Civ. Code §§ 1714.22(e)–(f) (2018).
[23] *E.g.*, N.J. Stat. § 24:6J-4(a)(1) (2018).
[24] *E.g.*, Ky. Rev. Stat. § 217.186 (2018).

patients to acquire naloxone without a patient specific prescription or with a pharmacist-written prescription as "relaxed prescription requirements."

Table 1 provides the adoption date of each naloxone access provision in each state until the end of 2016. By 2016, 40 states extended some form of legal immunity to naloxone providers, 45 states extended legal immunity to lay administrators of naloxone, 43 states authorized third party prescribing of naloxone, and 45 states authorized pharmacists to provide naloxone without a prescription from another medical practitioner. Previous research on naloxone access has largely focused on the effect of having any of these provisions, rather than analyzing each effect separately (Rees et al. 2019; Doleac and Mukherjee 2018). Research on other opioid policy responses (Buchmueller and Carey 2017; Dave et al. 2017; Powell et al. 2018) and law and economics research generally (McMichael et al. 2019) demonstrates that the value of statutory schemes depend greatly on exactly which provisions states enact in a scheme. As a result, one of the core contributions of this empirical analysis is disentangling the effects of various naloxone access provisions.

Naloxone access laws' legal liability provisions immunize various groups from sanctions arising out of the provision or administration of naloxone. Colorado's naloxone access law provides typical language for a statute providing civil immunity: "A person who is permitted by law to prescribe or dispense an opiate antagonist shall not be liable for any civil damages resulting from such prescribing or dispensing."[25] The Colorado statute provides similar language for anyone who administers, rather than prescribes or dispenses, naloxone: "A person . . . who acts in good faith to administer an opiate antagonist to another person whom the person believes to be suffering an opiate-related drug overdose event shall not be liable for any civil damages for

[25] Colo. Rev. Stat. § 13-21-108.7(4)(a) (2018).

acts or omissions made as a result of such act."[26] Analogously, Illinois' naloxone access law provides that "A health care professional who, acting in good faith . . . prescribes or dispenses an opioid antagonist" to patients who may be able to administer naloxone to themselves or another individual experiencing an overdose "shall not" be subject to "any criminal liability."[27]

Some states provide a more limited form of immunity to providers and administrators, conditioning criminal or civil damages immunity upon "reasonable care."[28] In Tennessee for example, immunity from damages attaches to "any licensed health care practitioner who prescribes or dispenses an opioid antagonist" to "a person at risk of experiencing an opiate related overdose" or "a family member, friend, or other person in a position to assist a person at risk of experiencing an opiate-related" overdose, but only if the practitioner exercises "reasonable care."[29] Tennessee's statute provides a similar limitation for damages immunity for individuals that administer naloxone to individuals experiencing an overdose.[30] Likewise, California's naloxone access statute states that licensed health care providers who issue a prescription for naloxone, and any other person who possesses, distributes, or administers naloxone, who "acts with reasonable care shall not be subject to . . . criminal prosecution."[31]

The use of "reasonable care" as a limitation for damages from medical malpractice is peculiar, given that the ordinary standard for proving negligence in a medical malpractice claim is itself reasonable care.[32] Ordinary principles of statutory interpretation indicate that these immunity provisions must change *something* about the conditions under which a health care practitioner or individual administering naloxone may be held civilly liable, while

[26] *Id.* at § 108.7(3) (2018).
[27] 20 Ill. Stat. § 301/5-23(d)(1) (2018).
[28] *E.g.*, Tenn. Code §§ 63-1-152(b), (g)(1) (2018).
[29] *Id.*
[30] *Id.* at §§ 152(b), (g)(2).
[31] Cal. Civ. Code §§ 1714.22(e)–(f) (2018).
[32] *E.g.*, Tenn. Code § 29-26-115(a) (2018) ("In a health care liability action, the claimant shall have the burden of proving . . . that the defendant acted with less than or failed to act with ordinary and reasonable care in accordance with such standard.").

simultaneously reading reasonable care to have the same meaning throughout a state's code (Scalia and Garner 2013). A minority of statutes requiring reasonable care define particular acts by a provider or administrator as evidence of reasonable care.[33] North Carolina provides that "evidence of the use of reasonable care in administering the drug shall include the receipt of basic instruction and information on how to administer the opioid antagonist."[34] Tennessee additionally requires that administrators complete an online overdose prevention course.[35] Such reasonable care statutes probably require providers and administrators to take some step to make sure that the individual who receives naloxone can recognize an overdose, successfully use naloxone, and call for emergency medical services afterwards to ensure the person survives.[36] Such steps are not onerous, and it is unlikely that a doctor or pharmacist would furnish naloxone without providing such basic instructions. As a result, in my empirical analyses that follow I will pool these conditional legal immunity statutes together with the absolute immunity statutes I discuss above.[37]

Third party provisions enable doctors to prescribe and pharmacists to dispense naloxone to individuals who intend to administer the medication to someone else who is at risk of experiencing an opioid overdose. For example, New Jersey's statute provides that "A prescriber or other health care practitioner . . . may prescribe or dispense an opioid antidote directly or through a standing order, to any recipient who is deemed by the health care practitioner to be capable of administering the opioid antidote to an overdose victim in an emergency."[38] Such statutes recognize that the individual who is best situated to prevent an overdose might not be an

[33] *E.g.*, 2013 N.C. Laws 2013-23.
[34] 2013 N.C. Laws 2013-23.
[35] Tenn. Code § 63-1-152(e) (2018).
[36] *E.g.*, Idaho Stat. § 54-1733B (2018).
[37] My conclusions are generally robust to separating reasonable care statutes, but the results become harder to present the more statutes that are included.
[38] N.J. Stat. § 24:6J-4(a)(1) (2018).

opioid user themselves or even a first responder, but a family member or friend.[39] The final category of statutes that this paper investigates are statutes which enable an individual to receive naloxone without a patient-specific prescription from a doctor. Exemplary statutes include Kentucky's naloxone access law, which authorizes pharmacists to prescribe naloxone to a patient who has not seen a doctor,[40] and New Jersey's statute, which authorizes a prescription through standing order.[41]

States passed each of these statutes hoping to reduce fatal opioid overdoses. However, making drug use safer has competing influences on the opioid overdose rate that a state will observe. On the one hand, saving an individual experiencing an overdose prevents a fatality; on the other, it is theoretically possible that it will induce users to engage in riskier activity. The next Section explores these two channels of action for naloxone policy and reviews the relevant academic literature.

B. Life-Saving or Risk-Encouraging? The Effects of Naloxone Access

Naloxone access laws have a theoretically ambiguous effect on the probability that an individual experiences a fatal overdose. The lifesaving medicine will tend to decrease the probability that any opioid overdose will ultimately take a person's life; it also may create a moral hazard, inducing drug users to take more drugs as the drugs become less risky (Pauly 1968). Moreover, legal access and actual access to naloxone are not equivalent, and the statutes may do little to make naloxone actually available if non-legal factors continue to prevent individuals from accessing the medicine. This Section explores those effects in detail and identifies why an empirical study is necessary to determine whether naloxone access laws are ultimately beneficial.

[39] *E.g.*, Tenn. Code. § 63-1-152(b)(2) (2018).
[40] Ky. Rev. Stat. § 217.186 (2018).
[41] N.J. Stat. 24:6J-4 (2018).

In the absence of a naloxone access law, naloxone will only be carried by emergency medical services personnel (and not even all of them) (Faul et al. 2015). Doctors will also generally be authorized to prescribe naloxone to an individual to self-administer if the individual experiences an overdose, but doctors will not be able to prescribe naloxone to a third party who could assist the individual.[42] Studies that pre-date the onset of naloxone access laws indicate that most doctors were unwilling or unsure if they were willing to prescribe naloxone to patients for self-administration and that retail pharmacies failed to carry naloxone regardless (Coffin et al. 2003). Nevertheless, similarly timed surveys of opioid users indicated strong support for being able to acquire a naloxone prescription to self-administer (Seal et al. 2003). Under this pre-naloxone access regime, opioid users consume some level of drugs.[43] Whatever level of opioids individuals consume, they face some risk of an overdose which is generally increasing in the amount of drugs consumed (Dasgupta et al. 2016). The actual risk any user faces is likely to vary with individual characteristics and the circumstances of use, particularly the individual's tolerance to the drug and the type of drug used (Lipato and Terplan 2018).

The first-order effect of any naloxone access law will be to decrease the risk that an opioid user experiences a fatal opioid overdose at any level of consumption. Provider criminal immunity provisions and civil immunity provisions decrease the cost of providing naloxone to any patient, thereby increasing the likelihood that a healthcare practitioner will provide naloxone to a current user (Shavell 2004). Administrator civil and criminal immunity provisions operate similarly, increasing the likelihood that an individual will seek out a naloxone prescription and

[42] *E.g.*, Commonwealth v. Brown, 904 N.E.2d 452, 454–55 (Mass. App. 2009) (affirming the conviction of a doctor who illegally prescribed medications to third parties in violation of Massachusetts' controlled substances act).
[43] There is long-standing and unresolved debate in the health economics literature about whether addiction comports with rational actor models of consumption, such that it is fair to characterize an addict's consumption as "choosing" to consume a good to maximize utility subject to a budget constraint (Becker and Murphy 1988; Laporte et al. 2017). For my purposes here, it is sufficient that individuals consistently respond to economic incentives with regard to goods normally thought of as "addictive" (Manning et al. 1995) (finding evidence that light, medium, and heavy drinkers are responsive to price, though heavy drinkers are less responsive).

use that naloxone if they possess it. States that require reasonable care for immunity provide an additional wrinkle. On the one hand, requiring some costly level of care for immunity will chill the propensity to provide naloxone (Braddock and Snyder 2005). However, in the case of naloxone, the "reasonable care" standard ensures that most users who receive naloxone will have received information about how to recognize an overdose, how to administer naloxone, and the importance of calling for medical help after administration. Such measures may on net *increase* the effectiveness of naloxone provision beyond general immunity as a result. In any case, such measures are unlikely to eliminate any benefit that exists for extending immunity to providers or administrators. In the majority of states which also authorize naloxone access to third parties who may be in a position to assist someone experiencing an overdose, even more individuals are likely to possess naloxone because the population who can legally purchase the drug has increased; permitting patients to acquire naloxone from a pharmacist without an appointment from another practitioner will have a similar effect. The aggregate effect of such statutes will therefore be to increase the probability that an individual experiencing an overdose can either self-administer naloxone *or* will be near a third party who can do so, thereby decreasing the probability that a fatal overdose occurs for any level of opioids consumed.

However, naloxone access laws could have a variety of secondary effects that undermine their tendency to save lives. If opioid use is safer, it is possible that users may choose to consume more opioids (Doleac and Mukherjee 2018). Anecdotal evidence from state legislators and police suggests that some opioid users engage in riskier drug use when naloxone is available (Siegelbaum 2016; Jorgensen 2017), though no statistical evidence exists supporting these anecdotes with respect to opioid use (Firah 2017).[44] Moreover, previous research indicates that

[44] Previous research has shown that consumption of other addictive substances, like cigarettes, varies with changes in the perceived riskiness of the good (Viscusi 1998).

individuals who voluntarily enrolled in naloxone pilot programs self-report using less heroin following the program (Seal et al. 2005; Wagner et al. 2010). In theory, potential increases in use could be so severe that the fatal overdose rate remains unchanged or even increases. Similarly, if doctors can co-prescribe naloxone to patients who use prescription opioids, doctors could possibly be more willing to prescribe opioids to patients who are more likely to abuse drugs (American Medical Association 2017). Those “marginal patients” are relatively riskier by definition and may be more likely to fatally overdose than other patients. Doctors are likely more willing to engage in such risky practices when they are protected from liability, though some researchers have argued that co-prescribing naloxone cannot increase liability risk (Davis et al. 2016).

Naloxone may also function as a substitute for calling for emergency medical assistance following an overdose (Seal et al. 2003). If naloxone was a perfect substitute for emergency medical services, this would not be a problem. But naloxone has a shorter half-life in the human body than the opioids causing the overdose it treats; calling emergency medical services is critical for saving individuals who overdose from a large quantity of opioids because otherwise they may suffer another overdose without consuming any more drugs (Kim et al. 2009). While it is virtually impossible for the re-overdose problem to eliminate all of the benefits of naloxone availability (as long as some naloxone treated individuals do not re-overdose, it cannot), it could dampen the lifesaving effects that would exist if medical assistance was always summoned following administration. Additionally, emergency medical services may be an effective institution for guiding opioid dependent patients toward medication-assisted addiction treatment, which would have long-term benefits beyond an individual overdose reversal (D’Onofrio et al. 2015).

Finally, naloxone access laws may have no effect or a perverse effect on individuals' actual (rather than legal) access to naloxone. The FDA declared naloxone drug shortages for approximately 23 months between June 2010 to July 2013 (Rosenberg 2018). Media sources have documented that even in states that have passed naloxone access laws, many pharmacies do not actually stock the drug (Harper 2018). If statutes do not enable individuals to actually acquire naloxone, then they will have very little effect on opioid overdose rates. Worse, naloxone access laws could cause shortages and price increases that crowd out first responders from using naloxone. Over the same time period that states have enacted naloxone access laws, the retail price of naloxone has dramatically increased (Gupta et al. 2016; Rosenberg 2018). To the extent naloxone access laws may exacerbate the price increases that would have occurred otherwise by increasing demand for naloxone at any price, the statutes may be pricing out municipalities who would furnish first responders with naloxone if the price was lower (Honig 2017).

Previous research has not clearly established whether the potential risk-decreasing or risk-increasing effects of widespread naloxone access dominate. Rees et al. (2019) found mixed evidence that the passage of a naloxone law decreased fatal opioid overdoses. Using annual state-level fatality rates covering 1999 to 2014 from the National Vital Statistics System ("NVSS"), they investigated the effect of naloxone access laws on all opioid fatalities as well as heroin and non-heroin fatalities separately. They defined a naloxone access law as any statute that provides civil and criminal immunity for a lay administrator, any statute that provides civil and criminal immunity for naloxone prescribers, or any statute that permits third party prescribing. Their empirical estimates utilized a difference-in-differences empirical specification and demonstrated that the adoption of naloxone access laws decreased the opioid fatality rate by 9-11%, with the largest effects concentrated on non-heroin overdoses.

Similarly, McClellan et al. (2018) used a random effects model to estimate the association between annual-state level overdose fatality rates (from the 2000 to 2014 NVSS data) and lagged naloxone access laws. They demonstrated that passing any naloxone access law (defined as a statute designed to increase layperson naloxone access) was associated with a decrease in overdose fatality rates of 14%, with the strongest effects observed among African Americans and states that extended immunity to physicians. Both Rees et al. (2019) and McClellan et al. (2018) drew on the National Survey of Drug Use and Health to present evidence that naloxone access laws did not increase the probability that an individual reported non-medical use of prescription opioids.

Rees et al. (2019) and McClellan et al. (2018)'s results sharply contrast with those of Jennifer Doleac and Anita Mukherjee (2018), who presented evidence that naloxone access laws had no effect on overdose fatalities, and in some circumstances, may have even increased them. Doleac and Mukherjee (2018) analyzed the effect of naloxone access laws on metropolitan areas across the U.S. using fatal overdose data from the NVSS[45] covering the years 2010 to 2015 and using the same definition of a naloxone access law as Rees et al. (2019). They present evidence that naloxone access laws generally had no discernible effect on fatalities, but they did increase opioid-related crime and emergency room visits.

Overall, the existing research on naloxone access does not provide clear evidence for states to rely on. The previous research leaves open several crucial questions, most prominently whether naloxone access laws decrease fatalities. Beyond that threshold question, the literature provides little evidence of what effect the several naloxone statutes passed in 2015 and 2016 had, or the effectiveness of different naloxone access provisions on the basis of race, sex, or age. No

[45] Duleac and Mukherjee (2018), use the restricted access National Vital Statistics data, which contains more detailed geographic information associated with fatalities, while Rees et al. (2019) uses the publicly available version of the data. I use the restricted access data for my fatalities, though I do not limit myself to urban areas as Duleac and Mukherjee (2018) do. *See infra*, Part 3.B.

research has yet investigated the effectiveness of naloxone access laws by county urbanization. This chapter investigates each of these questions, providing a holistic view of which naloxone provisions provide a benefit and which provisions cause risky behavior, for whom, and in which contexts. To do so, this chapter exploits a rich and detailed dataset on opioid fatalities and state laws, which I present in the next Part.

III. Empirical Methodology

This chapter draws on several data sources to study the effects of naloxone access laws. As discussed in Section A, I combine monthly fatality data at the county level with several sources of information on counties to measure the causal effect of naloxone access laws while controlling for a variety of confounding variables. Section B presents the methodology that I apply to this data to arrive at my empirical estimates.

A. Data Sources

I use the National Vital Statistics System's multiple cause of death all county micro data files. The data contain detailed information on each individual death certificate issued in the United States, including the decedent's date of death, the location of death at the state and county level, the decedent's state and county of residence, and the decedent's education, sex, race, age, marital status, and causes of death indexed by International Classification of Diseases (Tenth Revision) ("ICD-10") code. The ICD-10 coding system is the standard method for classifying causes of death in U.S. government data. The ICD-10 codes associated with fatal overdoses from opiates are T40.0 (opium), T40.1 (heroin), T40.2 (other opioids), T40.3 (methadone), T40.4 (other synthetic narcotics), and T40.6 (other/unspecified narcotics). I utilize NVSS data covering the period from 2006 – 2016.

From the fatality counts in the vital statistics data, I construct monthly counts of fatalities due to any opioid, heroin, pain medication, synthetic opioids, and other opioids[46] that occur in each U.S. county and month that the data cover.[47] The different categories are not mutually exclusive—overdoses that involved multiple types of opioids (e.g., heroin *and* pain medication) constitute 15.1% of the sample; I include such fatalities in the counts of all relevant categories. Analyzing the data at the county-month level is consistent with Jennifer Doleac and Anita Mukherjee's previous research and enables me to identify the effect of individual naloxone access law provisions; analyzing the data at the state-year level would prevent accurate identification of the individual provisions which are the focus of this research. Because my data is at the county-month level, many (approximately 75%) of the observations exhibit no fatal overdoses. As discussed in Section IV.1, I perform Poisson regressions to determine whether this characteristic of the dataset drives my results and find that it does not.

Figure 2 presents opioid fatalities over time across the U.S. as a whole. As the figure shows, fatalities increased every year that my data cover from approximately 18,000 fatalities in 2006 to approximately 44,000 in 2016. Fatalities increased steadily until 2013, at which point fatal overdoses grew rapidly in each following year. I further transform these counts into monthly fatality rates per 100,000 county residents by dividing each by the population of the relevant county and multiplying by 100,000. The monthly rates of fatal overdoses constitute the dependent variables in my analyses that follow.

[46] I classify any fatality with an ICD-10 code of T40.2 and T40.3 as pain medication fatalities, T40.4 deaths are classified as synthetic opioids, and T40.6 are classified as "other." This classification scheme is consistent with other work documenting opioid fatalities (Rudd et al. 2016).

[47] Importantly, I assign fatalities to the county that an individual died in rather than their county of residence. The NVSS data indicate that approximately 86% of individuals experiencing a fatal opioid overdose do so in the county in which they live. Counting fatalities where they occur, rather than where the decedent resided, is likely most appropriate for this research given that naloxone availability in the area in which an individual uses opioids, rather than the jurisdiction in which they live (when the two differ), is more likely to determine whether naloxone is available to administer in the case of an overdose. The results that I present in Part IV are robust to using either method of counting fatalities because the overwhelming majority of overdoses occur in an individual's county of residence.

My primary explanatory variables of interest are a series of binary variables indicating whether a county is in a state that has enacted a naloxone access law in the relevant time period. I include four variables to control for different naloxone access law regimes. The variables indicate whether a statute included: (1) provider criminal or civil immunity, (2) administrator criminal or civil immunity, (3) third party prescription authorization, and (4) provisions enabling prescription by standing order or authorizing a pharmacist to prescribe naloxone. As Table 1 demonstrated, the provider and administrator immunity provisions are often paired, but there is sufficient heterogeneity in what provisions states passed and the timing of passage to identify all four provisions separately. The relevant statutes were identified using the Prescription Drug Abuse Policy System's database, and I read each statute to confirm the coding assigned by the System. The model treats a statute as in effect (and sets the value of the corresponding variable equal to 1) in any month where the provision was in effect for a majority of days in that month.

In addition to naloxone access laws, I determine whether a state had a functioning prescription drug monitoring program or medical marijuana law that permitted marijuana to be dispensed to treat pain. Prescription drug monitoring programs require or permit prescribers to record prescriptions of certain substances (particularly opioids) in a database that other medical providers can (and in some cases and states, must) access (Paulozzi et al. 2011). The goal of such programs is to prevent patients from receiving multiple concurrent opioid prescriptions. Scholars have credited monitoring programs with reducing opioid overdoses associated with doctor shopping and pill mills (Johnson et al. 2014; Griggs 2015). Medical marijuana laws, on the other hand, potentially provide patients with an alternative therapy for pain. Some studies have found that medical marijuana laws have decreased opioid fatalities (Powell et al. 2018). However, the estimated effects of such statutes have varied greatly depending on the exact provisions in such statutes; in the aggregate, the evidence of the effect of medical marijuana laws on opioid use, abuse, and overdoses is mixed. I also control for whether a state has enacted medical malpractice tort reforms; data on each state's provisions are from Avraham (2018). In particular, I control for whether a state has caps on non-economic damages or punitive damages in medical malpractice cases and whether the state has eliminated joint and several liability in medical malpractice.

Finally, I gather time-variant county characteristics from several different sources. I gather data on county-level macroeconomic characteristics from the Bureau of Labor Statistics' Quarterly Census of Employment and Wages. The Quarterly Census on Employment and Wages publishes quarterly reports on employment and wages at the county level. Controlling for local macroeconomic conditions is important given that several papers have demonstrated that local macroeconomic conditions are positively associated with drug abuse (Carpenter et al 2017), although opioid-specific studies have found the opposite effect (Hollingsworth et al. 2017). I utilize county-level demographic information from the Census Bureau, including the county population, the percentage of the county population that is white, and the average age of county residents. I gather an annual count of the amount of police officers in each county in the United States from the 2006 to 2016 FBI Crime in the United States Publications. Police presence will have a complex relationship with the overdose fatality rate—more police may decrease drug use through enforcement or serve as first responders who can treat an overdosing individual with naloxone. Local communities may also hire more police as drug rates increase.

I also draw on National Plan and Provider Enumeration System's National Provider Identifier ("NPI") Registry to construct counts of various medical providers at the county level throughout the time that my data cover. All medical providers who are required to comply with the Health Insurance Portability and Accountability Act of 1996 (more commonly referred to by its acronym, "HIPAA")[48] or who bill Medicare for services must obtain an NPI.[49] The information associated with any given NPI is publicly available. The NPI Registry provides the taxonomy of the provider as well as the provider's address. I collapse the NPI registry's data into a count of pharmacies, hospitals, pain clinics, and emergency medical technicians in each county in the United States for each month that my data cover. The NPI data will not capture *every* such medical provider, as some may choose not to accept Medicare. For example, EMTs are particularly likely to be undercounted, as they will not always be required to register individually.

Table 2 provides summary statistics for each of the variables I use in this chapter. The average county has a monthly opioid fatality rate of 0.815 per 100,000 residents, which corresponds to 8.2 fatalities per year in an average county[50]—double the average rate at which individuals die at work (Viscusi and Masterman 2017) and only 30% smaller than the nationwide rate of suicide fatalities (National Institute of Mental Health 2018). More than half of all opioid fatalities involved semi-synthetic opioids, which include pain medications prescribed by a doctor, as well as any illicitly obtained drugs which contain the same compounds. Urban counties have the highest rate of opioid fatalities, though many fatalities occur in suburban and rural areas as well. The mean weekly wage is $890, and the average age is 38 years.

B. Identifying the Causal Effect of State Laws

The primary goal of the empirical analysis in this chapter is to provide evidence of the *causal* effect that each naloxone access law provision has on opioid fatality rates, rather than demonstrating how naloxone access laws correlate with fatal overdose rates. Of course, the gold

48 42 U.S.C. §§ 300gg, 1320 (2018).
49 *See generally* 45 C.F.R. Part 162 (2018) (explaining the rationale for the NPI system and the exact circumstances under which a health provider must obtain one).
50 This was calculated using the unweighted average county population of 839,645 individuals.

standard for causal inference would be a randomized experiment (Greiner 2008; McMichael 2019).[51] Ideally, an experiment would randomly enact naloxone access laws containing different combinations of provisions in each county in the United States. In such a world, the causal effect of any single provision would simply be the difference between average fatal overdose rates in counties with the provision of interest and average fatal overdose rates in counties without the provision of interest. Clearly, it is impossible to perform such an experiment—a researcher cannot practically or ethically randomly assign individuals to live under different legal regimes or create county-specific legal regimes that differ from the states that they are in.[52] The best alternative approach to measuring a causal effect is to identify treatment and control groups and eliminate all possible confounding factors, thereby mimicking a laboratory experiment to the closest extent possible.[53] In my study, the "treatment groups" will be counties located in a state that has enacted a naloxone access law at the time of interest. Conversely, the "control groups" will be counties located in a state that has *not* enacted a naloxone access law at the time of interest.

Counties in both the treatment and control groups will exhibit different fatal opioid overdose rates over time. Such differences can be broken down into components that are related to the adoption of a naloxone access law and those that are not. The factors that affect opioid fatality rates but do not correlate with the adoption of a naloxone access law can be ignored when trying to determine the effect of naloxone access laws, because such factors will not cause counties under a naloxone access law to have systematically higher or lower fatality rates than

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[51] An important caveat to the superiority of laboratory experiments is the limits to their external validity (Schram 2005).

[52] State home rule provisions dictate the powers of city and county governments in each state. For a recent review of each state's home rule provisions, see Baker and Rodriguez (2009).

[53] Empirical research designs that replicate as much as possible the random treatments of a laboratory experiment are often referred to as quasi-experimental (Carr 2017) (exploring differences-in-differences approaches to studying the effect of policy technology like license plate readers).

counties not under a naloxone access law (Wooldridge 2009). However, changes in opioid fatality rates that are attributable to factors which correlate with both fatality rates and the adoption of a naloxone access law must be accounted for in my analysis. For example, the opioid fatality rate has grown generally over time, as has the quantity of states which have adopted naloxone access laws—a simple "before and after" estimate of the effect of naloxone access laws would therefore mistakenly attribute increases in fatalities attributable to general time trends to the naloxone access law. Similarly, time-invariant state and county characteristics like the number of months the state legislature is in session or county geography may correlate with opioid fatality rates and affect the state's ability to enact a naloxone access law. Rural states and counties may have higher opioid fatality rates, and they may also be less likely to adopt naloxone access laws because states would incur higher costs to train geographically spread-out first responders in treating overdoses. Simply comparing counties that are subject to a law with those that are not would, as a result, attribute the higher fatality rates to not having a naloxone access law rather than the underlying geographic characteristics. Because of these non-random correlations between county opioid fatality rates and the existence of a law, the simple comparison that would be appropriate in a real experiment will probably not yield an accurate estimate of the effect of naloxone access laws on opioid fatality rates.

Isolating the changes in fatal opioid overdose rates attributable to naloxone access laws can be accomplished using a "differences-in-differences" model (Bertrand et al. 2002). Such models have been used extensively in the academic literature and in courts[54] to estimate the causal effects of laws and private conduct. To illustrate how the model works, consider Davidson

[54] *E.g.*, Messner v. Northshore Univ. Health Sys., 669 F.3d 802, 825–26 (2012) (concluding that a differences-in-differences model was an appropriate methodology for an expert to determine the likely impact of a merger); *In re* Chocolate Confectionary Antitrust Litig., Civil Action No. 1:08–MDL–1935, 2013 WL 11305184, at *7–8 (M.D. Pa. May 10, 2013) (discussing an expert's differences-in-differences estimates of price increases that an antitrust conspiracy caused).

County, Tennessee and Jefferson County, Alabama as examples. Both counties are urban, contain the most populous cities of the states in which they are located (Nashville and Birmingham), and Tennessee and Alabama themselves neighbor each other. In June 2014, the fatal opioid overdose rate in Davidson County was 1.94 fatalities per 100,000 county residents. In July 2014, Tennessee's naloxone access law became effective, enabling friends or family members of opioid users to acquire a prescription for naloxone, immunizing prescribing doctors and individuals who administer naloxone from damages attributable to the naloxone prescription or administration, and authorizing doctors to prescribe naloxone via standing order.[55] In August 2014, Davidson County's overdose fatality rate increased to 2.39 fatalities per 100,000 county residents. The difference between the two rates (0.45 fatalities per 100,000 residents) includes both the effect of the naloxone access law as well as general time trends. Meanwhile, in June 2014, Jefferson County's fatal overdose rate was 2.12 fatalities per 100,000 residents, and the fatality rate increased to 3.33 fatalities per 100,000 residents in August 2014. Alabama's naloxone access law was not in force until June 2015, so the increased fatality rate of 1.21 fatalities per 100,000 residents is entirely attributable to general time trends, not a naloxone access law. Taking the difference between both of these differences isolates the portion of Davidson County's fatality rate change that is attributable to Tennessee's naloxone access law rather than the nationwide increases in fatality rates over time that affected Jefferson County. The "difference-in-differences" model therefore estimates that Tennessee's naloxone access law decreased Davidson County's fatal opioid overdose rate by 0.76 fatalities per 100,000 county residents.

The differences-in-differences model that I employ performs an analogous calculation for every county in the United States during each month from January 2006 to December 2015. I

[55] Tenn. Code Ann. § 63-1-152 (2018).

calculate the effect using ordinary least squares regression.[56] To account for correlations in the error term for multiple counties within a single state, I cluster the standard errors in my model at the state level (Cameron and Miller 2015). I also weight each county-month observation by the population of the county in that month, consistent with previous research estimating the effect of naloxone access laws (Doleac and Mukherjee 2018; Rees et al 2019). Doing so ensures that naloxone access provisions that affect greater amounts of people will count "more" in my estimates. The result of the model is an estimate of the average effect across the United States of the effect of adopting a naloxone access law. Further, because I use data from every state and each state adopted naloxone access laws with slightly different combinations of provisions, I can isolate the effect of each naloxone access law's provision individually.[57]

The basic differences-in-differences model provides a valid estimate of the causal effect of a naloxone access law's effect as long as the evolution of overdose fatality rates in each county in the model is occurring at the same rate before the county is treated by a naloxone access law. This requirement is known as the "parallel trends assumption." For example, the Davidson County-Jefferson County estimate above would be invalid if the general effect of time in Jefferson County was greater than that in Davidson County. If similar factors caused fatality rates to increase by 0.45 in both counties, but Jefferson County-specific factors that vary over time also increased Jefferson County's fatality rate by 0.76, then the naloxone access law would

[56] I utilize the reghdfe Stata package to perform the ordinary least squares estimation, as it is dramatically faster than the default package in Stata (Correia 2017). Some research, such as Rees et al. (2019), favors Poisson regression for estimating the effects of count data (such as the number of fatalities occurring at a particular time). Post estimation tests on Poisson estimates of my data indicate that my sample is significantly overdispersed, which biases Poisson standard errors (Cameron and Trivedi 1990). While the usual alternative to Poisson regression for overdispersed count data is negative binomial regression, negative binomial regression suffers from incidental parameters bias when differences-in-difference models are used (Allison and Waterman 2002). I use ordinary least squares over the alternatives because it provides an unbiased estimate for overdispersed count data in a differences-in-differences model.

[57] The fact that I observe fatality rates every month is critical for isolating the effect of naloxone access laws. Because so many states adopted statutes in the same year (see Figure 1), annual analysis would consider each of those statutes to have occurred at the same time and it would be impossible to isolate the effect of the provisions I consider.

have actually had *no effect* on opioid fatality rates, and the difference-in-differences estimate would have been positively biased.

In my estimates in Part IV, I account for the potential bias from time-variant county characteristics by controlling for other factors that could possibly be correlated with both the adoption of a naloxone access law and the opioid fatality rate, including the average wage of workers in the county, county employment-to-population ratios, the county population, the percent of the county's population that is white, the average age in the county, and the number of pharmacies, pain clinics, EMTs per 100,000 residents, and police per 100,000 residents that are in each county during each time period in my data. All time *invariant* county characteristics (such as geography or the structure of state governments) are also accounted for in the model by comparing the evolution of fatality rates within a county over time, as was done in the Davidson and Jefferson county examples. Mechanically, within-county variation is calculated by including county-specific indicator variables for each of the 3,145 counties in my data. I also include county-specific time trends in the model to account for county characteristics that evolve over time which may influence the opioid fatality rate in a particular county. For example, if some states adopt policies over time that influence opioid fatalities but I do not control for those policies in the model, the county-specific time trends will limit the bias from excluding those policies. Including these time trends relaxes the parallel trends assumption so that the model provides an unbiased estimate of the effect of naloxone access laws as long as the changes in opioid fatality rates themselves are changing at parallel rates (Mora and Reggia 2018). Statistical tests examining whether this empirical specification satisfies the parallel trends assumption are in the Technical Appendix and indicate that my differences-in-differences model provides a valid estimate of the causal effect of naloxone access laws.

IV. The Effect of Naloxone Access Laws on Fatal Opioid Overdoses

This Part presents my empirical estimates of the effect of naloxone access laws on opioid overdose fatalities. As the results in Section A demonstrate, studying naloxone access laws at a broad level is inadequate to reveal the effects of these laws. Examining the different provisions of naloxone access laws reveals that provisions enabling individuals to receive naloxone without visiting a medical professional other than a pharmacist decrease opioid overdose rates. Section B examines whether the effectiveness of naloxone access differs on the basis of an individuals' sex, race, ethnicity, or age. The effects of naloxone access are concentrated in individuals who are white, male, and 25 to 44 years old—the demographic groups with some of the highest opioid fatality rates. Section C analyzes how naloxone access affects fatalities caused by different opioids. The effects are heterogeneous; the evidence suggests that naloxone is most effective at reducing fatalities from heroin and synthetic opioids such as fentanyl. Section D divides my sample into rural, suburban, and urban counties. Difference-in-differences estimates in the rural, suburban, and urban subsamples indicate that naloxone access exclusively benefits individuals in urban areas.

A. Naloxone Access Laws and the Need for Provision-Level Analysis

Figure 3 presents the difference-in-differences estimates of naloxone access laws. Each bar represents a different estimate. For brevity, I provide only the estimated effects of the naloxone access laws; the full results of the difference-in-differences model are available in the Technical Appendix. The first estimate corresponds to the estimated average effect of any naloxone access law, while every other bar corresponds to the estimated average effect of a particular provision.[58] The lines that bracket the main bar illustrate the 95% confidence interval for each estimate.[59]

My difference-in-differences estimates indicate that enacting any naloxone access law has little effect on the monthly opioid overdose rate. The difference-in-differences model indicates that the average county in a state with a naloxone access law has a 7.7% higher monthly opioid fatality rate.[60] However, the standard error of the estimate is sufficiently large such that the estimate is not statistically significant, meaning there is insufficient evidence that the true effect is greater than zero.[61] If the empirical analysis stopped at this level of generality, we would conclude that naloxone access laws most likely had little to no effect on overdose fatalities.

However, estimating the model at the naloxone access *provision* level reveals that two different provisions have statistically significant effects on monthly opioid overdose rates. Extending legal immunity to naloxone providers has no statistically significant impact on overdose fatality rates.[62] Statutes that provide legal immunity to lay administrators of naloxone increase opioid overdose rates by 0.09 fatalities per month per 100,000 residents, or about 11%.[63] Statutes that authorize prescribers to prescribe naloxone to individuals who are friends or family members of opioid users has no significant effect.[64] Finally, statutes that authorize pharmacists to provide naloxone without the patient needing to receive a prescription from a medical

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[58] *See supra*, Part 3.2 for a discussion of all county characteristics that the model controls for.
[59] The 95% confidence interval contains the set of values such that, conditional on the observed data, the probability that the true effect of the indicated provision is within the confidence interval is 95% (Kmenta 1997). The 95% confidence interval is calculated by adding and subtracting the standard error of the difference-in-differences estimate multiplied by 1.96 to and from the difference-in-differences estimate.
[60] The point estimate from the model is an increase of 0.06 fatalities per 100,000 county residents. Dividing the point estimate by the mean fatality rate of 0.76 provides the percent increase.
[61] $p = 0.254$
[62] $p = 0.557$.
[63] $p = 0.073$.
[64] $p = 0.193$.

professional other than the pharmacist decrease fatalities by 0.08 fatalities per month per 100,000 residents, about 9% relative to the base opioid fatality rate.[65]

The results demonstrating that relaxing prescription requirements reduces fatal overdoses are robust to changes to the empirical model that I utilize. As evidence, the Technical Appendix provides regression results which use Poisson regression,[66] rather than ordinary least squares as well as estimates varying the use of geography-specific time trends. The Poisson regression results are entirely consistent with the ordinary least squares results and indicate that administrator legal immunity increases overdose fatalities while relaxing prescription requirements decreases fatalities. Likewise, the ordinary least squares models using different geographic time trends find results consistent with those in Figure 3. The models including no geography-specific time trends tend to find larger effects of naloxone access but are otherwise similar.

These initial results demonstrate the importance of analyzing naloxone access statutes at the provisional level. While the basic "any law" results are consistent with previous research finding no effect of naloxone access (Doleac and Mukherjee 2018), the estimated effect of provisions removing the requirement for a patient-specific prescription is consistent with research that demonstrated naloxone access laws decrease fatalities (Rees et al. 2019). However, it remains unclear why provisions extending legal immunity to individuals who administer naloxone increases fatalities. In order to further explore what fatalities the naloxone access laws are preventing and what mechanisms are driving the effects, the next Section examines how naloxone affects different demographic groups.

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[65] $p = 0.022$.

[66] Poisson regression assumes that the dependent variable follows a Poisson distribution, and is often used to analyze count data (such as the number of fatalities occurring over a particular time frame. When Poisson regression is appropriate, it will yield more precise estimates than ordinary least squares. However, as discussed *supra*, note 56, Poisson regression has drawbacks of its own in this particular research, chiefly the risk of biased standard errors that increase the risk of finding no effect where one actually exists, or finding an effect where one does not exist.

B. Differences by Sex, Race, Ethnicity and Age

A long line of research demonstrates that drug use and abuse patterns differ substantially on the basis of sex, race, and ethnicity (Wallace et al. 2000). Demographic characteristics vary with access to medical care (Pletcher et al. 2008) and interactions with the criminal justice system (Mustard 2001). Most germane to this research, fatal overdose rates differ significantly by sex, race, ethnicity, and age. The monthly fatal overdose rate of men is 0.91 fatalities per 100,000 men, while the female monthly fatal overdose rate is 0.48 fatalities per 100,000 women. The average monthly opioid fatality rates for white, black, and Latino individuals are 0.91, 0.43, and 0.28 fatalities per 100,000 individuals in the relevant demographic groups. Fatality rates increase with age until individuals are 45 to 54 years old, with 1.29 fatalities per 100,000 45 to 54-year-old individuals and decrease thereafter. Naloxone access laws operate at the intersection of drug use, medical care, and crime; as a result, it is worth examining whether the value of removing naloxone's prescription requirement is shared equitably across demographic groups.

Figure 4 presents difference-in-differences estimates of the effects of naloxone access provisions by sex. The first bar in each pair corresponds to the effect of the indicated naloxone access provision on fatal male opioid overdoses, while the second bar corresponds to the effect on fatal female opioid overdoses. The results are generally consistent with Figure 3. Provider legal immunity has no statistically significant effect on fatalities for either men or women.[67] Legal immunity for lay administrators increased male overdose fatalities by 0.11 fatalities per 100,000 individuals, or 13%.[68] Third party provisions do not have a statistically significant impact for either men or women.[69] The provisions loosening prescription requirements

[67] For men, $p = 0.770$; for women, $p = 0.326$.
[68] For men, $p = 0.042$; for women, $p = 0.312$.
[69] For men, $p = 0.333$; for women, $p = 0.884$.

significantly decrease male fatal overdoses by 0.09 overdoses per month and female fatal overdoses by 0.04 per month, approximately a 9% decrease for both men and women.[70]

Next, Figure 5 presents difference-in-differences estimates of the effects of naloxone access provisions by race and ethnicity. The first bar in each set presents the effect of naloxone access provisions on fatal overdose rates of white individuals, the second bar presents the effect on fatal overdose rates of African Americans, and the third bar presents the effect on Latino fatal overdose rates.[71] The results exhibit substantial heterogeneity by race and ethnicity. For white individuals, provider legal immunity and third party prescribing do not exhibit a significant impact on overdose rates.[72] Administrator legal immunity causes a statistically significant increase in white opioid fatality rates.[73] But as in many of the previous models, relaxed prescription requirements cause a significant decrease in overdose fatalities.[74] The estimate indicates that permitting individuals to receive naloxone either via a standing order prescription or from a pharmacist with prescribing authority decreases the white overdose fatality rate by 10%. For individuals who are black, the results indicate that providing legal immunity to naloxone providers causes a statistically significant increase in opioid fatality rates, but the coefficient on administrator immunity is insignificant.[75] Third party provisions decrease black fatal overdose rates by 22%,[76] though relaxing prescription requirements does not have an individually significant effect.[77] Finally, for Latino individuals, provider legal immunity, administrator legal immunity, and the no prescription requirement exhibit no statistically

[70] For men, $p = 0.052$; for women, $p = 0.031$.
[71] I also estimated analogous models for individuals of Native American, Pacific Islander, and Asian descent. The difference-in-differences model produced statistically insignificant results for each of these groups. Because many counties have extremely few individuals in these groups, the estimates exhibited very large standard errors, and I have omitted them from the figure to preserve the integrity of the figure.
[72] For provider immunity, $p = 0.848$. For third party provisions, $p = 0.562$.
[73] $p = 0.007$.
[74] $p = 0.025$.
[75] For provider immunity, $p = 0.006$. For administrator immunity, $p = .412$.
[76] $p = .009$.
[77] $p = .360$.

significant effect.[78] Permitting third party prescribing significantly decreases the Latino opioid fatality rate by 21%.[79]

Finally, Figure 6 presents the effects of naloxone access by 10-year age groups. Dividing the sample into several smaller groups increases the variance of each estimate, yielding larger confidence intervals on average. Nevertheless, the estimates exhibit several patterns based on age. Provider legal immunity has a statistically insignificant impact on fatality rates for every age group except for individuals who are 65 or older.[80] Administrator legal immunity statistically significantly increases opioid fatalities for individuals who are between 25 and 44 years old, but has no significant effect on the other five age groups.[81] Each estimate for third party prescription provisions is statistically insignificant.[82] The results for provisions which loosen prescription requirements differ by age group; such provisions decrease the fatality rate for the 15 to 24 years age group by 13%,[83] the 35 to 44 years age group by 11%,[84] and the over 65 years age group by 19%.[85]

The differences in effects by demographic groups could manifest for multiple reasons. The statutes could differentially affect the probability that different demographic groups acquire naloxone for self-administration. Similarly, third party prescribing laws will have differential effects by demographic group if the probability that a friend or family member acquires naloxone is different by group. Finally, effects could differ because the likelihood of successfully using naloxone to revive someone differs by demographic group. For example, the effect of third party

[78] The significance tests for provider immunity, administrator immunity, and no prescription requirements yield $p = 0.700, p = 0.233$, and $p = 0.501$.
[79] $p = 0.021$.
[80] For the oldest group, $p = 0.054$. For all other age groups, $p > 0.250$.
[81] For the 35 to 44 years old age group, $p = 0.016$. For the 15 to 24 years and 25 to 34 years age groups, $p = 0.130$ and $p = 0.096$. For the remaining age groups, $p > 0.530$.
[82] $p > 0.300$ for all age groups.
[83] $p = 0.019$.
[84] $p = 0.018$.
[85] $p = 0.035$.

prescribing for Latino and black individuals observed in Figure 3 could be the result of relatively more non-white individuals acquiring naloxone as a result of racial and ethnic differences in social networks (Ajrouch et al. 2001; Janevic 2001; Hofferth 1984); but, non-white users being more likely to be in a position to help when someone is actually experiencing an overdose could also explain the results. Because my data do not enable me to observe how many individuals actually purchase naloxone following adoption of the law, I cannot determine which mechanism drives the differential effects by demographic group. Nevertheless, the inability to determine precisely which mechanism drives the differential effect does not change the implications of the model as to the expected effect of implementing a particular naloxone access provision.

C. Differences by Drug Type

Different factors contribute to the use, misuse, and abuse of different opioids (Jones 2013). Scholars in the public health literature continue to debate whether the "opioid epidemic" is truly a single epidemic, or whether the United States is really suffering from separate illicit opioid and prescription pain medication abuse epidemics (Kolodny et al. 2015). It is likely that policy responses will have differential effects on users of different opioids. Users of pain medication are more likely to see a doctor while acquiring the opioids they use, increasing the likelihood that a doctor could offer a prescription for naloxone.[86] Heroin users may be relatively more likely to be committing a crime while using (because heroin is itself illegal); as a result, fatalities from such drugs could be more sensitive to statutes that provide criminal immunity while administering naloxone. If users of different drugs respond to naloxone access laws differently, or if naloxone administration is more effective in reversing overdoses associated with some drugs compared to others, policy responses will need to be tailored as the drugs involved in

[86] For example, the CDC recommends co-prescribing naloxone to patients with a history of opioid overdose or substance abuse disorder, patients receiving high opioid doses, and patients with concurrent benzodiazepine use (Dowell 2016).

fatalities evolve over time. To illustrate, heroin and synthetic opioids (including fentanyl)[87] were both individually involved in 13% of fatal overdoses from 2006 to 2008, but those numbers increased to 37% and 33% over 2014 to 2016. Because fentanyl is significantly more potent than prescription opioids, it can take more naloxone to reverse an overdose attributable to fentanyl consumption. As a result, it is critical that future policy responses be effective at decreasing heroin and synthetic opioid fatalities.

Figure 7 presents the results of estimating a separate difference-in-differences model for fatalities from four different categories of opioids: heroin, pain medications, synthetic opioids, and other or unidentified opioids. The "other opioids" category includes opioids that could not be or otherwise were not identified at the time of autopsy.[88] According to the NVSS data that I utilize, heroin, pain medication, synthetic opioid, and other opioid fatalities were associated with 39%, 47%, 29%, and 9% of fatal opioid overdoses in 2015. Because some fatal overdoses involve multiple opioids and I include such multiple opioid fatalities in each appropriate category, these figures add up to more than 100%.

The results in Figure 7 demonstrate that naloxone access laws have different effects on fatalities involving different drug types. Heroin fatalities are unaffected by provider legal immunity or third party prescribing, though administrator legal immunity and relaxed prescription requirements have a statistically significant impact. Administrator legal immunity increases heroin fatalities by 0.04 fatalities per month per 100,000 residents, while allowing prescribing without seeing a practitioner other than a pharmacist decreases heroin fatalities by

[87] In recent years, fentanyl overdoses have accounted for an increasing proportion of fatal overdoses (Ingraham 2018).

[88] More broadly, underidentified drug poisonings may be a major problem for determining an accurate count of individuals who have suffered opioid overdoses (Buchanich et al. 2018) (noting that the actual number of opioid overdose deaths may be substantially higher than reported numbers due to uncoded death certificates). Even if opioid fatalities are undercounted, the measurement error in my data will not bias my results if undercounting is random, as classic measurement error in dependent variables does not generally bias regression results (Kmenta 1997).

0.06 per month per 100,000 residents.[89] For pain medication fatalities only provider legal immunity has a statistically significant effect, which is estimated to increase fatalities involving pain medication by 0.05 fatalities per month per 100,000 county residents.[90] No provision had a statistically significant impact on overdoses for synthetic opioids or "other" opioids.

D. Differences by Urban and Rural Areas

As with the different drug types reviewed in Section C, opioid abuse patterns differ significantly between urban and rural areas (Keyes et al. 2014). The prevailing narrative of the opioid epidemic is that it has been largely fueled by opioid misuse in rural areas (CDC 2018b). The counties with the highest opioid prescribing rates tend to be rural—for example, Mohave County in Arizona and Nye County in Nevada have opioid prescribing rates more than double the national average (CDC 2016). In fact, average fatal opioid overdose rates are higher in urban counties than rural counties. But, the counties where the opioid epidemic has taken the *most* lives are disproportionately rural. Fifty-seven of the one hundred counties with the highest opioid overdose rates in 2015 were rural counties, even though the average overdose rate in rural counties is smaller. And, after other county characteristics are accounted for, areas with higher population have substantially smaller opioid fatality rates; a 1% increase in a county's population is associated with a 0.6% decrease in the opioid fatality rate.[91]

Many policy responses to the opioid epidemic rely upon institutions and actors that are lacking in rural areas. The challenge of few resources in rural areas is particularly germane to the effect of naloxone access laws—even if naloxone can be legally acquired, the few pharmacies in rural areas may simply not carry naloxone or may charge high prices that foreclose access for many individuals. If states do not permit pharmacists to prescribe naloxone or permit prescribing

[89] For administrator immunity, $p = 0.048$. For the prescription provisions, $p < 0.001$.
[90] $p = 0.061$.
[91] *See infra*, Appendix Table A1.

by standing order, the cost of traveling to a doctor may be prohibitive in rural areas. More broadly, researchers in the health literature have recognized that individuals in rural areas lack financially and geographically accessible primary health care (Laditka et al. 2009; Richards et al. 2015). If naloxone access laws have little effect in rural areas, policymakers will need to recalibrate policy efforts to reduce fatalities in rural areas.

To investigate whether naloxone access law effects differ based on how urban an area is, Figure 8 presents difference-in-differences estimates of naloxone access laws on urban, suburban, and rural counties.[92] The estimates in Figure 8 indicate that naloxone access laws have very little effect on opioid fatality rates outside of urban counties. The estimated effects for all four provisions are statistically insignificant for both rural and suburban counties.[93] The lack of an effect in rural counties is consistent with public health research demonstrating that physician shortages, cultural and financial barriers, and transportation difficulties plague rural access to health care (Douthit 2015). In urban counties, provisions extending legal immunity to lay administrators cause a significant increase of 0.13 fatalities per month per 100,000 residents.[94] And consistent with the evidence presented in Sections A, B, and C, provisions relaxing prescription requirements cause a significant decrease of 0.17 fatalities per month per 100,000 residents.[95]

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[92] I adapt the National Council for Health Statistics ("NCHS") Urban-Rural Classification scheme for this analysis. I classify a county as urban if the NCHS classification of a county is "Large central metro" or "Large fringe metro." I classify a county as suburban if the NCHS classification of a county is "Medium metro" or "Small metro." Finally, I classify a county as rural if the NCHS classification is "Micropolitan" or "Noncore" (U.S. Department of Health and Human Services 2014).

[93] For rural counties, the p-values range from 0.425 (provider immunity) to 0.707 (lay administrator immunity). For suburban counties, the p-values range from 0.288 (third party prescribing) to 0.534 (relaxed prescription requirements).

[94] $p = 0.020$.

[95] For third party provisions, $p = 0.072$. For the prescription provisions, $p = 0.008$.

V. Toward an Optimal Naloxone Policy

The results in Part IV provide strong evidence that naloxone access without a prescription can save many lives. This Part explores what steps states and the federal government can take to capitalize on this evidence. In Section A, I recommend that the federal government and states take further steps to make naloxone available to anyone without a prescription. In Section B, I discuss the evidence that my regressions provide on the effect of liability immunity. While the provisions addressing provider immunity generally had no significant effect, the results of my difference-in-differences model offer evidence that providing legal immunity to administrators increases fatalities.

A. Removing Prescription Requirements

The results in Part IV indicate that naloxone access provisions that allow individuals to obtain naloxone via a standing order prescription or a prescription from a pharmacist could save approximately 3,030 lives nationwide per year.[96] As of the end of 2016, five states and Washington, D.C. still did not permit prescribing naloxone by standing order or by a pharmacist. The provisions that relax prescription requirements enable individuals, be they opioid users themselves or friends or family members of opioid users, to obtain naloxone without the inconvenience or expense of going to a doctor first. The decreased financial cost of receiving naloxone from a pharmacy, without having to pay another health care provider's fee, as well as removing geographic barriers to access associated with needing to visit a non-pharmacist prescriber, are likely the primary mechanism for the decreased fatalities. Drug users often face barriers to receiving medical treatment, and it is likely that those barriers also make it difficult to seek a prescription for naloxone that could save their lives (Mowbray et al. 2010).

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[96] Relaxing prescription requirements decreases the overdose rate in the average county by 0.077 fatalities per month per 100,000 residents. Multiplying by 12 to annualize the rate and multiplying by the whole U.S. population of approximately 328,000,000 (divided by 100,000) yields 3,030 lives saved annually.

Optimal naloxone policy should therefore focus on making naloxone available without a prescription. Doing so would expand the benefits of the prescription relaxing statutes studied here. State laws that permit doctors to issue standing orders and that authorize pharmacists to prescribe naloxone work around the fact that the FDA continues to classify naloxone as a prescription drug. The best solution would be for the FDA to promulgate a regulation which allows naloxone to be sold at retail locations without any prescription at all. The Food, Drug, and Cosmetic Act requires drugs which are potentially toxic or which require supervision by a health care practitioner to safely use to be dispensed only upon a written prescription.[97] The Act authorizes the FDA to permit a drug to be sold over-the-counter whenever a prescription requirement is "not necessary for the protection of the public health."[98] The FDA states that over-the-counter treatment is typically appropriate for drugs when (1) the benefits of over-the-counter treatment outweigh the risks, (2) the potential for abuse is low, (3) consumers can use them for self-diagnosed conditions, (4) they can be adequately labeled, and (5) health care practitioners are not needed for the safe and effective use of the product (U.S. FDA 2018c).

Over-the-counter treatment for naloxone is appropriate under the FDA's prevailing standard. Naloxone has no recreational benefit and cannot be abused (Chamberlain and Klein 1994). Opioid users as well as their friends and family members are capable of diagnosing opioid overdoses, as ample evidence from pilot naloxone programs demonstrates. Moreover, the risks of mistaken diagnosis are small as the effects of inappropriate administration of naloxone are minimal. The FDA itself developed a consumer-friendly model Drug Facts Label for naloxone (Staman 2018). Naloxone may be safely administered in the case of an overdose using either the autoinjector or nasal spray administration methods without a doctor present. And as this research

[97] 21 U.S.C. § 353(b)(1) (2018).
[98] *Id.* at § 353(c).

has made clear, the public health benefits of allowing naloxone to be purchased without a prescription dramatically outweigh the costs. Thousands of lives could be saved annually by increasing the product's availability. Even if there is some small moral hazard effect of naloxone access laws which causes increased consumption of opioids or an uptick in opioid related crime, the benefit in lives saved will outweigh such effects.

Full over-the-counter classification is critical to ensuring that naloxone is available in rural areas. As Figure 8 demonstrates, current state regimes do not affect fatalities in rural areas. Even if every single state passed a standing order provision or pharmacist-prescribing provision, individuals would still need to access a pharmacy that actually stocks naloxone for naloxone access laws to have a meaningful impact. Because many individuals living in rural areas have few geographically or financially accessible pharmacies that would stock naloxone (Casey et al. 2008), state level policies will be insufficient. Over-the-counter treatment would permit naloxone to be sold in gas stations, grocery stores, and other locations that are likely to be more accessible to individuals in rural areas. However, in the Technical Appendix, I test whether the effect of naloxone access laws is greater in urban, suburban, and rural areas with more pharmacies and find little evidence that geographic access to pharmacies drives the lack of an effect in rural areas.[99] Expanding the number of retailers may yield more retailers willing to stock naloxone and may also have the added benefit of reducing naloxone prices, at least to the extent that market power of local retailers rather than the pricing decisions of manufacturers drives the high cost of naloxone currently in the market (Sorenson 2000).

[99] *See* Appendix Table A9.

B. Removing Immunity for Liability

My empirical results indicate that providing liability immunity to naloxone providers has a very small effect, if any, on opioid overdose fatalities. Conversely, my difference-in-differences estimates consistently demonstrate that providing legal immunity to individuals who administer naloxone increases overdose fatalities. It is not clear why administration immunity has the opposite effect of making a prescription easier to acquire. This Section discusses why those estimates may exhibit increases in opioid fatalities as a result of the immunity.

It is unlikely that the observed effect is the result of too many states enacting statutes with overlapping provisions at the same time, preventing proper isolation of the effect of administrator legal immunity. Twenty-eight states passed an administrator immunity provision in combination with other provisions and never altered their naloxone access regime again, but the remaining twenty-two states altered their regimes in a manner that enabled disentangling the effect of the administrator immunity provision. California, Connecticut, the District of Columbia, and Rhode Island each amended their code by adding only administrator immunity without any other naloxone access provisions at some point in my data. South Dakota's naloxone access law enacted every provision *except* for the lay administrator immunity provision. These changes ensure that the effect I estimate is the average effect of a lay administrator provision rather than correlations with the other provisions that I analyze.

It is possible that the effect is being driven by behavior in outlier states. Re-estimating the model 51 times and individually dropping each state and Washington, D.C. illustrates that the lay-administrator coefficient is only significant in regressions that include both New York and Washington state. In the extra models that I run which exclude New York, lay administrator immunity is statistically insignificant,[100] but the sum effect of standing orders and pharmacist

[100] $p = 0.122$.

prescription authority remains significant.[101] Likewise, in the models excluding Washington, lay administrator immunity is statistically insignificant,[102] but the effect of the beneficial provision retains its statistical significance.[103] The implementation of administrator immunity laws may have been systematically different in those two states in a way that causes the model to yield an increase in opioid fatalities.

Finally, it is possible that extending immunity to administrators truly does cause a change in behavior that is different from the change caused by providing naloxone without a patient specific prescription from a non-pharmacist practitioner. The latter provisions are likely taken advantage of primarily by non-opioid using individuals, while the administration provision can affect individuals who use opioids as well as third parties. Perhaps such individuals tend to be more risk-seeking when naloxone access laws are implemented, or they are misinformed as to the circumstances under which legal immunity attaches. But it is not clear whether the administrator immunity actually changed legal incentives, given that there exists no evidence of any cases of states charging naloxone administrators with criminal assault for administering naloxone or plaintiffs suing for damages for battery in the absence of an immunity statute.[104] Another alternative is that the requirements for immunity in a naloxone statute are complex enough to actually make it *less* likely that an individual is immune from liability by administering naloxone rather merely than calling for emergency medical services (Sightes et al. 2018). For example, in Indiana immunity only attaches to individuals who administer naloxone, summon emergency medical assistance, remain on the scene, and cooperate with law enforcement.[105] Moreover, legal immunity only attaches to individuals who actually administer

[101] $p = 0.042$.
[102] $p = 0.147$.
[103] $p = 0.033$.
[104] A Westlaw search for "naloxone and administ*" performed on October 29, 2018 yielded no such cases.
[105] Ind. § 15-42-27-2 (2018).

naloxone; thus individuals who are engaged in illegal activity and present when emergency services arrive but did not administer naloxone will not be immune from criminal or civil liability generally. Such statutes could chill attempts to seek medical care for individuals experiencing an overdose as a result. Finally, it is possible that liability is not salient to providers until the discussion of conditions for immunity highlights the circumstances under which health care providers could be held liable. If providers do not know that providing naloxone could expose them to civil or criminal liability, a statute providing immunity may chill naloxone provision that was already occurring if it informs doctors about a new risk.

Future naloxone policy should focus less on the legal immunity of providers and administrators and more on actually making naloxone accessible to individuals and communities that need it. If naloxone is made available without a prescription, the immunity of naloxone providers will not generally matter. Moreover, as an empirical matter, states have brought more criminal charges or civil suits against doctors for inappropriately prescribing opioid medications than for prescribing naloxone to individuals.[106] Doctors and administrators may simply not respond strongly to legal sanctions as an incentive when deciding whether to provide life-saving medicine (Shavell 2002). Because my estimates for the effect of administrator immunity are positive and significant, avoiding such statutes may be the best course of action until further research identifies why those statutes increase opioid fatalities, though as discussed above, the evidence on the effect of immunity is mixed.

[106] A Westlaw search for "crim* and naloxone" performed on October 29, 2018 yielded no cases indicating that a defendant was charged with criminal possession of naloxone or inappropriate prescribing of naloxone, nor being sued for negligence by any plaintiff. *See also* (Davis et al. 2015). Though, defendants *have* been charged with distributing Suboxone, a prescription drug containing both buprenorphine and naloxone that is used for treating opioid addiction. *E.g.,* Commonwealth v. Wilks, No. 2132, 2013 WL 11254080, at *1–2 (Sup. Ct. Penn. Oct 2, 2013); Commonwealth v. Caraballo, 965 N.E. 2d 194, 196 (Mass. App. Ct. 2012). Unlike pure naloxone, Suboxone does have recreational benefits and is not generally used to reverse an overdose. Contrast the lack of suits for naloxone with media reports of several lawsuits against doctors for negligent distribution of opioids (Nedelman 2017).

VI. Conclusion

Opioid fatalities continue to grow year over year, with an estimated 72,000 individuals experiencing a fatal overdose in 2017. Providing naloxone to third parties and enabling individuals to acquire naloxone without first incurring the expense of visiting a non-pharmacist medical professional have significantly decrease the opioid fatalities experienced each year. There is also evidence that extending legal immunity to administrators may increase the amount of opioid fatalities. I estimate that extending legal immunity to naloxone providers has no effect on fatalities. The effects are concentrated among opioid users in urban areas, suggesting that alternative policy responses will be necessary to reduce fatalities in rural areas that exhibit the highest opioid fatality rates. These results contribute significantly to the literature examining the effects of naloxone access by isolating which provisions tend to decrease fatalities, offering evidence of provisions that increase fatalities, and exploring exactly who the provisions have benefitted and harmed.

The federal government can continue the push to broaden naloxone access. I recommend that the FDA promulgate regulations which permit individuals to acquire naloxone nationwide without any form of a prescription. Given that naloxone access today still puts some barriers in front of consumers (asking a pharmacist for a prescription, determining whether a standing order is in effect), my estimates are an understatement of how many lives could be saved if the FDA took this measure. Moreover, my data do not answer how many individuals actually receive naloxone. In rural areas, naloxone being legal to acquire will not be the same as naloxone being *easy* to acquire. For counties that the opioid epidemic has hit the hardest, the distinction will make the difference between life and death for opioid users. Further research must be done to investigate how policymakers can expand possession of naloxone rather than merely expand legal access to it. Direct distribution similar to the early pilot programs that began the naloxone movement may be key. State naloxone access statutes, even those that evidence demonstrates are helpful at reducing fatalities, are a single part of the numerous steps that policymakers must take to turn the tide on the epidemic.

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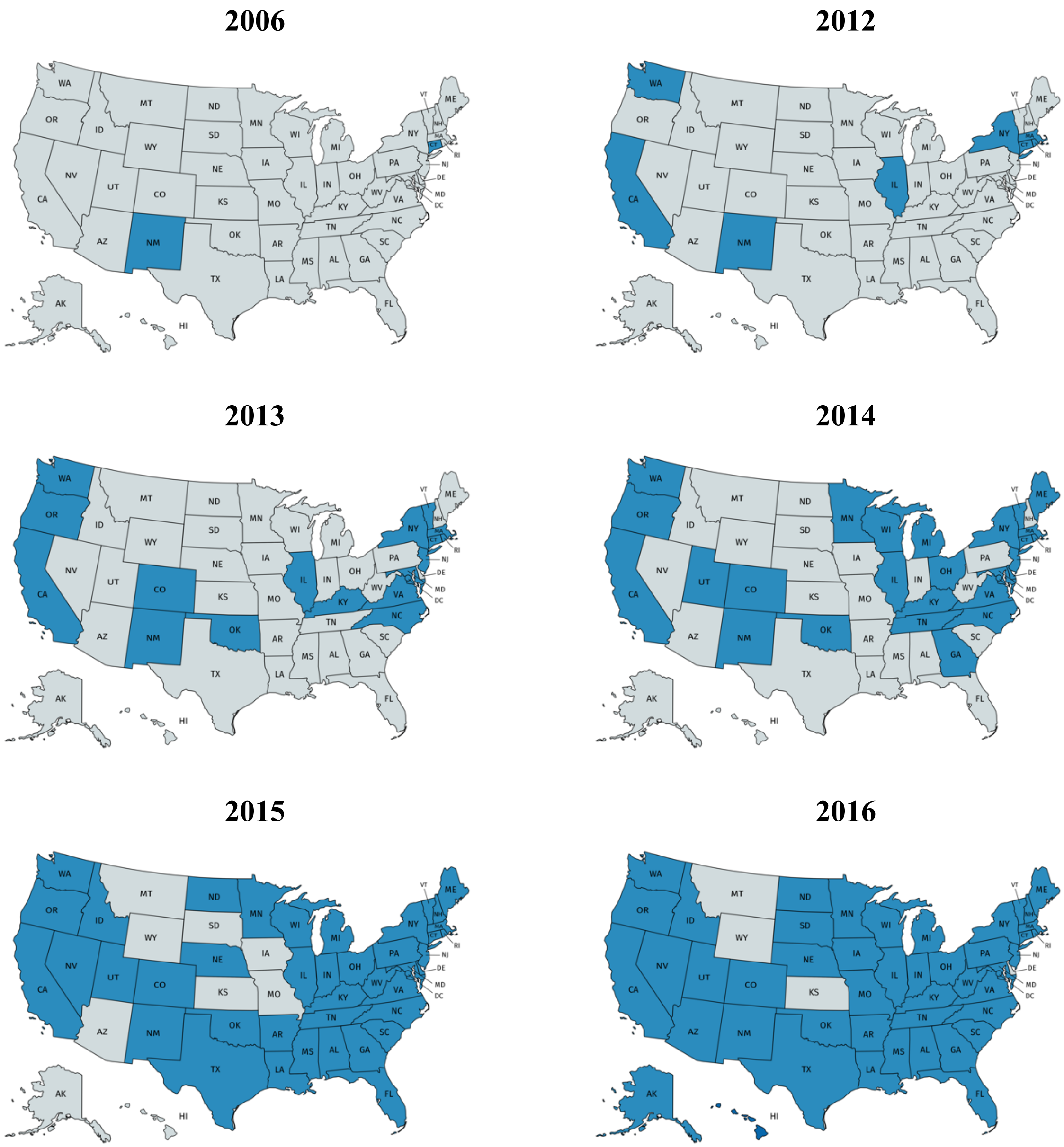
Figures

Figure 1: Evolution of state naloxone access laws over time



Note: Highlighted states have naloxone access laws in force at the end of the specified year.

Figure 2: National opioid fatalities

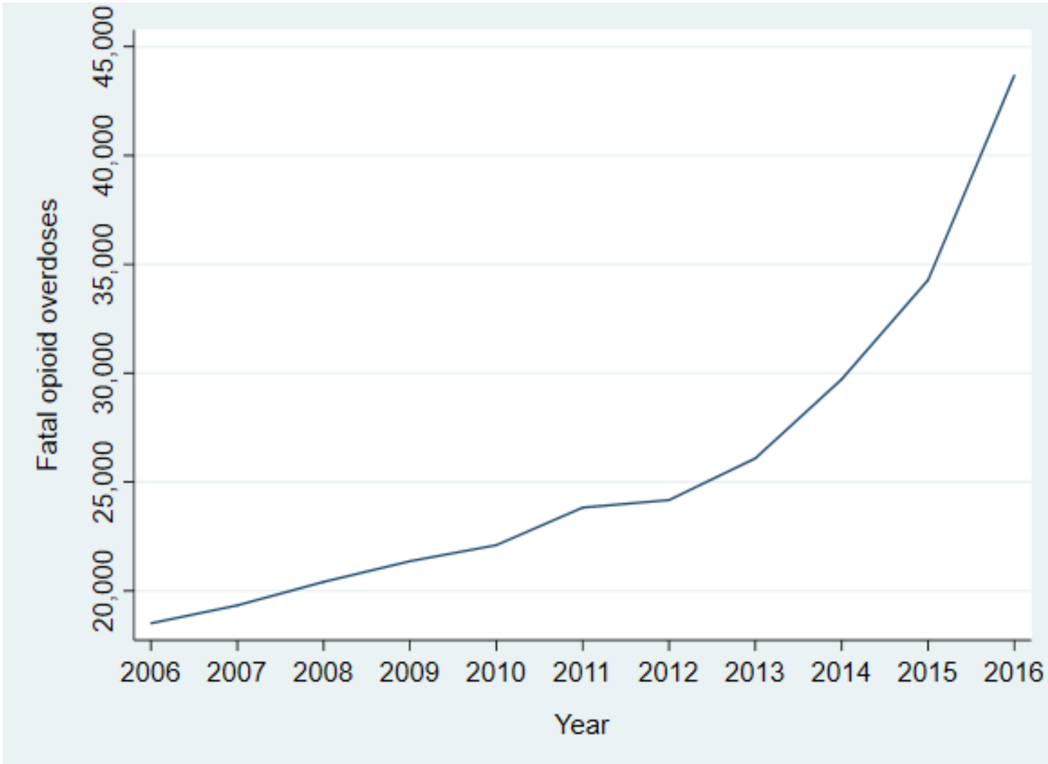
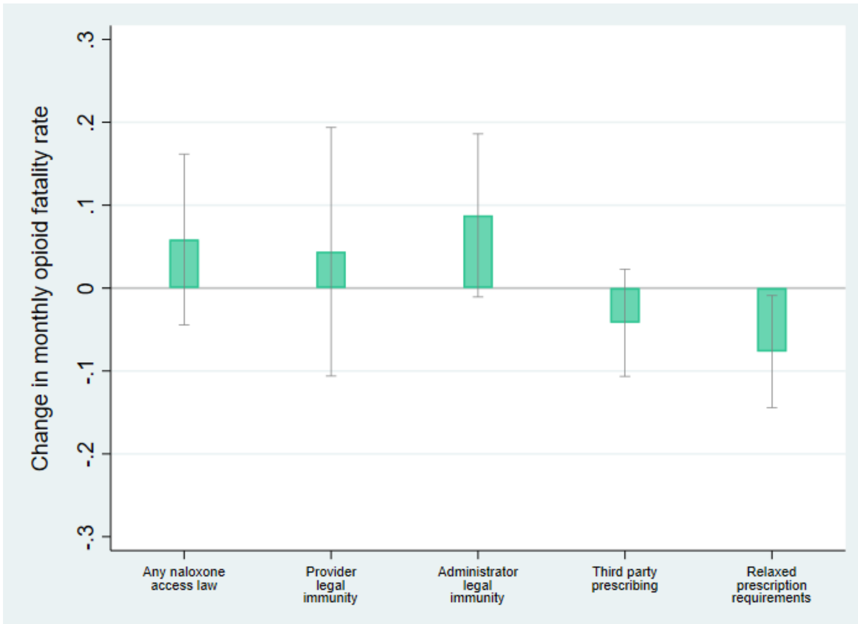
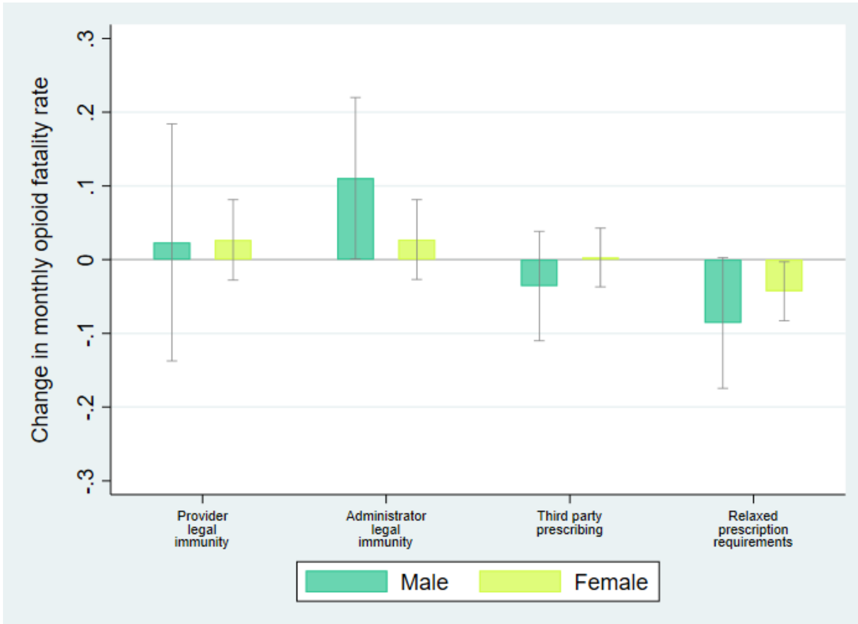


Figure 3: Effect of naloxone access provisions



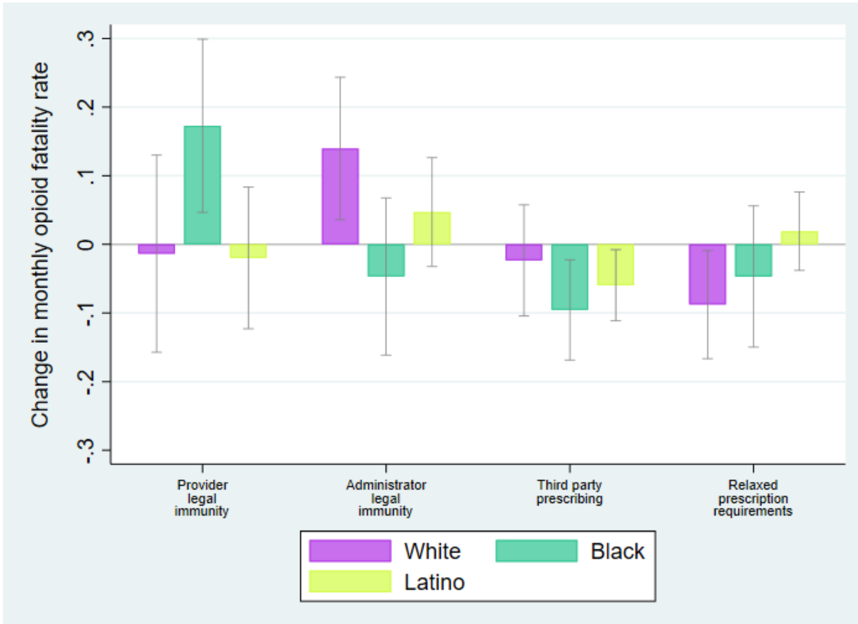
Notes: N = 414,498. Each bar represents the change in monthly opioid fatalities in the average county per 100,000 county residents. The average monthly fatality rate is 0.815 fatalities per month per 100,000 residents. The regression results from which this figure was derived are reported in Appendix Table A1.

Figure 4: Effects of naloxone access provisions by sex



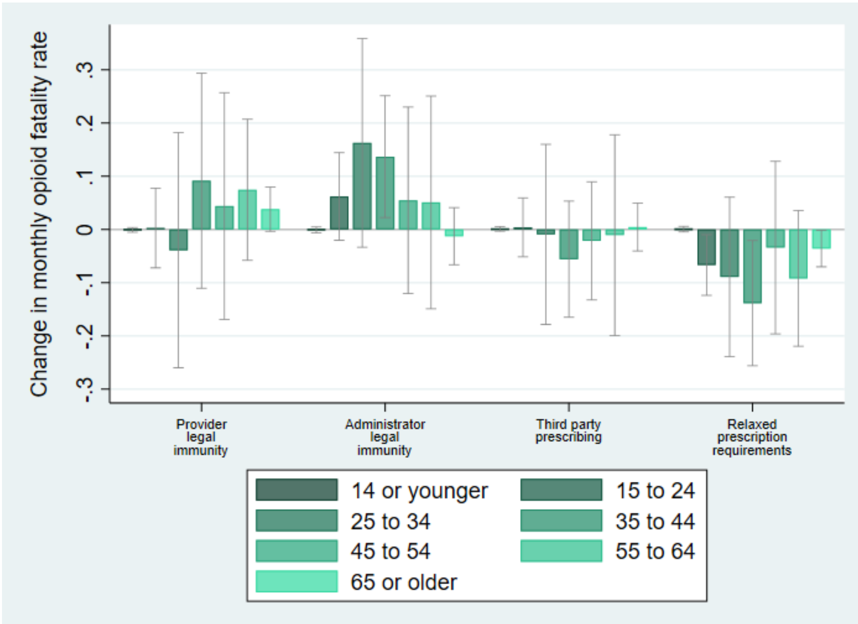
Notes: N = 414,498. Each bar represents the change in monthly fatalities in the average county per 100,000 male or female county residents. The average monthly fatality rates for men and women are 0.910 and 0.477 fatalities per month per 100,000 male and female residents. This figure was derived from regression results reported in Appendix Table A2.

Figure 5: Effects of naloxone access provisions by race and ethnicity



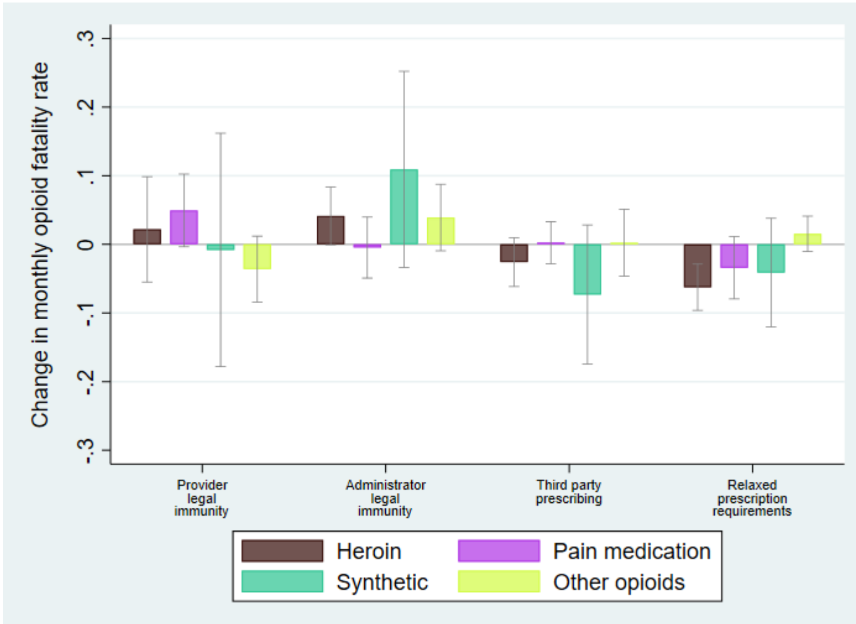
Notes: N = 414,498. Each bar represents the change in monthly fatalities in the average county per 100,000 white, black, or Latino county residents. The average monthly fatality rates for white, black and Latino individuals are 0.914, 0.431, and 0.277 fatalities per month per 100,000 residents of the relevant group. This figure was derived from regression results reported in Appendix Table A3.

Figure 6: Effects of naloxone access provisions by age group



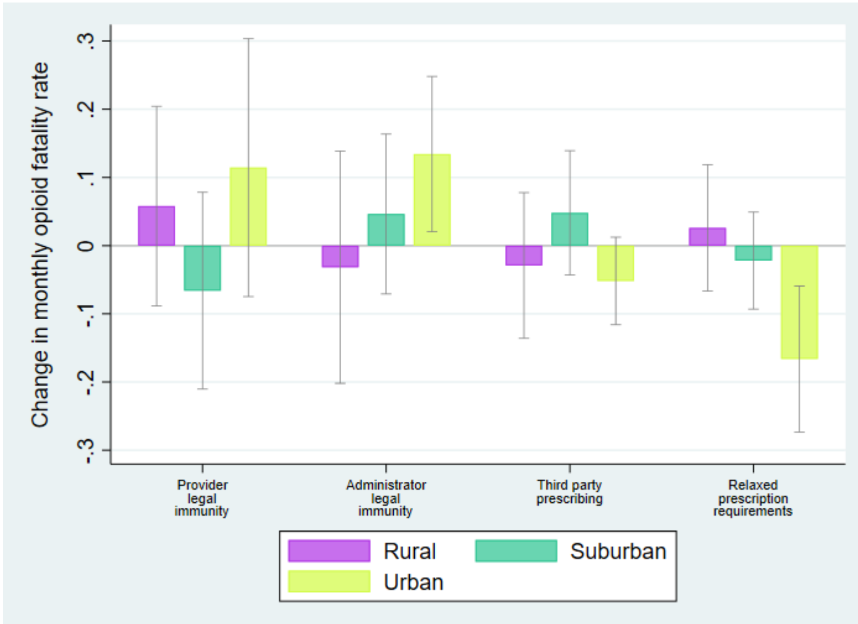
Notes: N = 414,498. Each bar represents the change in monthly fatalities in the average county per 100,000 county residents in the indicated age group. The average monthly fatality rate for each age group is 0.010 (14 years or younger), 0.513 (15 to 24 years), 1.212 (25 to 34 years), 1.203 (35 to 44 years), 1.290 (45 to 54 years), 0.923 (55 to 64 years), and 0.192 (65 years or older) fatalities per 100,000 county residents in the indicated age group. This figure was derived from regression results reported in Appendix Table A4.

Figure 7: Effect of naloxone access provisions by drug type



Notes: N = 414,498. Each bar represents the change in monthly fatalities associated with the indicated opioid in the average county per 100,000 county residents. The average monthly fatality rates for heroin, pain medication, synthetic opioids, and other opioids are 0.210, 0.470, 0.166, and 0.091 fatalities per month per 100,000 residents. This figure was derived from regression results reported in Appendix Table A5.

Figure 8: Effect of naloxone access provisions by urbanization



Notes: N = 414,498. Each bar represents the change in monthly fatalities in the average rural, suburban, or urban county per 100,000 county residents. The average monthly fatality rates for rural, suburban, and urban counties are 0.510, 0.610, and 0.782 fatalities per month per 100,000 residents. This figure was derived from regression results reported in Appendix Table A6.

Tables

Table 1: Naloxone access provision adoption date by state

State	Provider legal immunity	Lay administrator legal immunity	Third party prescribing	No prescription
Alabama	June 2015	June 2015	June 2015	June 2015
Alaska	March 2016	March 2016	March 2016	March 2016
Arizona	August 2016	August 2016	August 2016	August 2016
Arkansas	July 2015	July 2015	July 2015	July 2015
California	January 2008*	January 2011*	January 2014	January 2014
Colorado	May 2013	May 2013	April 2015	April 2015
Connecticut	October 2003	October 2014	July 2015	July 2015
Delaware	August 2014	-	-	August 2014
District of Columbia	-	April 2013	-	-
Florida	June 2015	June 2015	June 2015	July 2016
Georgia	May 2014	May 2014	May 2014	May 2014
Hawaii	August 2016	August 2016	August 2016	August 2016
Idaho	July 2015	July 2015	July 2015	July 2015
Illinois	August 2015	January 2010	January 2010	January 2010
Indiana	May 2015	May 2015	May 2015	May 2015
Iowa	July 2016	July 2016	July 2016	July 2016
Kansas	-	-	-	-
Kentucky	-	July 2013	July 2013	July 2013
Louisiana	August 2015	August 2015	August 2015	August 2015
Maine	August 2016	August 2016	May 2014	October 2015
Maryland	October 2015	October 2015	October 2013	October 2015
Massachusetts	-	July 2014	July 2012	July 2014
Michigan	October 2014	October 2014	October 2014	-
Minnesota	May 2014	May 2014	-	May 2014
Mississippi	July 2015	July 2015	July 2015	July 2015
Missouri	September 2016	September 2016	-	September 2016
Montana	-	-	-	-
Nebraska	June 2015	June 2015	June 2015	-

Nevada	October 2015	October 2015	October 2015	October 2015
New Hampshire	June 2015	June 2015	June 2015	June 2015
New Jersey	July 2013	July 2013	July 2013	July 2013
New Mexico	April 2001	April 2001	April 2001	March 2013
New York	-	July 2014	February 2007	July 2014
North Carolina	April 2013	April 2013	April 2013	April 2013
North Dakota	August 2015	August 2015	August 2015	August 2015
Ohio	March 2014	March 2014	March 2014	August 2015
Oklahoma	-	-	November 2013	November 2014
Oregon	-	June 2013	June 2013	June 2013
Pennsylvania	December 2014	December 2014	December 2014	December 2014
Rhode Island	-	July 2012	March 2014	March 2014
South Carolina	June 2015	June 2015	June 2015	June 2016
South Dakota	July 2016	-	July 2016	July 2016
Tennessee	July 2014	July 2014	July 2014	July 2014
Texas	September 2015	September 2015	September 2015	September 2015
Utah	May 2014	May 2014	May 2014	June 2016
Vermont	July 2013	July 2013	July 2013	July 2013
Virginia	April 2014	July 2013	July 2013†	April 2014
Washington	August 2015	June 2010	June 2010	August 2015
West Virginia	June 2015	June 2015	June 2015	June 2016
Wisconsin	April 2014	April 2014	April 2014	April 2014
Wyoming	-	-	-	-

Note: Each cell provides the first month and year that a state's naloxone access provision was in effect for a majority of the month. Data on the effective dates of each statute were obtained from the Prescription Drug Abuse Policy System (http://pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139). The table does not provide information on laws passed after December 2016.

* California's provider legal immunity and lay administrator legal immunity provisions applied only to Alameda, Fresno, Humboldt, Los Angeles, Mendocino, San Francisco, and Santa Cruz counties until January 2014.

† Virginia repealed its third-party prescription provision when it enacted its provision permitting prescription by standing order, effective April 2014. Between July 2013 and April 2014, doctors in state approved programs could prescribe naloxone to third parties.

Table 2: Summary statistics

Variable	Mean	Median	Standard deviation
Monthly opioid fatalities per 100,000 residents			
All opioids	0.815	0.486	1.174
Heroin	0.210	0.000	0.484
Pain medication (semi-synthetic opioids)	0.470	0.198	0.831
Synthetic opioids	0.166	0.000	0.536
Other opioids	0.091	0.000	0.338
Naloxone access laws:			
Any naloxone access law	0.341	0.000	0.474
Provider legal immunity	0.195	0.000	0.396
Administrator legal immunity	0.238	0.000	0.426
Third party provision permitted	0.266	0.000	0.442
Relaxed prescription requirements	0.191	0.000	0.393
County characteristics			
Mean weekly wage ($ 2015 thousands)	0.893	0.849	0.242
Employment to population ratio	0.498	0.413	0.440
Population (hundreds of thousands)	4.235	3.072	3.710
White population (%)	0.769	0.834	0.204
Mean age	38.101	37.901	2.964
Medical services and first responder counts:			
Pharmacies	1.126	0.190	5.366
Hospitals	0.249	0.060	0.539
Pain clinics	0.013	0.060	0.042
Police (per 1,000 residents)	0.819	0.614	0.950
EMTs (per 1,000 residents)	0.006	0.002	0.025
Other laws:			
PDMP	0.883	1.000	0.321
Must-access PDMP	0.086	0.000	0.281
Medical marijuana legal	0.147	0.000	0.354
Recreational marijuana legal	0.013	0.000	0.114
Noneconomic damage caps	0.603	1.000	0.489
Punitive damage caps	0.687	1.000	0.464
Joint and several liability reforms	0.673	1.000	0.469

Note: N = 414,498. Summary statistics are weighted by county population.

Technical Appendix

The regression equation that I use to estimate my difference-in-differences models is as follows:

$$Opioid\ Fatality\ Rate_{ct} = \alpha + \beta_1 NAL_{st} + X_{ct}\beta + \gamma_c + \delta_t + \theta_{it} + e_{ct} \quad (1)$$

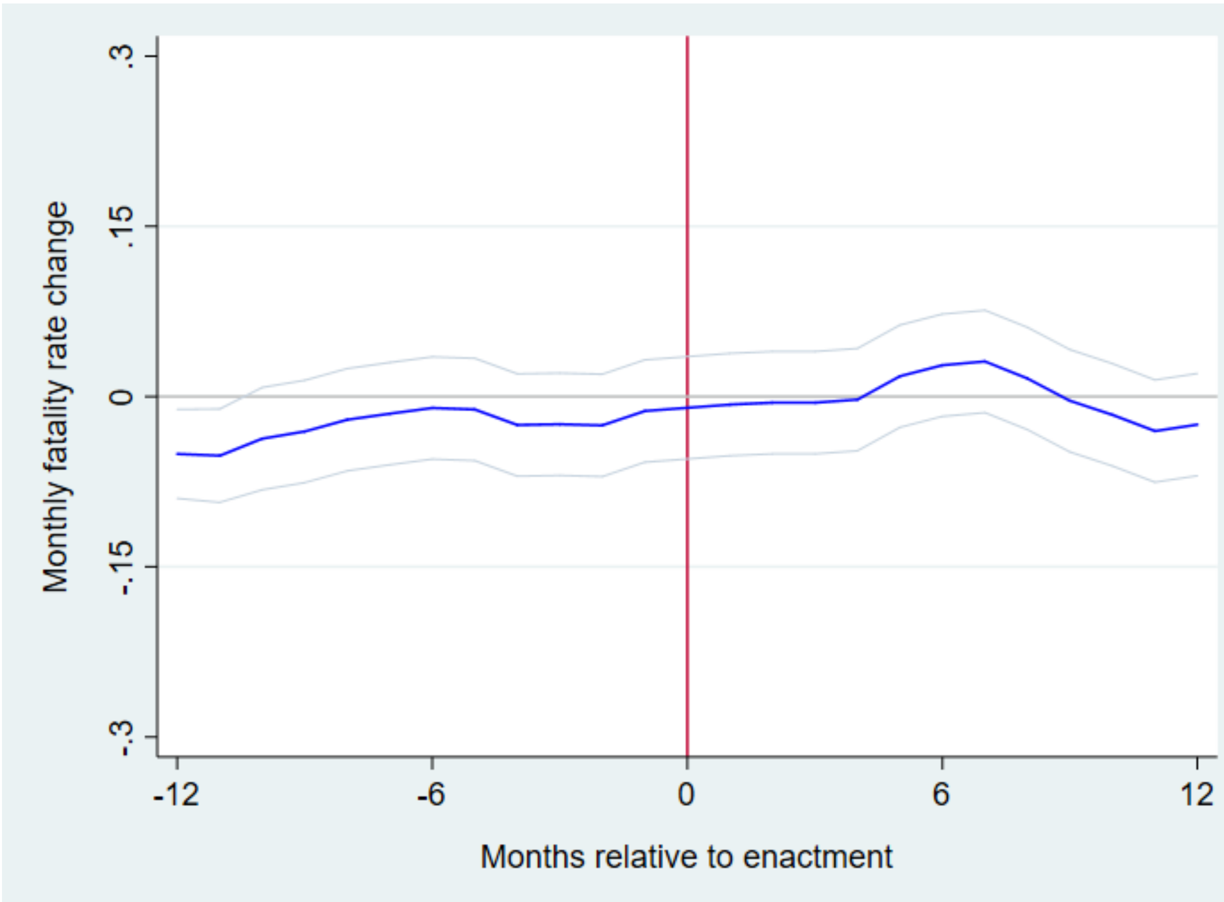
In this equation, c indexes counties, s indexes states, and t indexes months. The variable NAL_{st} indicates whether state s has an active naloxone access law at time t. The variable α is a constant term. The variables X_{ct} are time-variant county characteristics. The term γ_c is a series of county-specific fixed effects, which account for the variation in fatality rates attributable to time-invariant county characteristics. The term δ_t is a series of monthly fixed effects, accounting for the variation in fatality rates attributable to national time trends. The term θ_{it} is a series of county-specific time trends. The error term is e_{ct}. The parameter β_1 is the difference-in-differences estimate of the effect of naloxone access laws and is therefore the parameter of interest.

The results that I present in Figures 3 through 8 use some variant of the regression model presented in equation 1. In Figure 3, I estimate two variants of this equation. In the first, NAL_{st} is a single indicator variable equal to one if state s has any naloxone access law in force at time t. In the second variant, NAL_{st} is a vector of four indicator variables. The four variables indicate whether state s has a naloxone access law in force which contains one of the four naloxone access provisions of interest. Figures 4 through 8 use substantially the same regression equation but estimate it with a different dependent variable. In Figure 4, the dependent variables are either the male or female opioid fatality rate. In Figure 5, the dependent variables are the fatality rates for individuals who are white, black, or Latino. Figure 6 uses opioid fatality rate by ten-year age groups as the dependent variable. Figure 7 uses four different dependent variables: the heroin fatality rate, the pain medication fatality rate, the synthetic opioid fatality rate, and the fatality rate for unidentified opioids. Finally, Figure 8 applies equation 1 to three distinct subsamples of my data: rural counties, suburban counties, and urban counties. The full regression results for each of these models are presented in Appendix Tables A1 through A6.

In addition, Figures Appendix A1 and A2 provide explicit tests of the parallel trends assumption necessary for the model to provide a valid estimate of the causal effect of naloxone access laws. Both figures are an event study of the effects of naloxone access law. The bold center line in each figure is a three-period moving average of the estimated difference between opioid fatality rates in counties where a naloxone access law is in effect and those where a naloxone access law is not in effect, after controlling for county fixed effects, monthly time trends, county-specific time trends, and the time-varying county characteristics in my dataset. The lighter lines bracketing the bold line are the 95% confidence intervals associated with the estimate. The estimates to the left of the vertical line at the time of enactment test the parallel trends assumption, while the estimates to the right show the evolution of the effect of naloxone access laws over time. Statistically insignificant pre-enactment estimates indicate that the parallel trends assumption is satisfied. The results broadly indicate the assumption is not violated and the model is valid. Figure A1 shows pre-enactment estimates which are never distinguishable from zero. For most provisions, Figure A2 supports an analogous conclusion. The pre-enactment estimates are only ever statistically significant for statutes extending immunity to providers or administrators. As a result, the results corresponding to these statutes should be interpreted with caution. The remaining pre-trends are generally very close to zero, indicating that the difference-in-differences model provides valid estimates of the causal effect of naloxone access provisions.

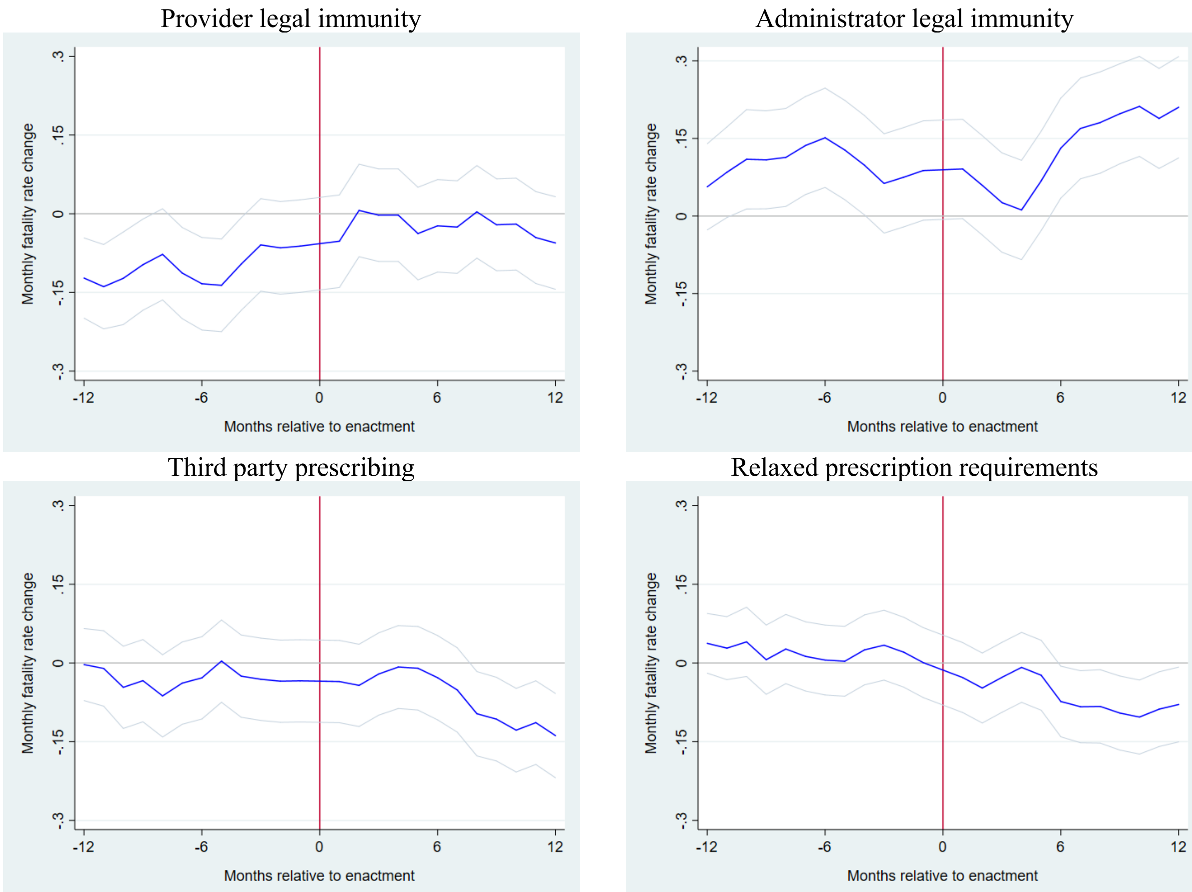
Appendix Figures

Figure A1: Naloxone access laws generally



Note: N = 414,498. The center line presents a three-month moving average of the difference-in-differences point estimates of the difference in opioid fatality rates between counties treated by any naloxone access law and untreated counties. The bracketing lines provide the 95% confidence interval. The underlying regression controls for state fixed effects, month fixed effects, county-level time trends, and the covariates in Appendix Table A1, column 1.

Figure A2: Provision level estimates of the effect of naloxone access laws



Note: N = 414,498. The center line presents a three-month moving average of the difference-in-differences point estimates of the difference in opioid fatality rates between counties treated by the relevant provision and untreated counties. The bracketing lines provide the 95% confidence interval. The underlying regression controls for state fixed effects, month fixed effects, county-level time trends, and the covariates in Appendix Table A1, column 2.

Appendix Tables

Table A1: Difference-in-differences estimates of the effect of naloxone access laws

Variable	(1) Any law model	(2) Provision level analysis
Any naloxone access law	0.059	--
	(0.051)	
Provider legal immunity	--	0.044
		(0.075)
Administrator legal immunity	--	0.088
		(0.049)*
Third party prescribing	--	-0.042
		(0.032)
Relaxed prescription requirements	--	-0.077
		(0.034)**
Mean weekly wage ($ 2015 thousands)	0.040	0.032
	(0.055)	(0.054)
Employment to population ratio	0.428	0.406
	(0.594)	(0.605)
Population (hundreds of thousands)	-0.150	-0.146
	(0.130)	(0.127)
White Population (%)	-2.922	-3.270
	(1.667)*	(1.621)**
Mean age	-0.021	-0.017
	(0.039)	(0.040)
Pharmacies	-0.016	-0.016
	(0.006)***	(0.006)***
Hospitals	-0.265	-0.256
	(0.267)	(0.268)
Pain clinics	1.095	1.044
	(1.554)	(1.487)
Police (per 1,000 residents)	-0.020	-0.021
	(0.020)	(0.021)
EMTs (per 1,000 residents)	-0.385	-0.354
	(0.329)	(0.334)
PDMP	0.098	0.109
	(0.059)	(0.064)*
Must access PDMP	0.107	0.106
	(0.031)***	(0.031)***
Medical marijuana legal	0.130	0.116
	(0.052)**	(0.050)**
Recreational marijuana legal	-0.076	-0.068
	(0.060)	(0.055)
Noneconomic damage caps	-0.026	-0.017
	(0.038)	(0.037)
Punitive damage caps	0.103	0.103
	(0.038)***	(0.038)**
Joint and several liability reforms	-0.165	-0.156
	(0.056)***	(0.054)***

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A2: Poisson regression estimates of the effect of naloxone access laws

Variable	(1)	(2)	(3)
Provider legal immunity	-0.018	0.024	0.049
	(0.077)	(0.045)	(0.057)
Administrator legal immunity	0.167	0.101	0.081
	(0.058)***	(0.029)***	(0.034)**
Third party prescribing	-0.001	-0.028	-0.041
	(0.046)	(0.034)	(0.030)
Relaxed prescription requirements	-0.127	-0.073	-0.065
	(0.068)*	(0.037)**	(0.034)*
Mean weekly wage ($ 2015 thousands)	0.017	0.022	-0.032
	(0.059)	(0.066)	(0.046)
Employment to population ratio	-0.311	-0.226	-0.263
	(0.158)**	(0.149)	(0.138)*
Population (hundreds of thousands)	3.416	-0.317	-2.060
	(0.822)***	(0.821)	(1.097)*
White Population (%)	-0.039	-0.010	0.024
	(0.011)***	(0.014)	(0.031)
Mean age	-0.006	-0.009	-0.013
	(0.004)*	(0.004)**	(0.005)**
Pharmacies	-0.104	-0.069	-0.020
	(0.039)***	(0.026)***	(0.083)
Hospitals	-0.104	0.455	1.063
	(0.480)	(0.276)*	(0.920)
Pain clinics	-0.000	-0.001	-0.000
	(0.000)	(0.000)**	(0.000)
Police (per 1,000 residents)	-0.018	-0.001	-0.002
	(0.024)	(0.017)	(0.027)
EMTs (per 1,000 residents)	0.221	0.024	0.028
	(0.077)***	(0.057)	(0.058)
PDMP	0.099	0.108	0.115
	(0.076)	(0.056)*	(0.056)**
Must access PDMP	-0.031	0.099	0.107
	(0.070)	(0.048)**	(0.044)**
Medical marijuana legal	-0.205	-0.063	-0.043
	(0.093)**	(0.061)	(0.056)
Recreational marijuana legal	0.061	0.115	0.106
	(0.056)	(0.060)*	(0.053)**
Noneconomic damage caps	0.091	0.146	0.143
	(0.065)	(0.091)	(0.086)*
Punitive damage caps	0.389	-0.193	-0.190
	(0.060)***	(0.090)**	(0.085)**
Joint and several liability reforms	-6.901	-3.852	-1.066
	(0.928)***	(0.677)***	(0.838)
State and month fixed effects	X	X	X
State time trends		X	X
County time trends			X

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A3: Ordinary least squares estimates under different specifications

Variable	(1)	(2)	(3)
Provider legal immunity	-0.044	0.027	0.044
	(0.110)	(0.072)	(0.075)
Administrator legal immunity	0.141	0.087	0.088
	(0.087)	(0.050)*	(0.049)*
Third party prescribing	0.081	-0.032	-0.042
	(0.057)	(0.032)	(0.032)
Relaxed prescription requirements	-0.161	-0.076	-0.077
	(0.086)*	(0.035)**	(0.034)**
Mean weekly wage ($ 2015 thousands)	-0.051	0.062	0.032
	(0.074)	(0.051)	(0.054)
Employment to population ratio	0.313	0.433	0.406
	(0.315)	(0.305)	(0.605)
Population (hundreds of thousands)	-0.224	-0.136	-0.146
	(0.063)***	(0.063)**	(0.127)
White Population (%)	0.966	-1.080	-3.270
	(1.184)	(0.876)	(1.621)**
Mean age	-0.078	-0.081	-0.017
	(0.021)***	(0.024)***	(0.040)
Pharmacies	0.000	-0.006	-0.016
	(0.004)	(0.004)	(0.006)***
Hospitals	0.111	0.077	-0.256
	(0.099)	(0.087)	(0.268)
Pain clinics	0.170	0.821	1.044
	(0.385)	(0.242)***	(1.487)
Police (per 1,000 residents)	-0.001	-0.001	-0.000
	(0.000)	(0.000)	(0.000)
EMTs (per 1,000 residents)	-0.002	-0.000	-0.004
	(0.001)*	(0.001)	(0.003)
PDMP	0.275	0.109	0.109
	(0.097)***	(0.064)*	(0.064)*
Must access PDMP	0.029	0.106	0.106
	(0.066)	(0.030)***	(0.031)***
Medical marijuana legal	0.073	0.124	0.116
	(0.092)	(0.053)**	(0.050)**
Recreational marijuana legal	-0.235	-0.067	-0.068
	(0.105)**	(0.056)	(0.055)
Noneconomic damage caps	0.031	-0.015	-0.017
	(0.030)	(0.037)	(0.037)
Punitive damage caps	0.073	0.104	0.103
	(0.063)	(0.038)***	(0.038)**
Joint and several liability reforms	0.334	-0.156	-0.156
	(0.066)***	(0.057)***	(0.054)***
State and month fixed effects	X	X	X
State time trends		X	X
County time trends			X

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A4: Naloxone access provision effects by sex

Variable	(1) Male fatalities	(2) Female fatalities
Provider legal immunity	0.023	0.027
	(0.080)	(0.027)
Administrator legal immunity	0.111	0.027
	(0.055)**	(0.027)
Third party prescribing	-0.036	0.003
	(0.037)	(0.020)
Relaxed prescription requirements	-0.086	-0.043
	(0.044)*	(0.020)**
Mean weekly wage ($ 2015 thousands)	0.036	0.005
	(0.074)	(0.030)
Employment to population ratio	-0.287	-0.096
	(0.161)*	(0.069)
Population (hundreds of thousands)	-0.133	-0.053
	(0.114)	(0.052)
White Population (%)	-1.618	-0.805
	(0.987)	(0.492)
Mean age	0.009	-0.001
	(0.028)	(0.011)
Pharmacies	-0.021	-0.004
	(0.004)***	(0.001)***
Hospitals	-0.052	-0.021
	(0.110)	(0.032)
Pain clinics	0.540	0.730
	(0.942)	(0.540)
Police (per 1,000 residents)	0.003	-0.019
	(0.023)	(0.015)
EMTs (per 1,000 residents)	0.001	-0.136
	(0.541)	(0.276)
PDMP	0.170	0.069
	(0.098)*	(0.036)*
Must access PDMP	0.123	0.049
	(0.042)***	(0.019)**
Medical marijuana legal	0.157	0.037
	(0.064)**	(0.024)
Recreational marijuana legal	-0.035	-0.044
	(0.080)	(0.025)*
Noneconomic damage caps	-0.016	-0.014
	(0.059)	(0.023)
Punitive damage caps	0.100	0.065
	(0.054)*	(0.019)***
Joint and several liability reforms	-0.189	-0.108
	(0.085)**	(0.067)

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A5: Naloxone access provision effects by race and ethnicity

Variable	(1) White	(2) Black	(3) Latino
Provider legal immunity	-0.014	0.173	-0.020
	(0.071)	(0.063)***	(0.051)
Administrator legal immunity	0.140	-0.047	0.047
	(0.052)***	(0.057)	(0.040)
Third party prescribing	-0.023	-0.096	-0.059
	(0.040)	(0.036)**	(0.026)**
Relaxed prescription requirements	-0.088	-0.047	0.019
	(0.039)**	(0.051)	(0.028)
Mean weekly wage ($ 2015 thousands)	0.045	-0.003	0.012
	(0.073)	(0.059)	(0.034)
Employment to population ratio	-0.310	-0.311	-0.062
	(0.166)*	(0.117)**	(0.079)
Population (hundreds of thousands)	-0.140	-0.070	-0.029
	(0.105)	(0.074)	(0.041)
White Population (%)	-0.914	-4.050	-0.639
	(0.851)	(1.194)***	(0.619)
Mean age	-0.005	0.041	-0.002
	(0.031)	(0.018)**	(0.009)
Pharmacies	-0.015	-0.012	-0.013
	(0.003)***	(0.010)	(0.006)**
Hospitals	-0.068	-0.180	0.042
	(0.086)	(0.112)	(0.043)
Pain clinics	1.271	0.124	0.121
	(1.051)	(0.806)	(0.407)
Police (per 1,000 residents)	-0.000	0.000	0.000
	(0.000)	(0.000)	(0.000)
EMTs (per 1,000 residents)	-0.000	-0.004	0.004
	(0.005)	(0.002)**	(0.005)
PDMP	0.168	0.006	0.119
	(0.082)**	(0.062)	(0.079)
Must access PDMP	0.073	0.088	-0.004
	(0.037)*	(0.037)**	(0.034)
Medical marijuana legal	0.110	0.230	0.055
	(0.062)*	(0.092)**	(0.024)**
Recreational marijuana legal	-0.096	0.408	0.027
	(0.072)	(0.240)*	(0.034)
Noneconomic damage caps	-0.001	-0.015	0.008
	(0.039)	(0.036)	(0.050)
Punitive damage caps	0.110	-0.017	-0.008
	(0.054)**	(0.056)	(0.032)
Joint and several liability reforms	-0.120	-0.524	-0.143
	(0.079)	(0.344)	(0.040)***

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A6: Naloxone access provision effects by age group

Variable	≤ 14 years	15–24 years	25–34 years	35–44 years	45–54 years	55–64 years	≥ 65 years
Provider legal immunity	-0.001	0.003	-0.039	0.091	0.044	0.074	0.038
	(0.002)	(0.037)	(0.110)	(0.101)	(0.106)	(0.066)	(0.021)*
Administrator legal immunity	-0.001	0.062	0.163	0.137	0.055	0.051	-0.013
	(0.003)	(0.041)	(0.098)	(0.057)**	(0.087)	(0.099)	(0.027)
Third party prescribing	0.001	0.004	-0.009	-0.056	-0.022	-0.011	0.004
	(0.002)	(0.028)	(0.084)	(0.054)	(0.055)	(0.094)	(0.022)
Relaxed prescription requirements	0.001	-0.067	-0.089	-0.139	-0.034	-0.092	-0.036
	(0.003)	(0.028)**	(0.075)	(0.058)**	(0.081)	(0.063)	(0.017)**
Mean weekly wage ($ 2015 thousands)	0.007	-0.007	-0.015	-0.078	0.110	0.216	-0.080
	(0.009)	(0.058)	(0.131)	(0.123)	(0.080)	(0.086)**	(0.038)**
Employment to population ratio	-0.001	-0.185	-0.434	-0.360	-0.417	-0.149	-0.139
	(0.011)	(0.090)**	(0.194)**	(0.212)*	(0.229)*	(0.348)	(0.121)
Population (hundreds of thousands)	-0.003	-0.025	-0.210	-0.215	-0.179	-0.143	-0.039
	(0.004)	(0.057)	(0.159)	(0.137)	(0.179)	(0.177)	(0.047)
White Population (%)	0.021	-1.065	-1.832	0.001	-3.008	1.067	0.439
	(0.064)	(0.552)*	(1.351)	(1.765)	(1.836)	(1.413)	(0.685)
Mean age	0.001	0.003	-0.031	-0.019	0.031	-0.012	-0.006
	(0.001)	(0.021)	(0.052)	(0.039)	(0.038)	(0.020)	(0.012)
Pharmacies	-0.000	-0.009	-0.020	-0.029	-0.020	0.124	0.014
	(0.000)	(0.005)*	(0.004)***	(0.005)***	(0.007)***	(0.169)	(0.066)
Hospitals	0.003	-0.050	-0.028	-0.025	-0.119	-0.055	-0.084
	(0.005)	(0.035)	(0.111)	(0.136)	(0.170)	(0.356)	(0.084)
Pain clinics	-0.029	0.757	-0.101	-0.275	1.866	0.849	0.723
	(0.037)	(1.143)	(1.544)	(0.852)	(1.319)	(1.304)	(0.510)
Police (per 1,000 residents)	0.001	-0.005	0.028	-0.004	-0.020	-0.066	0.016
	(0.001)	(0.019)	(0.111)	(0.046)	(0.032)	(0.037)*	(0.018)
EMTs (per 1,000 residents)	-0.050	0.147	-0.798	-0.458	-0.515	0.284	0.835
	(0.041)	(0.281)	(0.828)	(0.899)	(0.832)	(0.853)	(0.526)
PDMP	-0.004	0.106	0.385	0.188	0.106	0.064	-0.002
	(0.002)*	(0.054)*	(0.153)**	(0.140)	(0.101)	(0.068)	(0.021)
Must access PDMP	-0.002	0.054	0.135	0.119	0.194	-0.082	-0.002
	(0.002)	(0.037)	(0.062)**	(0.065)*	(0.063)***	(0.128)	(0.028)
Medical marijuana legal	-0.002	0.031	0.176	0.194	0.185	0.019	0.009
	(0.002)	(0.035)	(0.084)**	(0.078)**	(0.089)**	(0.040)	(0.014)
Recreational marijuana legal	-0.006	-0.064	-0.090	-0.313	0.050	-0.021	0.004
	(0.003)	(0.078)	(0.137)	(0.117)***	(0.117)	(0.052)	(0.013)
Noneconomic damage caps	-0.003	-0.010	-0.022	-0.005	-0.089	0.046	0.005

	(0.004)	(0.034)	(0.101)	(0.090)	(0.068)	(0.043)	(0.027)
Punitive damage caps	-0.004	-0.023	0.172	0.255	0.201	-0.186	0.036
	(0.005)	(0.044)	(0.107)	(0.073)***	(0.111)*	(0.060)***	(0.021)*
Joint and several liability reforms	0.010	-0.139	-0.275	-0.203	-0.299	-0.309	-0.058
	(0.005)*	(0.038)***	(0.102)***	(0.171)	(0.089)***	(0.056)***	(0.016)***

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A7: Naloxone access provision effects by drug type

Variable	Heroin	Pain medication	Synthetic opioids	Other opioids
Provider legal immunity	0.022	0.049	-0.008	-0.036
	(0.038)	(0.026)*	(0.085)	(0.024)
Administrator legal immunity	0.041	-0.005	0.109	0.039
	(0.021)*	(0.022)	(0.071)	(0.024)
Third party prescribing	-0.026	0.002	-0.073	0.002
	(0.018)	(0.015)	(0.050)	(0.024)
Relaxed prescription requirements	-0.062	-0.034	-0.041	0.015
	(0.017)***	(0.023)	(0.039)	(0.013)
Mean weekly wage ($ 2015 thousands)	0.002	0.028	0.044	-0.003
	(0.016)	(0.032)	(0.042)	(0.019)
Employment to population ratio	0.576	-0.183	0.504	-0.243
	(0.517)	(0.182)	(0.610)	(0.290)
Population (hundreds of thousands)	0.046	-0.104	0.010	-0.127
	(0.122)	(0.056)*	(0.108)	(0.124)
White Population (%)	-3.485	-1.265	-2.586	3.138
	(3.125)	(0.997)	(1.657)	(3.389)
Mean age	-0.010	-0.009	0.002	-0.019
	(0.018)	(0.017)	(0.027)	(0.014)
Pharmacies	-0.006	-0.005	-0.010	-0.002
	(0.004)*	(0.002)***	(0.005)**	(0.002)
Hospitals	-0.132	0.008	-0.392	0.051
	(0.158)	(0.058)	(0.301)	(0.092)
Pain clinics	-0.569	2.080	-0.653	0.528
	(0.871)	(0.817)**	(1.318)	(0.675)
Police (per 1,000 residents)	0.015	-0.031	0.007	-0.011
	(0.013)	(0.018)*	(0.017)	(0.012)
EMTs (per 1,000 residents)	-0.270	0.109	-0.323	0.035
	(0.147)*	(0.186)	(0.265)	(0.086)
PDMP	0.045	-0.005	0.141	0.017
	(0.028)	(0.026)	(0.074)*	(0.008)**
Must access PDMP	0.018	0.056	0.047	0.011
	(0.013)	(0.027)**	(0.035)	(0.013)
Medical marijuana legal	0.041	0.039	0.108	0.001
	(0.021)*	(0.027)	(0.035)***	(0.023)
Recreational marijuana legal	-0.039	0.037	-0.163	0.060
	(0.033)	(0.025)	(0.056)***	(0.028)**
Noneconomic damage caps	-0.003	0.008	-0.041	0.004
	(0.022)	(0.020)	(0.048)	(0.008)
Punitive damage caps	0.039	0.040	0.030	0.016
	(0.049)	(0.014)***	(0.035)	(0.008)**
Joint and several liability reforms	-0.085	-0.055	-0.123	0.007
	(0.051)	(0.053)	(0.041)***	(0.009)

Note: N = 414,498. All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A8: Naloxone access effects by county urbanization

Variable	Rural	Suburban	Urban
Provider legal immunity	0.058	-0.066	0.115
	(0.073)	(0.072)	(0.093)
Administrator legal immunity	-0.032	0.046	0.134
	(0.085)	(0.058)	(0.056)**
Third party prescribing	-0.029	0.048	-0.052
	(0.053)	(0.045)	(0.032)
Relaxed prescription requirements	0.026	-0.022	-0.166
	(0.046)	(0.035)	(0.053)***
Mean weekly wage ($ 2015 thousands)	0.306	-0.068	-0.025
	(0.153)*	(0.095)	(0.057)
Employment to population ratio	0.612	0.628	0.205
	(0.293)**	(0.550)	(0.613)
Population (hundreds of thousands)	-0.565	-0.237	-0.104
	(1.523)	(0.163)	(0.125)
White Population (%)	1.049	-4.847	-4.562
	(2.368)	(5.903)	(1.886)**
Mean age	-0.054	-0.092	0.004
	(0.046)	(0.084)	(0.047)
Pharmacies	-0.074	0.000	-0.022
	(0.182)	(0.003)	(0.012)*
Hospitals	0.476	-0.568	-0.216
	(0.700)	(0.451)	(0.243)
Pain clinics	-11.330	-2.421	1.245
	(8.964)	(2.693)	(1.664)
Police (per 1,000 residents)	-0.000	0.000	-0.001
	(0.000)	(0.000)	(0.001)
EMTs (per 1,000 residents)	-0.001	-0.005	0.002
	(0.003)	(0.004)	(0.053)
PDMP	0.012	0.120	0.111
	(0.073)	(0.099)	(0.074)
Must access PDMP	0.031	0.072	0.165
	(0.033)	(0.037)*	(0.044)***
Medical marijuana legal	0.033	0.039	0.176
	(0.052)	(0.047)	(0.061)***
Recreational marijuana legal	-0.031	-0.108	-0.074
	(0.049)	(0.082)	(0.079)
Noneconomic damage caps	-0.035	-0.051	-0.007
	(0.035)	(0.055)	(0.040)
Punitive damage caps	0.090	0.061	0.133
	(0.045)*	(0.044)	(0.065)**
Joint and several liability reforms	-0.053	-0.154	-0.329
	(0.056)	(0.097)	(0.062)***
Observations	238,488	82,232	50,484

Note: All regressions include county and month fixed effects and county-specific linear time trends. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A9: Naloxone access effects by county pharmacy counts

Variable	All counties	Rural	Suburban	Urban
Provider legal immunity	0.005	0.043	-0.061	-0.099
	(0.069)	(0.060)	(0.073)	(0.115)
Provider legal immunity × pharmacies	0.028	0.317	-0.000	0.116
	(0.017)*	(1.032)	(0.001)	(0.048)**
Administrator legal immunity	0.100	-0.034	0.152	0.161
	(0.049)**	(0.081)	(0.065)**	(0.063)**
Administrator legal immunity × pharmacies	-0.004	0.032	-0.269	-0.005
	(0.005)	(0.931)	(0.115)**	(0.007)
Third party prescribing	-0.037	-0.012	0.019	-0.064
	(0.036)	(0.054)	(0.052)	(0.046)
Third party prescribing × pharmacies	-0.007	-0.377	0.054	-0.005
	(0.010)	(0.471)	(0.146)	(0.013)
Relaxed prescription requirements	-0.077	0.008	-0.102	-0.123
	(0.036)**	(0.048)	(0.042)**	(0.059)**
Relaxed prescription requirements × pharmacies	0.005	0.351	0.214	0.005
	(0.009)	(0.476)	(0.084)**	(0.013)
Effect in mean county:				
Provider legal immunity	0.037	0.058	-0.062	0.116
	(0.070)	(0.072)	(0.073)	(0.086)
Administrator legal immunity	0.095	-0.033	-0.047	0.151
	(0.049)*	(0.083)	(0.083)	(0.061)
Third party prescribing	-0.044	-0.031	0.058	-0.073
	(0.033)	(0.052)	(0.085)	(0.042)*
Relaxed prescription requirements	-0.071	0.025	0.056	-0.113
	(0.034)**	(0.046)	(0.049)	(0.070)*
Observations	414,498	238,488	82,232	50,484

Note: All regressions control for mean weekly wage, employment to population ratios, population levels, white population (%), mean age, number of pharmacies, hospitals, and pain clinics, police and EMTs per capita, whether a state has a PDMP or must-access PDMP, whether medical and recreational marijuana are legal, and whether the state has non-economic damage caps, punitive damage caps, and joint and several liability reform in medical malpractice cases. All regressions include county and month fixed effects and county-specific linear time trends. The effects in the mean county are calculated by adding the relevant provision coefficient to the product of the relevant interaction and the number of pharmacies in the average counties in the appropriate subsample. Standard errors in parentheses are clustered at the state level. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

CHAPTER 2: THE EFFECTIVENESS OF FDA BOXED WARNINGS: EVIDENCE FROM PRESCRIPTION OPIOIDS

I. Introduction

The United States is currently in the midst of the worst drug overdose epidemic in its history (Kolodny et al. 2015). More than 330,000 individuals in the United States have experienced a fatal opioid overdose since 1999, with 33,000 individuals dying in 2015 alone. The increasing rate of opioid overdoses has contributed significantly to the uptick in overall mortality for white Americans that researchers in the health economics literature have documented (Case and Deaton 2015, 2017). Remedying this public health crisis has become a policy priority and an intense area of scholarly and popular interest.

This chapter evaluates one of the Food and Drug Administration's ("FDA") responses to the epidemic: requirements that manufacturers of opioids place boxed warnings on their medications' drug labels. Boxed warnings (also known as "black box warnings" due to the bold black box that surrounds them on drug labels) are the FDA's strongest signal that a medication bears serious risks that a health care provider should know before prescribing it. Approximately 15% of drugs that the FDA approved between 1975 and 2009 have received one or more boxed warnings (Frank et al. 2014). In September 2013, the FDA announced that it would require a boxed waring informing providers and patients about the risks of abuse, overdose, and death from taking or misusing extended release opioid analgesics. Measuring the effect of these boxed warnings is critical, as both the FDA and other federal agencies have argued that information shocks can be effective in combatting the opioid epidemic (President's Commission on Combating Drug Addiction and the Opioid Crisis 2017). While researchers have found boxed warnings effective in other circumstances (Bradford and Kleit 2014; Parkinson et al. 2014;

Viscusi 1991), no existing research has measured the effect that opioid boxed warnings have had on prescriptions or fatal overdoses.

I use a differences-in-differences methodology to measure the effect of opioid boxed warnings. The 2013 boxed warnings directed prescribers to "assess each patient's risk," and "monitor patients regularly for the development" of addictive behaviors.[1] Such language indicates that prescribers should prescribe fewer opioids to patients who may develop abusive behaviors, such as individuals with repeat opioid prescriptions. Likewise, patients at an objectively higher risk of an opioid overdose should also receive fewer prescriptions following the boxed warnings. The warnings also explicitly identified two subgroups of patients presenting unique risks: children, who are particularly at risk of opioid poisoning due to accidental ingestion, and women who are pregnant, whose prolonged opioid use could cause neonatal opioid withdrawal symptoms. I exploit the warning's targeted language to separate my sample into treated and untreated populations. Using the 2011–2016 waves of the Medical Expenditure Panel Survey, I isolate the causal effect of the boxed warning on the treated populations by comparing the proportion of individuals with an active opioid prescription before and after the warning across the targeted and non-targeted groups.

My analyses demonstrate that the FDA's boxed warning was effective at reducing prescriptions to individuals who had previously had an opioid prescription. Individuals with a previous opioid prescription were 35.5% less likely to be prescribed an opioid after the introduction of the boxed warning. Patients who are high risk or that the warning specifically targeted had opioid prescriptions at rates that are statistically indistinguishable from patients who are low risk or not targeted before and after the introduction of the boxed warning. I also present

[1] The full text of the boxed warning is provided and discussed in Section II.

evidence that when health care providers prescribed opioids to individuals who have previously had a prescription, they prescribed 6% fewer pills per month on average.

The rest of this paper proceeds as follows. Section II provides relevant background on boxed warnings in general and the boxed warning I study here. Section III reviews the relevant academic literature. Section IV presents a brief theoretical model of health care practitioner and patient interaction that informs this empirical study. Section V presents my empirical strategy in greater detail and identifies the data sources that I utilize. Section VI presents the effect of the 2013 boxed warnings on opioid prescriptions rates as well as the average quantity of opioids that a patient receives. Section VI also presents evidence that the reduction in prescriptions is attributable to changes in both patient and provider risk perceptions. Section VII discusses the implications of my results.

II. Background

The Food, Drug, and Cosmetic Act of 1938 required that prescription drugs bear adequate warnings against dangerous uses and dosages. 21 U.S.C. §§ 301 et seq. (2018). As a result, the FDA requires drug manufacturers to create drug labels directed to healthcare professionals that include detailed information including indications and contraindications, dosage, administration instructions, as well as any risks of adverse reactions or abuse. 21 C.F.R. pts. 201, 314, 601 (2018). Manufacturers then make these practitioner-directed drug labels available to physicians, pharmacists, and other healthcare providers by renting space in the Physicians' Desk Reference and online resources. By default, prescription drug labels are not made generally available to patients, though a curious patient could find a particular drug label using resources on the Internet.[2] In circumstances where patient-directed labeling is necessary

[2] The FDA makes many prescription drug labels available on its website. For example, the label for oxycontin is available here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf (last visited Oct. 21, 2018).

for patients to safely use a drug, the FDA additionally requires that manufacturers create a non-technical label in the form of a medication guide or patient package insert.[3]

Boxed warnings are the most serious warnings that the FDA can provide on a prescription drug label, patient package insert, or medication guide. As an illustration of the final language and the prominence of boxed warnings on drug labels, Figure 1 presents the first page of the current OxyContin drug label.[4] The FDA states that it will require a boxed warning whenever (1) a drug presents a risk of a life-threatening or permanently disabling adverse reaction, (2) there is a serious adverse reaction that can be prevented or mitigated by appropriate patient selection and management, avoiding or adding concomitant therapies, or avoiding uses in certain clinical situations, or (3) the FDA has concluded that the drug can only be safely used under restricted use or distribution under 21 CFR §§ 314.520 and 601.42 (2018) (U.S. FDA 2011). The FDA's criteria for requiring boxed warnings have remained stable over time; while the FDA issued its guidance on the issue in 2011, researchers documented the same factors guiding the FDA's decision many years earlier (Beach et al. 1998). A requirement that prescription drug labels contain a boxed warning is usually paired with a requirement that a medication guide containing similar information be distributed to patients with prescriptions. For example, the FDA requirement to add a boxed warning studied here also required manufacturers to provide substantially similar but more patient-accessible language in a medication guide (U.S. FDA 2018).

[3] In particular, the FDA requires patient labeling in the form of a medication guide if (1) patient labeling could prevent serious adverse effects, (2) the drug has serious risks that a patient should be made aware of, because information concerning the risk could affect the patient's decision to use, or to continue to use, the drug, or (3) the drug is important to health and adherence to directions is critical to ensure the drug's effectiveness. 21 C.F.R. § 208.1. (2018). Patient package inserts are required for oral contraceptives and estrogens (21 C.F.R. §§ 310.501, 310.515 (2018)), and are otherwise voluntarily provided by manufacturers. The FDA must approve the language included in both medication guides and patient package inserts.

[4] The "recent change" noted below the boxed warning on the OxyContin label is the addition of the bottom-most bullet in the warning, which warns of the danger of combining benzodiazepine medications and opioids.

Because boxed warnings are the strongest information signal that the FDA can send to prescribers and patients, prescription opioids have been a natural target for such warnings as the prescription drug epidemic has developed. In September 2013, the FDA announced that it would require manufacturers of extended-release opioids to place a boxed warning on the labels of their medications. The 2013 announcement contained proposed language, which remained the same when the warnings were finalized in April 2014. The boxed warnings reflected regulators' growing concern with overdoses attributable to extended release opioid abuse. The language that the FDA required on the warnings is as follows:

> WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME.
>
> <u>Addiction, Abuse, and Misuse</u>
> [Tradename] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing [Tradename], and monitor all patients regularly for the development of these behaviors and conditions.
>
> <u>Life-threatening Respiratory Depression</u>
> Serious, life-threatening, or fatal respiratory depression may occur with use of [Tradename]. Monitor for respiratory depression, especially during initiation of [Tradename] or following a dose increase. Instruct patients to swallow [Tradename] whole; crushing, chewing, or dissolving [Tradename] can cause rapid release and absorption of a potentially fatal dose of [Tradename].
>
> <u>Accidental Exposure</u>
> Accidental consumption of even one dose of [Tradename], especially by children, can result in a fatal overdose of [Tradename].
>
> <u>Neonatal Opioid Withdrawal Syndrome</u>
> For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of [Tradename] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening and requires management according to protocols developed by neonatology experts.

(FDA 2013).[5]

The warning provides concrete, operative language that informs prescribers what the risks of opioids are and who faces those risks. The warning informs prescribers that opioid abuse can kill a patient. If this portion of the warning provided any new information to prescribers and

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[5] The warning also contained additional language not included here for products that interact with alcohol.

prescribers are able to predict which patients are relatively more or less likely to suffer a fatal overdose from a prescription opioid (alone or in combination with other opioids and medications), the warning may decrease prescriptions to riskier patients. Researchers and the Centers for Disease Control ("CDC") have developed guidelines to assist prescribers in determining the risk of opioid abuse (CDC 2018; Ciersielska et al. 2016), but it is not clear whether such tools enable prescribers to distinguish patients likely to suffer a fatality rather than those likely to abuse opioids without suffering an overdose. If doctors cannot successfully discern which patients are high risk, the boxed warning may not actually change prescribing patterns to high-risk patients.

In the same paragraph, the warning instructs prescribers to monitor patients for the development of abusive behaviors. Such a warning may encourage prescribers to scrutinize patients who have had a previous opioid prescription. Relatedly, because patients will very rarely observe the boxed warning for a drug before they have received a prescription for the drug, any effect of the warning on the preferences of patients is unlikely to manifest until after a patient has received a drug once. Prescribers may also rely on repeat use as a heuristic for overdose risk, given that current opioid use is correlated with future opioid use, (Shah, Hayes, and Margin 2017; Mierch et al. 2015) and an individual's risk of overdose is associated with length of opioid use (Sehgal et al. 2012).

Finally, the latter half of the warning explicitly identifies risks to two particular demographic groups: children and pregnant women. Children may suffer an overdose easily through accidental consumption, so prescribing such drugs to children is inadvisable. Alternatively, doctors may emphasize proper drug storage techniques to patients with a large family at the time of prescribing, in which case the boxed warning would have no effect on prescriptions to children. The warning also states that the use of opioids by pregnant women may cause neonatal opioid withdrawal syndrome,[6] and so the warning could prompt prescribers to prescribe fewer opioids to this population as well. As discussed further in Section 4, the operative language discussed here provides the basis for my empirical identification strategy.

III. Literature Review

This chapter contributes to the expanding literature evaluating policy responses to the opioid epidemic. A large part of this literature has focused on evaluating state policy responses. For example, researchers have found mixed evidence of the effects of naloxone access laws, which expand the ability of opioid users, their friends or family members, or others to access naloxone, which rapidly reverses the effect of an overdose (Doleac and Mukherjee 2018; McClellan et al. 2018; Rees et al. 2019). Other work has demonstrated that state Medicaid expansions under the Patient Protection and Affordable Care Act, Pub. L. 111-148 (2010), dramatically increased medication-assisted treatment for opioid use disorders (Meinhofer and Witman 2018). Another line of research has investigated whether medical marijuana laws decrease opioid abuse and overdoses, as marijuana is a plausible substitute for both medical and non-medical opioid use (Bradford and Bradford 2016). Such work has generally found that medical marijuana is associated with fewer opioid overdose deaths, though the results depend on how liberal or stringent regulations on dispensaries are (Powell et al. 2018).

Of particular relevance to this research, a subset of the research on state policies and opioids has focused on the effectiveness of state laws designed to reduce multiple provider episodes. Beyond users visiting multiple providers to acquire drugs for their own use, previous

[6] The most recent evidence suggests that pain medication use during pregnancy may not cause neonatal opioid withdrawal syndrome as often as the boxed warning suggests. Older evidence indicates that between 55% and 94% of neonates exposed to any opioid in utero develop withdrawal symptoms (Hudak and Tan 2012). But more recent work finds that in the absence of other risk factors, short term prescription opioid use is associated with neonatal withdrawal symptoms in 0.4% of cases, and long-term use is associated with symptoms in 2.4% of cases (Desai et al. 2015). Co-exposure to certain other substances and genetic factors also affect the risk of symptoms (Sanlorenzo et al. 2018).

research has demonstrated that sellers of illicit opioids widely visit multiple providers to acquire a supply of prescription drugs (Rigg et al. 2012). Johnson et al. (2014) found that the adoption of a prescription drug monitoring program successfully reduced multiple provider episodes in Florida between 2010 and 2012. Similarly, Dave et al. (2017) and Buchmueller and Carey (2017) found that mandatory-access prescription drug monitoring programs, which require prescribers to confirm that a patient has not received another prescription for a controlled substance before prescribing the same substance to that patient, significantly curbed drug abuse. Using administrative data on overdose deaths and opioid addiction treatment, Popovici et al. (2017) found that statutes that make it a crime for a patient to knowingly fail to inform a prescriber that the patient is receiving a drug that the prescriber is prescribing from another prescriber as well decrease opioid treatment admissions. The previous research generally demonstrates that forcing prescribers to take certain actions, or punishing patients for failing to act, can effectively curtail drug abuse. This research contributes to the existing literature by providing evidence of how prescribing patterns change with information regulation approaches rather than behavioral mandates.

Relatively fewer papers have focused on the effect of federal responses to the opioid epidemic. Johnson et al. (2018) reviewed many of those efforts to date, including rapidly accelerating the release of opioid fatality data, increasing federal funds for opioid use disorder treatment, creating guidelines for opioid prescribing, and supporting community-based prevention efforts. Evidence suggests that funding treatment and community-based efforts may be an effective method of decreasing abuse (Weiss et al. 2015). However, the empirical effects of many federal efforts remain unmeasured. The FDA in particular has taken several actions, including the boxed warnings studied here, reformatting many opioids to make them abuse-deterrent, and reevaluating whether particular products should be withdrawn from the market due to their excessive risk. Alpert et al. (2016) presents evidence that the abuse-deterrent reformulation caused users to substitute heroin for the oxycontin they formerly abused. This analysis of the effect of opioid boxed warning contributes to this literature on federal responses to the opioid epidemic, particularly given recommendations from the White House that information regulation is appropriate in the future.

Finally, this paper contributes to the literature investigating the effects of boxed warnings and information regulation broadly. Like this chapter, this literature generally identifies the effect of boxed warnings by comparing prescribing rates to groups that warnings may have affected and groups the warnings should not have affected. Bradford and Kleit (2014) find that the boxed warnings that the FDA placed on non-steroidal inflammatory drugs in 2005 decreased the prescribing of such medications to patients, but the warning caused a small number of patients to substitute to prescription opioids. Shah et al. (2017) demonstrate that boxed warnings on smoking cessation agents, which warn of adverse neuropsychiatric events, were effective at decreasing use of one, but not both, of the medications bearing the warnings. The authors reason that the newness of one medication contributes to prescribers' willingness to discontinue prescribing it, as prescribers fail to update their risk beliefs for the older medication. Parkinson et al. (2014) demonstrates that FDA boxed warnings on antidepressant medications successfully reduce prescriptions to the group the warning targets, but that the effects of the boxed warning also spill over to non-targeted groups. Finally, Viscusi (1991) demonstrated that boxed warnings substantially decreased tetracycline prescriptions to children. These evaluations are part of a broader literature on the effect of regulating health and safety risks through information disclosure. As Magat and Viscusi (1992) discussed, risk warnings tend to induce rational responses from the audience of the warning. But, in situations of information overload or where reacting to a warning requires even modest effort, recipients of warnings will often fail to react appropriately to those warnings. This paper tests whether prescribers generally appropriately apply long and detailed boxed warnings informing prescriber about different risks to different groups.

IV. Model of Practitioner-Patient Interactions

The following game-theoretic model frames how boxed warnings may affect opioid prescription levels. Consider a patient who could visit a health care practitioner with prescribing authority for a condition for which the practitioner may prescribe an opioid. The patient could be seeking treatment for an acute injury, chronic pain, or the patient could claim to have either form of pain but actually be seeking to abuse opioids. In the first stage of the game, patients choose whether or not to incur a cost x to seek care. The cost x includes any fee the patient pays to seek care as well as the inherent value that the patient places upon being examined by a health care practitioner aside from receiving any medication. I assume that $x > 0$; otherwise patients would seek care at every available opportunity.[7] If the patient visits the health care practitioner, the practitioner receives some value $y > 0$, which incorporates their share of the fee and the value they place upon examining any patient. I assume without loss of generality that if a patient chooses not to seek care, both the patient and practitioner receive no benefit (a payout of 0).

If the patient visits the practitioner, the practitioner chooses whether to prescribe an opioid to the patient, prescribe the best alternative medication,[8] or provide no medication or therapy that the patient would not have consumed without visiting the practitioner. Patients know that practitioners will choose between a menu of treatment options (including possibly prescribing no medication at all). If the practitioner prescribes the patient an opioid, the patient

[7] Patients regularly elect to not seek care as a result of prices, though medical care is a relatively inelastic good (Ellis, Martins, and Zhu 2017).
[8] Circumstances where the health care practitioner recommends consuming over-the-counter medications are within the "best alternative medication" category as long as the patient would not have consumed them without visiting the health care practitioner.

receives some benefit $v(r_p)$, where $r_p \in [0,1]$ corresponds to the patient's belief about the probability of an adverse event from taking an opioid. The function $v(r_p)$ encompasses both the benefit to the patient of receiving a prescription (regardless of whether the patient plans on using the opioid to treat acute pain, chronic pain, or for recreational or other inappropriate use) and the disutility attributable to the perceived risk of an adverse event. The practitioner receives some value $c(r_p)$ from prescribing an opioid to patients, where $c(r_p)$ encompasses both the practitioner's altruistic value from helping a suffering patient, as well as their disutility from prescribing to a patient with a perceived adverse event risk of $r_d \in [0,1]$. I assume that $\frac{d}{dr_P} v(r_p) < 0$ and $\frac{d}{dr_d} c(r_d) < 0$ so that patients value opioids less and practitioners are less likely to prescribe opioids when they each believe the risk of an adverse event is higher. Analogously, a patient receives some benefit a from the best alternative medication to an opioid, and a practitioner receives some value b from prescribing the alternative medication. Regardless of whether an opioid is prescribed or not, if the patient visits the practitioner, the practitioner receives y and the patient loses x. I make no assumption about the relative values of $v(r_P), c(r_d)$, a, and b; whether patients receive a greater benefit from opioids or alternatives and whether practitioners prefer to prescribe opioids or alternatives will vary with each individual patient and practitioner. Let $c_p(r_p)$ be the value that patients expect practitioners to receive from prescribing an opioid, which is an increasing function of the patient's own risk beliefs. Let b_p be the value that patients expect practitioners to receive from prescribing the non-opioid alternative therapy. While real patients likely do not consciously predict $c_p(r_p)$ or b_p, they likely predict what treatment a practitioner is likely to recommend, which yields implicit values of $c_p(r_p)$ or b_p. Such implicit values are sufficient for this model. Figure 2 graphically presents this model using a game tree.

The Nash equilibrium behavior of practitioners and patients under the assumptions in the preceding paragraphs can be solved using backwards induction. Practitioners will prescribe an opioid to a particular patient if they believe it will have the greatest clinical benefit to the patient ($c(r_d) > b$ and $c(r_d) > 0$). Conversely, practitioners will prescribe the alternative medication when *it* has the greatest clinical benefit ($b > c(r_d)$ and $b > 0$). The value y is irrelevant to the practitioner's decision because the practitioner receives it regardless of the treatment they choose. Patients possessing beliefs $c_p(r_p)$ and b_p will therefore expect a practitioner to prescribe an opioid when $c_p(r_p) > b_p$ and $c_p(r_p) > 0$ and will expect a practitioner to prescribe an alternative medication whenever $b_p > c_p(r_p)$ and $b_p > 0$. When $c_p(r_p) < 0$ and $b_p < 0$, patients will expect the practitioner to prescribe no medication.

Whether a patient chooses to seek care will therefore be a function of the values they place on opioids and alternative medications ($v(r_p)$ and a), their beliefs about practitioner behavior ($c_p(r_p)$ and b_p), and the cost of care x. Consider first the circumstances under which a patient will not seek care. If the value of any medication to the patient is smaller than the cost to seek care ($v(r_p) < x$ and $a < x$), such as when a patient's pain is very minor, the patient will not do so. If the perceived value of all treatments to a patient exceeds the cost of care ($v(r_p) > x$ and $a > x$) but the patient believes that the practitioner perceives all treatments as having no clinical benefit ($c_p(r_p) < 0$ and $b_p < 0$), the patient will not seek care. This possibility corresponds to patients who think the health care practitioner will perceive their condition as too trivial to provide a treatment for, though they themselves think differently. In contrast, if a patient values all possible treatments more than the cost of care ($v(r_p) > x$ and $a > x$) and believes that a practitioner will be willing to prescribe *either* medication ($c_p(r_p) > 0$ or $b_p > 0$) they will seek care. Patients who seek care without a clear idea of what treatment they want (likely most patients) but are confident that the practitioner will provide some treatment more valuable than the cost of care fit into this latter category.

Next, consider a patient who values an opioid more than the cost of care but not an alternative medication ($v(r_p) > x$ but $a < x$). Such individuals may seek opioids for recreational or other misuse or may be patients for whom other treatments have proven ineffective. If such patients expect the practitioner to be unwilling to prescribe an opioid ($c_p(r_p) < 0$) or if they believe the practitioner will prefer to prescribe the alternative therapy ($b_p > c_p(r_p)$), they will not seek care. Finally, if such patients expect the practitioner to be willing to prescribe an opioid *and* prefer an opioid to available alternatives ($c_p(r_p) > 0$ and $c_p(r_p) > b_p$), they will seek care. For patients who value alternative treatments more than the cost of care but *not* an opioid, the results are symmetric. Such patients believe that opioids are too risky (or perhaps insufficiently effective) to be worth receiving but that alternative therapies *are* worth seeking.

Boxed warnings will affect the probability that a patient receives a prescription by affecting r_d, r_p, both r_d and r_p, or neither.[9] Let r_p^{BW} and r_d^{BW} be the patient and practitioner's beliefs about the risks of opioids following the introduction of the boxed warning. The effect of boxed warnings that do not influence anyone's risk beliefs is trivial—prescription levels remain unchanged relative to the original Nash equilibrium. Consider the scenario where a boxed warning increases only a practitioners' risk beliefs, so that $r_d^{BW} > r_d$. This scenario is particularly plausible given that boxed warnings are primarily directed to prescribers. Patients will generally only learn about a boxed warning *after* they have received a prescription in the medication guide or patient package insert, though a particularly diligent patient could research

[9] The analysis that follows assumes that boxed warnings increase the perceived risk of opioids. A boxed warning that *decreases* perceived risks causes prescription level *increases* analogous to the decreases explored here.

boxed warnings for all potential drugs that they may receive before seeking care. If $r_d^{BW} > r_d$, the clinical benefit of prescribing an opioid is smaller ($c(r_d^{BW}) < c(r_d)$) and the probability of a prescription, conditional on the patient visiting the practitioner at all, is lower. If $c(r_d) > b > c(r_d^{BW})$ and $b > 0$, practitioners will substitute from prescribing opioids to alternative medications. If $c(r_d) > 0 > c(r_d^{BW})$ and $b < 0$, practitioners will instead prescribe no medication following the boxed warning. Because r_P remains unchanged, patients will continue to seek care at the same rate. As a result, the probability of patients seeking care but receiving no prescription remains unchanged. If such patients are seeking an opioid for misuse, it is possible that multiple prescriber episodes may increase as such patients repeatedly seek out a practitioner willing to prescribe opioids. Eventually, such patients are likely to learn that practitioners risk beliefs have shifted and will reach an equilibrium level of prescription seeking, though the evolution of such beliefs are outside the scope of the model presented here.

Next, consider the scenario where boxed warnings increase patient beliefs but not practitioners' beliefs. This could occur if practitioners are already well-informed about the risks of opioids before the boxed warning, but patients are not. Patients could be exposed to the warning after they receive their first prescription and alter their risk beliefs when considering whether to seek a second prescription.[10] Because $r_p^{BW} > r_p$, $\frac{d}{dr_p} v(r_p) > 0$, and $\frac{d}{dr_p} c_p(r_p) > 0$, the value of an opioid to patients is smaller $\left(v(r_p^{BW}) < v(r_p)\right)$ and the patients' beliefs about the practitioners' perception of the benefit of an opioid is smaller $\left(c_P(r_p^{BW}) < c_p(r_p)\right)$. Given the Nash equilibrium behavior discussed above, patient behavior will change in response to the boxed warning only if $v(r_p) > x > v(r_p^{BW})$, $c_p(r_p) > 0 > c_p(r_p^{BW})$, or $c_p(r_p) > b_p >$

[10] Of course, patients could also learn about how addictive or risky a drug is after taking it without the boxed warning. However, Badger et al. (2007) suggests that even experienced opioid users are very bad at predicting the strength of future cravings.

$c_p(r_p^{BW})$; in other words, if the change in risk beliefs causes either the value of opioids to the patient or the perceived value to the practitioner of prescribing opioids to cross a threshold value. Patients with $v(r_p) > x > v(r_p^{BW})$ and $a < x$ will no longer seek care. Patients with $v(r_p) > x > v(r_p^{BW})$ and $a > x$ will only seek care if $b_p > 0$ and $c_p(r_p^{BW}) > b_p$. If $c_p(r_p) > 0 > c_p(r_P^{BW})$ and $b_p < 0$, or $c_p(r_p) > b_p > c_p(r_P^{BW})$, patients who are only willing to seek care if they believe they will receive an opioid ($v(r_p^{BW}) > x$ and $a < x$) will no longer seek care. In sum, patients will be less likely to seek care at all. When they do seek care, they will expect to receive alternative medications more often. However, practitioner behavior will remain unchanged. The total proportion of patients receiving opioids should fall. Finally, if boxed warnings increase the risk beliefs of both practitioners and patients, the effect of boxed warnings will be a combination of both of the above scenarios. Practitioners perceive a smaller clinical benefit of opioids and will be less likely to prescribe them to any patient that visits their office. Patients value opioids less and expect practitioners to value prescribing opioids less, so patients are less likely to visit the practitioner's office at all. The net impact will be fewer opioids in the population overall as well as fewer visits to the practitioner's office.

The model thus provides two critical insights. First, warnings will only affect observed opioid prescriptions if they affect either the risk beliefs of practitioners, patients, or both. If boxed warnings increase the perceived riskiness of prescribing opioids to certain groups of patients, then practitioners will be less likely to prescribe opioids to such patients, more likely to prescribe substitute medications, and more likely to prescribe nothing. Second, if warnings increase or decrease the risk beliefs of prescribers alone, patients will seek care at the same rate. If the game is considered dynamically, it is even possible that individuals could seek *more* care, as they search for a practitioner willing to provide beneficial treatment when patient and practitioner beliefs sufficiently diverge. But if boxed warnings increase the risk beliefs of patients, individuals should seek care less often. Testing whether patients seek care less often provides a way to determine whether boxed warnings affected patients' risk beliefs independently from prescribers' risk beliefs.

V. Identification Strategy and Data Sources

A. Empirical Methodology

I identify the causal effect of the FDA's boxed warnings on opioid prescriptions using a differences-in-differences methodology. My empirical specification estimates the following equation using ordinary least squares[11] where i indexes individuals and t indexes time:

$$Opioid\ Rx_{it} = \alpha + \beta_1 D_i + \beta_2 D_i Boxed\ Warning_t + X_{it}\beta + \theta_i + \delta_t + e_{it}. \quad (1)$$

The dependent variable $Opioid\ Rx_{it}$ is a binary variable equal to one if the individual i was prescribed an opioid at time t. The variable D_i is my main differencing variable, where D_i is equal to one if individual i is a member of the treated group of interest. The variable $Boxed\ Warning_t$ is an indicator variable equal to one if the time period is after September of 2013, the date the FDA announced the boxed warning changes.[12] The variables X_{it} are characteristics of the individual i that vary over time. These include age, marital status, family size, wage income, health insurance status, self-rated propensity to take risks, self-reported health status, census region, and education. The final terms, θ_i and δ_t, are individual and month-by-year fixed effects. After estimating whether boxed warnings affected opioid prescriptions, I also estimate alternative models where the dependent variables are the quantity of opioids

[11] I utilize the reghdfe Stata package to perform the ordinary least squares estimation, as it is dramatically faster than the default package in Stata (Correia 2017).
[12] Alternatively, I could utilize April 2014 as the trigger date for the boxed warning as this is when the requirements were finalized. However, because the language on the warnings remained the same and because media coverage of the warnings began in September 2013, I use the earlier date. My main results are robust to using either date.

supplied to an individual, the number of annual visits to a health care provider's office, and an indicator variable for whether a patient received a non-opioid pain medication.

The coefficient β_2 is the differences-in-differences causal estimate of the effect of boxed warnings on the treated population. The critical assumption for identification of the causal effect is that opioid prescribing rates would have evolved in a parallel fashion for the treated and untreated groups but-for the introduction of the opioid boxed warning.[13] If the boxed warning has any effect on the untreated groups, then the differences-in-differences estimator will only provide the effect on the treated group over the untreated group. If such effects exist, my estimates will be a lower bound on the actual effect of the boxed warnings. In most of my models, I include individual level time trends to relax the conditions under which the models will provide the true causal effect of boxed warnings. Mora and Reggio (2018) demonstrate that the inclusion of individual-level linear time trends significantly relaxes the assumption necessary for differences-in-differences to identify a causal effect. Instead of requiring parallel trends for the treated and untreated groups, including individual time trends yields the causal effect of a treatment if the treated and untreated group's trends are parallel or are evolving at a parallel rate. In each model, my standard errors are robust and clustered on the individual to account for serial autocorrelation of standard errors within multiple observations of the same person (Cameron and Miller 2015).

Based on the language of the boxed warning discussed in Section III, I analyze the following treated groups: (1) patients with a previous opioid prescription, (2) patients with higher opioid overdose fatality risks, and (3) patients who are children or pregnant.[14] Patients with a

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[13] Figures 3, 4, and 5, discussed in detail with my main results, explicitly test the parallel trends assumption using event study regressions. The figures indicate that the parallel trends assumption is met in my models controlling for individual time trends.

[14] As a robustness check, I also run each of the models classifying women who are married and between the ages of 20 and 40 as treated, as in Gruber (1994). The results of the pregnancy alone and specifically targeted model continue to show no statistically significant impact of the boxed warnings. I also run each of the models classifying

previous opioid prescription and those with objectively higher risks of opioid fatalities based on observable demographic characteristics are prime targets for prescribers that adhere to the boxed warning's command to assess each patient's risk and monitor for the development of abusive behaviors. If doctors are unwilling to change prescriptions that seem to be working for patients following new warnings, the estimates could reveal no effect on repeat users. Similarly, if doctors cannot discern patient-level risk on the basis of observable demographic characteristics (or characteristics that correlate with demographics but are not observable in the data), then the warning may have no effect on prescriptions to riskier users. The warning states that children can easily accidentally overdose; it is therefore possible that the boxed warning will affect prescription rates for children. Alternatively, physicians may encourage patients to store medications in a safe location in an effort to reduce the risk of accidental consumption. Finally, the warning on neonatal opioid withdrawal syndrome should only affect prescribers' propensity to prescribe opioids to pregnant women. I pool children and pregnant women into one large "specifically targeted" group for two distinct reasons. First, an effect for any of the groups requires prescribers to respond to explicit commands that the warnings direct toward clearly identifiable populations. Pooling the two groups makes sense because the warnings about each group test involve similar kinds of information. Second, and more mechanically, a very small portion of my sample is actually pregnant at any time. To avoid identifying an effect from small samples I pool both specifically treated groups.[15]

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individuals in the upper quartile of family size as treated or using a continuous measure of family size and found no effect of the boxed warning on this subpopulation.

[15] In the Appendix, I present the results without pooling the two groups and find results which are generally consistent with the pooled results.

B. Data Sources and Sample Characteristics

My primary data source in this chapter is the Medical Expenditure Panel Survey ("MEPS"). The MEPS is a set of large surveys of individuals and medical providers that collects data on the utilization of health services for the United States' non-institutionalized population. The survey has an overlapping design; each household is surveyed five times over two years. New households enter the survey each year so that each year's data contain responses from the new panel as well as the exiting panel. The months that each round of the survey covers differ from household to household. To facilitate comparisons across individuals, I transform the data so that observations are at the person-month level. Doing so prevents the duration of a round for a particular observation from affecting my estimates. I utilize data from the 2011–2016 waves in this chapter. My sample includes roughly 2,000,000 person-months from approximately 85,000 different individuals.

I use the prescribed medicines component of the MEPS to construct my primary dependent variables. The prescribed medicine file includes the prescription drugs that the respondent consumed during the survey period. Prescription drug records are collected from pharmacies following written release of records by a survey respondent. The data indicate what drugs (if any) the patient received, the Multum classification of the drugs,[16] how many days of medication the patient received for each drug, the prices paid for the drugs, whether it was the patient's first time taking the drugs, and if not, when the respondent first took the drugs. From these responses I identify whether a respondent took any opioid during the response period.

[16] Multum codes provide a taxonomy of all drugs. The Multum classification system has three levels, with each level providing greater specificity. The codes corresponding to opioid analgesics are 57-58-60 (narcotic analgesics) and 57-58-191 (narcotic analgesic combinations).

Additionally, for all individuals in my sample who use an opioid at any time, I identify whether they have previously received a prescription for the same opioid at any time.[17]

I combine data from MEPS prescribed medicine files with data from the MEPS household component files. The household component of the MEPS collects detailed information on demographic characteristics and medical expenditures. Demographic variables that I draw from the survey include sex, race, marital status, family size, pregnancy status, hourly wage, whether the individual possesses prescription drug insurance, age, education, census region, whether the individual considers themselves more likely to take risks than the average person (on a five-point Likert scale), and self-reported health status (also on a five-point Likert scale).[18]

Because the MEPS do not provide state identifiers for individuals, I cannot control for the state that an individual lives in or any relevant state policies that may affect my results. If omitted state policies were implemented after the introduction of the boxed warning, it could bias my results, attributing the effect of those omitted state laws to the boxed warning. Prescription drug monitoring programs, for example, likely decreased the probability of repeat users receiving opioids, while pain management clinic laws likely decreased the probability of anyone receiving a first or repeat prescription. But it is unlikely that omitted state policies drive the results I present. First, individual-level time trends would absorb some of the effect of such statutes. But more importantly, few states implemented monitoring programs or pain clinic regulations coincident with the introduction of the boxed warnings. By the beginning of 2013, every state but Missouri (and D.C.) had a prescription drug monitoring program; from 2013 to

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[17] The fact that I only observe previous prescriptions for individuals who take an opioid while I observe them does not endanger my estimates of the effect of boxed warnings on individuals who have a previous prescription. Because I include individual fixed effects in all of my empirical models, only individuals who switch from not having a previous prescription to having a previous prescription during the period I observe them would provide identifying variation for the model. Necessarily, such individuals will have an opioid while in my data, and no selection bias exists.

[18] In my analyses, I treat both five-point Likert scale variables as five individual indicator variables equal to 1 if a respondent provided a particular response and zero otherwise.

2016, only three states (Alabama, Georgia, and Wisconsin) adopted statutes meant to regulate pain management clinics (Prescription Drug Abuse Policy System 2018).

Finally, I augment the MEPS data with an individual level measure of objective opioid overdose risk constructed using the National Vital Statistic System's ("NVSS") multiple cause of death data files, the Current Population Survey, and Census population counts. The detailed process used to construct the individual fatality risk is presented in the Technical Appendix. Table 1 presents summary statistics for each of the variables that I utilize in my analysis.[19]

C. Personal Characteristics and Opioid Prescriptions

Before investigating the causal effect of boxed warnings on opioid prescriptions, it is informative to generally investigate the relationship between opioid prescriptions and the various demographic characteristics that are included in my data. As discussed in Section 3.1, my difference-in-differences estimation strategy controls for time-invariant individual characteristics using fixed effects, so the correlations between time-invariant personal characteristics and opioid prescriptions are not apparent in those regressions.

Table 2 presents the results of regressing opioid prescriptions on the individual characteristics presented in Table 1. The dependent variable in Table 2 is a binary variable equal to one if a respondent had an opioid prescription in the period of interest. In the first column, I present a basic model with no fixed effects. The second column adds monthly fixed effects to control for time-trends common across all individuals, including season effects and nationwide trends. The third column adds individual-level fixed effects to the previous models. The fourth and final column augments the model with individual-level time trends to control for any individual changes in propensity to consume opioids that change uniformly over time. While

[19] These summary statistics and all regressions are weighted using the MEPS' longitudinal weights so as to create a nationally representative sample.

many of the estimates in columns one and two are statistically significant (in the sense that they demonstrate a sufficiently strong relationship between opioid use and the relevant characteristic that the characteristic can be used to predict opioid use), most estimates lose their significance once individual time trends are included in the model. Statistical significance in the latter columns is more indicative of a causal relationship between individual characteristics and opioid use, while columns one and two demonstrate correlations that are useful for exploring who tends to use opioids. As discussed below, while many of the variables I study are associated with opioid use, only income, prescription drug insurance, age, and health appear causally related to the probability of having an opioid prescription.

The first two columns demonstrate that various demographic characteristics are significantly correlated with opioid prescriptions. Men are 1.3 percentage points less likely to receive an opioid prescription, while individuals who are white are 1.3 percentage points more likely to receive an opioid prescription, consistent with prior research (Janakiram et al. 2018). Married individuals are 0.8 percentage points less likely to have a prescription. Opioid use is decreasing in weekly wages until weekly wages reach roughly $2,000, at which point there is a positive correlation between wages and opioid use. At least for weekly wages below $2,000, this is consistent with previous research on the relationship between macroeconomic conditions and opioid use (Carpenter, McClellan, and Rees 2017; Hollingsworth, Ruhm, and Simon 2017). Consistent with medication consumption generally (Borrescio-Higa 2015), and opioids in particular (Olmstead et al. 2015), being sensitive to price, individuals with prescription drug insurance are more likely to receive an opioid prescription. Older individuals are more likely to receive an opioid prescription. The age coefficients increase monotonically, with individuals who are 14 years or younger being 6.6 percentage points less likely to receive a prescription than those who are 65 or older. Education has a non-monotonic association with prescriptions;

individuals who have less than a high school education or have a bachelor's degree or higher are (relative to those with a high school education) less likely to receive an opioid prescription. Relative to people who live in the Northeast census region, individuals in the South, Midwest, and West are 1.5, 2.1, and 0.1 percentage points more likely to receive an opioid prescription. Individuals who strongly disagree that they are riskier than the average person are half a percentage point more likely to receive an opioid prescription than others. This observation is consistent with Bretteville-Jensen (1999), who found that heroin users have a higher intertemporal discount rate (and implicitly are more risk averse), but in tension with Blondel, Lohéac, and Rinaudo (2007), which experimentally demonstrated that drug users exhibit risk-seeking preferences. Finally, healthier individuals are universally less likely to be prescribed opioids; those who rated their own health as excellent are thirty percentage points less likely than individuals who rate their own health as poor to be prescribed opioids, all else equal.

However, the correlations presented in the first two columns of Table 2 should be interpreted with caution. While including time fixed effects has little effect on the coefficients or the explanatory power of the model (the R^2 increases by only 0.01), most of the time variant characteristics discussed above are not statistically significant after individual fixed effects and individual time-trends are included in the model. Wage remains statistically significant and while the coefficients are smaller in magnitude, the implied inflection point remains at $2,000. Prescription drug insurance remains significant and constant. The relationship between age and opioid use becomes convoluted, indicating that non-age characteristics that vary over time explain the significance of age in the less-identified models. The full model actually indicates that individuals who are between 45 and 64 years old may be less likely to have an opioid prescription after individual time trends are accounted for. Finally, self-rated health status remains highly significant. Because pain is a very salient feature in one's own health, the health status effect is likely being driven by individuals who incur an injury or other painful condition. Most of the variables have stable magnitudes across the model, though the coefficients corresponding to poor health in the models including individual fixed effects and time trends are substantially smaller. After controlling for individual fixed effects and time trends, individuals with excellent health are only eight percentage points less likely to consume opioids than individuals who rate their own health as poor.

VI. The Effect of Opioid Boxed Warnings

A. Opioid Prescriptions

Table 3 presents the results of estimating equation 1 on my sample. For brevity, Table 3 only includes the coefficients of interest for each model.[20] The first column provides the base model estimates, where the regression includes only the identifying variable, its interaction with a variable indicating the boxed warning requirement is in place, and individual and month-by-year fixed effects. The second model is a covariate model which augments the base model by including each covariate from Table 2.[21] Finally, the third column provides a full model which includes individual-level time trends. Because including individual time trends substantially relaxes the assumptions necessary for causal inference in the model, the full model provides my preferred estimates of the effect of the 2013 boxed warnings. To provide evidence that the parallel trends assumption is satisfied in the full model, I also graphically present an event study using the full model results in Figures 3, 4, and 5. Figure 3 corresponds to the previous opioid user model, Figure 4 presents the effect of the boxed warning on relatively more risky users, and Figure 5 presents the results for groups that the warning specifically targeted. For all three

[20] Full results for each model are provided in the Appendix.
[21] Because individual level fatality risk from opioids is a linear combination of other variables in the model, the fatality risk regression omits the time-variant individual characteristics used to predict risk (marital status, region, and age variables) from the covariate and full models.

groups, the coefficients associated with the pre-warning period are statistically insignificant and do not exhibit a trend that threatens the validity of my difference-in-differences estimates.

The results in Table 3 and Figures 3, 4, and 5 demonstrate that boxed warnings only reduced prescriptions to individuals with a previous opioid prescription. In contrast, the warnings did not reduce prescriptions to individuals who are at objectively higher risk or to the specifically targeted groups. The only group that exhibits a consistently statistically significant effect of boxed warnings is individuals with a previous opioid prescription. The point estimate is extremely stable across models; the full model estimate indicates that the 2013 boxed warning decreased the probability than an individual who previously had an opioid prescription received a prescription by 17.1 percentage points. The 17.1 percentage point estimate corresponds to a 35.5% decrease in the mean probability that an individual with a previous opioid prescription receives another relative to the pre-boxed warning mean. The 35.5% decrease for the repeat user subpopulation implies a 20.2% decrease for the entire population. As illustrated in Figure 3, the effect of the law developed over time, as expected given that the information contained in the warnings needed to spread to prescribers. This delayed effect is consistent with previous research on the effect of boxed warnings (Viscusi 1991). Given that recent research has demonstrated that individuals who have previously used opioids are significantly more likely to abuse them in the future (Mierch et al. 2015; Shah et al. 2017), it makes sense that the boxed warnings prompted prescribers to provide fewer opioids to individuals that have previously had an opioid.

However, the boxed warnings did not have a statistically significant impact on prescriptions for riskier users or targeted groups. While Figure 5 shows that some of the post effects are individually distinguishable from zero for the specifically targeted group, the overall effect is not. Moreover, the point estimates for both riskier users and targeted groups is very small relative to the estimates for previous users. Two explanations present themselves for why the difference-in-differences estimates do not find an effect based on fatality risk. Prescribers may be unable to characterize their patients as more or less likely to fatally abuse opioids based on characteristics like sex, race, age, or where they live, or underlying risky behaviors that correlate with such demographic characteristics. Or more simply, demographic characteristics may not provide sufficient explanatory power to predict opioid fatalities, such that my measure of opioid risk suffers from too much measurement error, attenuating my estimates of the effect of boxed warnings on high-risk individuals.

Likewise, the lack of result for the specifically targeted categories is striking. The result is in contrast with previous boxed warning studies finding an effect of boxed warnings when the warning explicitly identifies a targeted group (Bradford and Kleit 2014; Parkinson et al. 2012). One explanation (that is untestable here) is that the boxed warning caused prescribers to warn patients about the risk of accidental ingestion of opioids by children but did not alter their prescribing patterns. Such a reaction would meaningfully change prescriber behavior but not in a way that the MEPS data can reveal. Another untestable possibility about why the warnings did not reduce prescriptions to pregnant women is that before the warning, many prescribers thought it was categorically unsafe to prescribe opioids to pregnant women, leading those prescribers to interpret the warnings to say that prescriptions to pregnant women are safe under some circumstances. Finally, it may be that prescribers and patients are generally attuned to the risks of drugs to children and pregnant women, such that identifying a risk to *these* particular groups actually has no effect on individual risk beliefs.

B. Prescription Length

As further evidence of the effect of boxed warnings on prescribing behavior, Table 4 presents difference-in-differences estimates of the effect of the boxed warnings on the supply of opioids prescribed to individuals, measured in days.[22] As with Table 3, Table 4 only contains the coefficients of interest from each regression.[23] While the results of Table 3 demonstrate that fewer individuals are received prescriptions generally, Table 4 provides evidence about whether prescription length is changing even for patients who prescribers deem sufficiently safe to receive a prescription. Table 4 also serves as a robustness check for the results in Table 3.

Table 4 provides evidence that individuals with a previous opioid prescription received statistically significantly shorter prescriptions after the FDA's boxed warning requirement. The base and covariate model in the first and second columns find that individuals with a previous prescription received one day's supply fewer pills per month. However, the effect is statistically insignificant in the full model, suggesting that the effect in the base and covariate model is driven by a general trend to prescribe fewer opioids to repeat users separate from the effect of the boxed warning. On the whole, the results in Table 3 and 4 provide strong evidence that the 2013 boxed warning decreased the prescribing of opioids to individuals with a previous opioid prescription. The model also finds a statistically significant ($p < 0.10$) decrease in days supplied for individuals in the targeted group in the base model, and an *increase* in days supplied in the full model ($p > 0.10$). The divergent results between the two models and the lack of corroboration of an effect on specifically targeted groups in the other tables indicate that this result is likely error rather than finding a true effect.

C. Annual Health Care Appointments

The previous sections have demonstrated that opioid boxed warnings decreased the opioids that individuals with a previous prescription consumed. However, the tests above have

[22] I use days of prescription because it ensures that different drugs at different strengths are measured consistently. Individuals who did not have an active opioids prescription are coded as a 0.
[23] Full results for each model are presented in the Appendix.

not resolved whether the reduction in consumption occurred because boxed warnings made users believe opioids were riskier, thereby reducing demand for opioids at any price, or made prescribers believe opioids were riskier, thereby decreasing the available supply of opioids for any user. The model in Section IV demonstrates that if users' risk beliefs are driving the decrease in opioid prescriptions, we would expect individuals to seek care less often. Conversely, if office visits remain constant it would indicate that patient risk beliefs remain unchanged, but prescribers provided fewer prescriptions even as patients continued to seek them. It could even be possible for appointments to increase while prescriptions decreased, if patients who could not get a prescription from a first prescriber visit others until they receive a prescription.

Table 5 presents my difference-in-differences estimates of the effect of boxed warnings on the number of annual visits to health care providers' offices.[24] As in my previous tables, the first column presents a base model, while the second column presents the difference-in-differences estimates for the effect of boxed warnings on the indicated group. Because the MEPS data only ask respondents about their *annual* visits, the data contain only two observations per individual and it is impossible to control for individual time trends. As Tables 3 and 4 demonstrate, individual time trends control for time-invariant characteristics that increase the likelihood that I am identifying the causal effect of boxed warnings. As a result, the estimates in Table 5 should be considered suggestive of the effect of boxed warning but are weaker evidence than the full model estimates in Table 3 and Table 4.

The analysis presented in Table 5 provides some evidence that patients had fewer appointments per year following the introduction of the opioid boxed warning. In the previous prescription model, I estimate that individuals with a previous prescription had 0.3 fewer annual visits on average, a decrease of approximately 15% relative to the mean. The decrease is

[24] As with Tables 3 and 4, only the coefficients of interest are presented. The tables in the present the full results.

consistent with the boxed warning increasing patients' perceived risk of opioids or their perception of prescribers' risk beliefs, thereby decreasing multiple provider episodes. The estimated coefficients for the fatality risk and specifically targeted models are small and statistically insignificant. Because I cannot control for individual time trends, it is impossible to know whether the identified effects would persist after doing so.

D. Substitution to Other Pain Medications

The evidence discussed above demonstrate that opioid prescriptions to individuals with a previous prescription decreased because of the boxed warning but do not identify whether prescribers substituted to writing prescriptions for other pain medications. Such substitution is critical to determining whether the boxed warnings provided an aggregate social benefit. Repeat opioid users clearly gain some benefit from using the medication and lose that benefit when they stop receiving a prescription unless they substitute to an alternative product or therapy or adequately taper off the medication so that it is not necessary. In the case of individuals who are using opioids to treat pain, substitution to non-opioid prescription pain medications would substantially mitigate the welfare loss to such individuals. Research has demonstrated that some combinations of non-opioid pain medication drugs are more effective than opioids at treating acute pain (Holdgate 2004; Moore and Hersh 2013).

Table 6 estimates the effect of opioid boxed warnings on non-opioid pain medication prescriptions. The estimating equation behind Table 6 is identical to equation 1, but I use non-opioid pain prescriptions as the dependent variable rather than opioid prescriptions.[25] The results from Table 6 provide weak evidence that boxed warnings increased prescriptions of non-opioid

[25] Data on non-opioid prescription consumption are also from the MEPS. The Multum codes associates with non-opioid pain medications are as follows: 57-58-59 (miscellaneous analgesics), 57-58-61 (non-steroidal anti-inflammatory agents), 57-58-62 (salicylates), 57-58-63 (analgesic combinations), 57-58-193 (antimigraine combinations), and 57-58-278 (cox-2 inhibitors). Some medications have multiple Multum codes that include both opioid and non-opioid combinations; in such cases I classify opioid and non-opioid combination drugs as opioids.

pain medications by 0.9 percentage points to individuals who previously had an opioid prescription. While 0.9 appears small relative to the magnitudes of the opioid prescription decreases observed in Table 3, it is nearly a 20% increase in non-opioid pain medication prescriptions. The effects are small and only significant at the ten percent level in the base and full models, but the estimated coefficients are remarkably stable across the three models. Substitution may not have been necessary for many patients if they tapered use such that an alternative medication was not necessary following the boxed warning. Of course, my data make it impossible to identify whether repeat opioid prescription users switched to illicit opioid sources or physical therapy or some other non-pharmaceutical pain therapy.

VII. Discussion

My results indicate that the FDA's boxed warnings decreased the quantity of opioids prescribed to individuals that had a previous opioid prescription but not to other groups that the warnings targeted. Boxed warnings decreased the probability of a prescription for repeat users and may have marginally decreased the quantity of pills such users received. The boxed warning also caused a 20% increase in non-opioid prescription pain medication use as previous opioid users substituted to other pain medications. These results indicate that the boxed warning generally benefited such users, as many individuals who still needed medication for pain following the introduction of the warning received it. My results indicate that at least some of the change in prescribing was due to patients' increased perceptions regarding the riskiness of opioids, though the results would also be consistent with decreasing multiple provider episodes in response to an increased perception of risk among prescribers.

The results provide evidence that repeat users of prescription medications that they acquire through legitimate medical channels are a population at relatively *lower* risk of fatal overdose. If that were not the case, the results for repeat users and individuals at a relatively higher risk of opioid overdose would have been consistent. These results therefore add to the evidence that illicit opioid use now drives the fatal overdose epidemic, rather than prescription opioids. Illicit opioids are a diverse set of drugs, containing both illegally obtained and counterfeit prescriptions as well as heroin and compounds containing fentanyl. To the extent that the primary goal of opioid policy is to reduce opioid fatalities, regulatory responses must aim to reduce the use of such illicit opioids in addition to decreasing prescriptions. However, it does not follow that the boxed warnings studied here were a failure. Reducing the use of an addictive substance when patients can (and do) substitute to alternative medications or non-pharmaceutical interventions is beneficial on its own.

Additionally, these results demonstrate that information-based efforts to reduce opioid use may be modestly successful. Beyond the boxed warnings studied here, the FDA required boxed warnings be placed on immediate release opioids in late 2016, and those warnings are substantially similar to those studied here (U.S. FDA 2016). Though there are some differences in language between the two warnings, prescribers may react to both warnings similarly and decrease prescriptions of immediate release opioids further. However, if the warnings studied in this paper had a large spillover effect, such a response may have occurred before the warnings were even implemented. Additional efforts to reduce opioid use through warnings and public information campaigns may be successful, though they may be unlikely to curtail use among the most dangerous users.

My results also indicate that the FDA (and regulators generally) should expect prescribers and patients to respond to warnings about the risks of opioids in a boundedly rational way. Prescribers apparently use previous opioid prescriptions as a shortcut to determine whether a patient is at greater risk from taking opioids. Previous research has demonstrated similar heuristic-based decisionmaking on the part of prescribers (Marewski and Gigerenzer 2012). As a result, regulators that incorporate boundedly rational responses into policy are more likely to achieve optimal outcomes (Sunstein 1997; Jolls et al. 1998; Cooper and Kovacic 2012). Regulators must appropriately calibrate warnings knowing that prescribers will take shortcuts and that patients are probably not self-assessing their own risk in light of the warning.

VIII. Conclusion

This paper has demonstrated that the FDA's 2013 requirement that manufacturers place a boxed warning on extended release opioids was generally successful at reducing repeat opioid prescriptions. Using difference-in-differences regression models, I find that the providers prescribed opioids to previous opioid users 35.5% less often, and with 1 day fewer opioids, following the boxed warning. Prescribers did not alter their opioid prescribing behavior to individuals at a higher fatal overdose risk or to those who were specifically targeted by the warning on the basis of their demographics, despite language in the boxed warning that should have caused fewer prescriptions to these groups.

The evidence I present here suggests that future boxed warnings from the FDA could have more success if they are more explicit about the groups to whom prescribers should provide fewer prescriptions. Prescribers responded to the boxed warning in this case by utilizing a clear heuristic (previous prescriptions) in the absence of clear standards to evaluate patient riskiness. Clear factors about how to evaluate patients may result in warnings that reduce the occurrence of extreme adverse events, though there is a persistent risk that prescribers may not incorporate a long list of risks into their prescribing behavior even when the instructions are as clear as possible. More pertinent to the ongoing opioid epidemic, the results demonstrate that the boxed warnings and similar information-providing policies can be of substantial utility in decreasing the use of risky prescription pain medications. Even if such policies cannot stem fatal overdoses, decreasing the use of opioids by repeat users has substantial private and social benefits.

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Figures

Figure 1: Current OxyContin boxed warning

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OXYCONTIN® safely and effectively. See full prescribing information for OXYCONTIN.

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS
***See full prescribing information for complete boxed warning*.**

- **OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.2)**
- **Accidental ingestion of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone. (5.2)**
- **Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.4, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.5, 7)**

----------------------------RECENT MAJOR CHANGES--------------------------

Box Warning	12/2016
Warnings and Precautions (5)	12/2016

---------------------------INDICATIONS AND USAGE---------------------------
OXYCONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use
- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

----------------------DOSAGE AND ADMINISTRATION-----------------------
- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow tablets intact and not to cut, break, chew, crush, or dissolve tablets (risk of potentially fatal dose). (2.1, 5.1)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in mouth. (2.1, 5.10)
- Do not abruptly discontinue OXYCONTIN in a physically dependent patient. (2.9)

Adults: For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.2, 2.3, 2.5)
Pediatric Patients 11 Years of Age and Older
- For use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OXYCONTIN. (2.4)
- See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.4, 2.5)

Geriatric Patients: In debilitated, opioid non-tolerant geriatric patients, initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.7, 8.5)
Patients with Hepatic Impairment: Initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.8, 8.6)

---------------------DOSAGE FORMS AND STRENGTHS---------------------
Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. (3)

------------------------------CONTRAINDICATIONS-----------------------------
- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

-----------------------WARNINGS AND PRECAUTIONS------------------------
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OXYCONTIN in patients with circulatory shock. (5.8)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OXYCONTIN in patients with impaired consciousness or coma. (5.9)
- Risk of Obstruction in Patients who have Difficulty Swallowing or have Underlying GI Disorders that may Predispose them to Obstruction: Consider use of an alternative analgesic. (5.10)

------------------------------ADVERSE REACTIONS------------------------------
Most common adverse reactions (incidence >5%) were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

------------------------------DRUG INTERACTIONS------------------------------
- CNS Depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If co-administration is required and the decision to begin OXYCONTIN is made, start with 1/3 to 1/2 the recommended starting dosage, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.6, 5.5, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OXYCONTIN if serotonin syndrome is suspected. (7)

Reference ID: 4028307

Figure 2: Game tree for patient-provider interaction

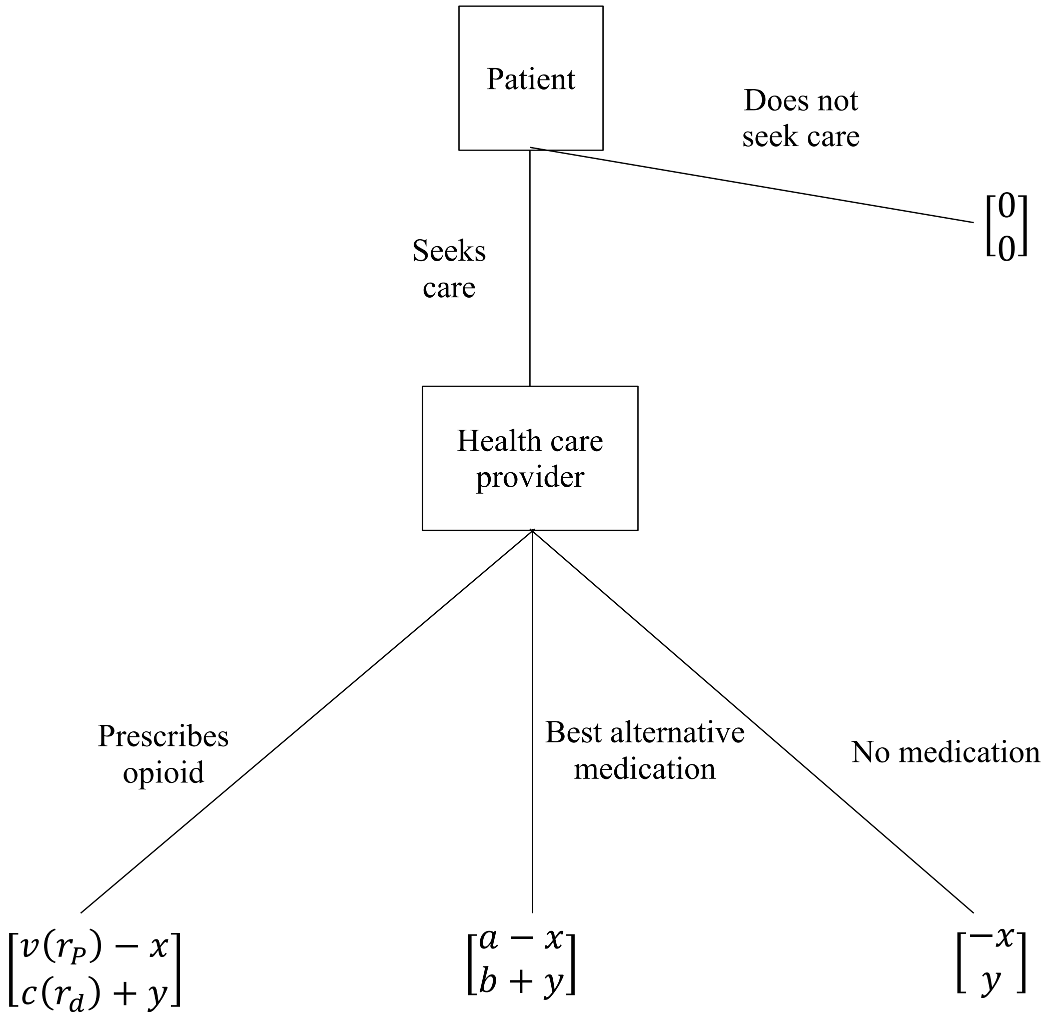


Figure 3: Event study of boxed warning effect on previous opioid users

Figure 4: Event study of boxed warning effect on riskier users

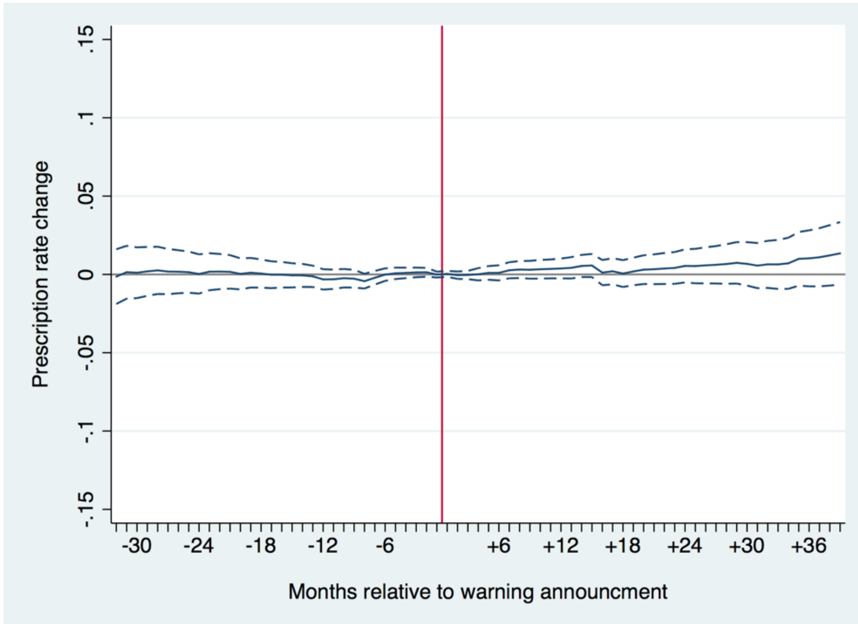
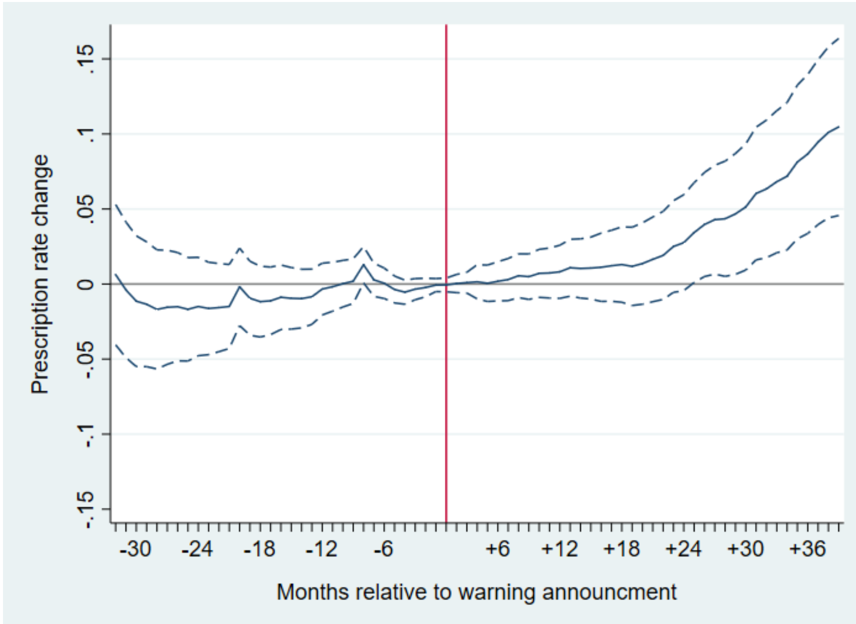


Figure 5: Event study of boxed warning effect on targeted groups



Tables

Table 1: Summary statistics

Variable	Mean	Median	Standard Deviation
Opioid prescription (%)	0.072	0.000	0.258
Previous opioid prescription	0.569	1.000	0.495
Days supplied	10.161	7.500	19.454
Non-opioid pain prescription (%)	0.048	0.000	0.214
Annual health care appointments	2.352	2.000	1.989
Male	0.488	0.000	0.500
White	0.779	1.000	0.415
Married	0.402	0.000	0.490
Pregnant	0.012	0.000	0.108
Family size	3.177	3.000	1.657
Weekly Wage ($ thousands)	0.366	0.000	0.608
Prescription drug insurance	0.556	1.000	0.497
Age			
14 years or younger	0.193	0.000	0.394
15 to 24 years	0.138	0.000	0.345
25 to 34 years	0.134	0.000	0.341
35 to 44 years	0.126	0.000	0.332
45 to 54 years	0.138	0.000	0.345
55 to 64 years	0.126	0.000	0.332
65 years or older	0.144	0.000	0.351
Education			
Less than high school	0.341	0.000	0.474
High school	0.269	0.000	0.443
Some college	0.196	0.000	0.397
Bachelor’s or higher	0.223	0.000	0.417
Census region			
Northeast	0.177	0.000	0.382
South	0.373	0.000	0.484
Midwest	0.213	0.000	0.410
West	0.236	0.000	0.425
Riskier than the average person			
Strongly agree	0.046	0.000	0.210
Agree	0.158	0.000	0.365
Neutral	0.158	0.000	0.364
Disagree	0.224	0.000	0.417
Strongly disagree	0.413	0.000	0.492
Health status			
Excellent	0.327	0.000	0.469
Very good	0.323	0.000	0.467
Good	0.244	0.000	0.430
Fair	0.082	0.000	0.275
Poor	0.024	0.000	0.154

Note: N = 2,000,734.

Table 2: OLS regressions of opioid prescriptions

Variable	(1)	(2)	(3)	(4)
Male	-0.013	-0.013	--	--
	(0.002)***	(0.002)***		
White	0.013	0.013	--	--
	(0.001)***	(0.001)***		
Married	-0.008	-0.008	-0.002	-0.006
	(0.002)***	(0.002)***	(0.007)	(0.009)
Weekly wage	-0.029	-0.029	-0.012	-0.012
($ thousands)	(0.003)***	(0.003)***	(0.006)**	(0.006)*
Weekly wage	0.007	0.007	0.004	0.003
($ thousands) squared	(0.001)***	(0.001)***	(0.002)**	(0.002)*
Prescription drug	0.007	0.007	0.011	0.013
insurance	(0.002)***	(0.002)***	(0.003)***	(0.004)***
Age				
14 years or younger	-0.046	-0.046	-0.001	0.003
	(0.003)***	(0.003)***	(0.011)	(0.016)
15 to 24 years	-0.027	-0.027	0.014	0.013
	(0.003)***	(0.003)***	(0.010)	(0.015)
25 to 34 years	-0.007	-0.007	0.002	-0.002
	(0.003)***	(0.003)***	(0.007)	(0.011)
45 to 54 years	0.014	0.014	-0.006	-0.026
	(0.003)***	(0.003)***	(0.007)	(0.012)**
55 to 64 years	0.027	0.027	0.004	-0.030
	(0.004)***	(0.004)***	(0.011)	(0.018)*
65 years or older	0.020	0.020	0.035	0.010
	(0.004)***	(0.004)***	(0.015)**	(0.024)
Education				
Less than high school	-0.018	-0.018	--	--
	(0.003)***	(0.003)***		
Some college	0.007	0.005	--	--
	(0.003)**	(0.003)*		
Bachelor’s or more	-0.015	-0.015	--	--
	(0.003)***	(0.003)***		
Census region				
South	0.015	0.015	0.003	-0.011
	(0.002)***	(0.002)***	(0.015)	(0.024)
Midwest	0.021	0.021	0.003	-0.012
	(0.003)***	(0.003)***	(0.017)	(0.026)
West	0.011	0.011	0.009	-0.010
	(0.002)***	(0.002)***	(0.016)	(0.023)
Riskier than average				
Strongly agree	-0.003	-0.003	0.001	-0.005
	(0.005)	(0.005)	(0.006)	(0.010)
Agree	-0.001	-0.001	-0.004	0.006
	(0.003)	(0.003)	(0.004)	(0.006)
Disagree	-0.001	-0.001	-0.005	-0.009
	(0.003)	(0.003)	(0.004)	(0.006)
Strongly disagree	0.006	0.006	0.001	0.006
	(0.003)**	(0.003)**	(0.004)	(0.006)
Health status				
Excellent	-0.049	-0.049	-0.023	-0.021
	(0.002)***	(0.002)***	(0.002)***	(0.002)***
Very good	-0.035	-0.035	-0.015	-0.013
	(0.002)***	(0.002)***	(0.002)***	(0.002)***
Fair	0.093	0.093	0.032	0.031
	(0.004)***	(0.004)***	(0.004)***	(0.004)***

Poor	0.254	0.254	0.081	0.066
	(0.009)***	(0.009)***	(0.008)***	(0.008)***
Monthly Fixed Effects		X	X	X
Individual Fixed Effects			X	X
Individual Time Trends				X
R^2	0.079	0.080	0.518	0.650

Note: N = 2,000,734. Standard errors robust and clustered on respondent. Dashes indicate variables excluded by the use of fixed effects. The age group “35 to 44 years” is omitted, “northeast” is the omitted census region, “high school” is the omitted education category, “neutral” is the omitted riskiness response, and “good” is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table 3: Difference-in-differences estimates of the effect of boxed warnings on receiving any opioid prescriptions

Variable	(1) Base model	(2) Covariate model	(3) Full model
Previous prescription	-0.190	-0.191	-0.171
	(0.011)***	(0.011)***	(0.013)***
Opioid fatality risk	0.000	0.000	-0.000
	(0.001)	(0.001)	(0.001)
Specifically targeted	-0.000	-0.001	0.003
	(0.003)	(0.003)	(0.004)

Note: N = 2,000,734. Dependent variable is a binary variable equal to one if the individual had filled an opioid prescription in the relevant month. Base models include the identifying variable, its interaction with a variable indicating the boxed warning requirement is in place, and individual and month-by-year fixed effects. Except in the opioid fatality risk regression, covariate models include each covariate from Table 2. The covariate model in the fatality risk regression omits the marital status, region, and age variables. Full models augment covariate model with individual level time-trends. Standard errors robust and clustered on individual respondent. All regressions control for individual and month-by-year fixed effects. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table 4: Difference-in-differences estimates of the effect of boxed warnings on days of opioid supply prescribed

Variable	(1) Base model	(2) Covariate model	(3) Full model
Previous prescription	-0.967	-0.966	-0.317
	(0.166)***	(0.168)***	(0.251)
Opioid fatality risk	0.059	0.060	0.005
	(0.037)	(0.037)	(0.020)
Specifically targeted	-0.097	-0.084	0.133
	(0.058)*	(0.052)	(0.061)**

Note: N = 2,000,734. Dependent variable is days of opioids supplied to an individual in a given month. Base models include the identifying variable, its interaction with a variable indicating the boxed warning requirement is in place, and individual and month-by-year fixed effects. Except in the opioid fatality risk regression, covariate models include each covariate from Table 2. The covariate model in the fatality risk regression omits the marital status, region, and age variables. Full models augment covariate model with individual level time-trends. Standard errors robust and clustered on individual respondent. All regressions control for individual and month-by-year fixed effects. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table 5: Difference-in-differences estimates of the effect of 2014 boxed warnings on annual number of health care appointments

Variable	(1) Base model	(2) Covariate model
Previous prescription	-0.323	-0.309
	(0.124)***	(0.123)***
Opioid fatality risk	0.001	0.001
	(0.002)	(0.002)
Specifically targeted	-0.004	-0.020
	(0.080)	(0.081)

Note: N = 142,974. Dependent variable is annual number of appointments. Base models include the identifying variable, its interaction with a variable indicating the boxed warning requirement is in place, and individual and month-by-year fixed effects. Except in the opioid fatality risk regression, covariate models include each covariate from Table 2. The covariate model in the fatality risk regression omits the marital status, region, and age variables. The full model cannot be estimated for this dependent variable because each respondent only answers the question corresponding to number of appointments once per year. Standard errors robust and clustered on individual respondent. All regressions control for individual and month-by-year fixed effects. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table 6: Difference-in-differences estimates of the effect of boxed warnings on nonopioid pain prescriptions

Variable	(1) Base model	(2) Covariate model	(3) Full model
Previous prescription	0.009	0.009	0.009
	(0.005)*	(0.005)**	(0.005)*
Opioid fatality risk	0.001	0.001	0.000
	(0.001)	(0.001)	(0.001)
Specifically targeted	-0.000	-0.000	0.002
	(0.002)	(0.002)	(0.003)

Note: N = 2,000,734. Dependent variable is days of opioids supplied to an individual in a given month. Base models include the identifying variable, its interaction with a variable indicating the boxed warning requirement is in place, and individual and month-by-year fixed effects. Except in the opioid fatality risk regression, covariate models include each covariate from Table 2. The covariate model in the fatality risk regression omits the marital status, region, and age variables. Full models augment covariate model with individual level time-trends. Standard errors robust and clustered on individual respondent. All regressions control for individual and month-by-year fixed effects. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Appendix

This Appendix presents how I calculated individual level opioid fatality risks. I draw upon three data sources: the National Vital Statistics System's ("NVSS") multiple cause of death data files, the Current Population Survey, and Census population counts. The NVSS data contain detailed information on individual deaths in the United States, including the decedent's sex, race, marital status, census region of death, month of death, and cause of death indexed by ICD-10 code.[26] The Current Population Survey contains estimates of the proportion of the U.S. population bearing the same characteristics. I draw data from 2011–2016 for all three data sources.

From the NVSS data I construct counts of individuals who experienced fatal opioid overdoses indexed by sex, race, census region of death, and month of death. Because the NVSS data are a census of fatalities, the remainder of the U.S. population contains all individuals who did *not* die of opioid fatalities. Using the Current Population Survey's information on national demographics and population counts from the United States Census Bureau, I create a complimentary count of all individuals who did not die of an opioid overdose, indexed by the exact same categories. These counts of deaths and non-deaths indexed by individual characteristics are organized into a dataset containing approximately 2,500 cells.

After constructing the dataset, I run a regression using these cells as observations. The estimating equation takes the following form:

$$Fatality_c = \alpha + X\beta + \gamma_c + e_c \tag{A1}$$

The dependent variable $Fatality_c$ is equal to one if the cell represents a count of individuals who died of an overdose, and zero otherwise. The independent variables X include

[26] The ICD-10 codes associated with opiate poisonings are T40.0 (opium), T40.1 (heroin), T40.2 (other opioids), T40.3 (methadone), T40.4 (other synthetic narcotics), and T40.6 (other/unspecified narcotics).

variables indicating whether a cell represents individuals who are male, white, married, what 10-year age group individuals represented by the cell are in, and which census region individuals represented by the cell live in. The variables γ_c are annual fixed effects. I weight each observation by the quantity of individuals that the observation represents. The estimated fatality rates that I assign to each individual in my sample are the fitted values from that regression. Appendix Table 1 provides the estimated coefficients from regressing equation A1.

Appendix Tables

Table A1: Predicted annual opioid fatality risk (per 10,000 individuals)

Variables	
Male	0.938
	(0.006)***
White	1.110
	(0.006)***
Married	-2.894
	(0.011)***
Age	
14 years or younger	-3.964
	(0.141)***
15 to 24 years	-2.909
	(0.015)***
25 to 34 years	-0.165
	(0.015)**
45 to 54 years	0.212
	(0.014)***
55 to 64 years	-0.363
	(0.014)***
65 years or older	-1.933
	(0.012)***
Census region	
South	0.212
	(0.008)***
Midwest	0.298
	(0.009)***
West	-0.279
	(0.008)***
Year	
2012	-0.005
	(0.009)
2013	0.071
	(0.009)***
2014	0.210
	(0.009)***
2015	0.386
	(0.010)***
2016	0.746
	(0.011)***

Note: N = 2,496 (1,480,865,347 frequency-weighted observations). The year 2011 is the omitted year category variable.

Table A2: Full results for "Table 3 – Previous prescriptions" Model

Variables	Base model	Covariate model	Full model
Boxed warning × previous opioid prescription	-0.190	-0.191	-0.171
	(0.011)***	(0.011)***	(0.013)***
Previous opioid prescription	0.061	0.062	-0.042
	(0.008)***	(0.008)***	(0.010)***
Married		-0.001	-0.002
		(0.007)	(0.009)
Weekly wage ($ thousands)		-0.015	-0.015
		(0.006)***	(0.006)**
Weekly wage ($ thousands) squared		0.004	0.003
		(0.002)**	(0.002)*
Prescription drug insurance		0.010	0.013
		(0.003)***	(0.004)***
Age: 14 years or younger		0.004	-0.000
		(0.011)	(0.016)
15 to 24 years		0.013	0.003
		(0.010)	(0.014)
25 to 34 years		0.001	-0.005
		(0.007)	(0.010)
45 to 54 years		-0.003	-0.021
		(0.007)	(0.012)*
55 to 64 years		0.010	-0.019
		(0.011)	(0.017)
65 years or older		0.046	0.024
		(0.015)***	(0.023)
Census region: South		0.004	-0.019
		(0.015)	(0.023)
Midwest		0.003	-0.023
		(0.017)	(0.025)
West		0.010	-0.013
		(0.016)	(0.022)
Riskier than average: Strongly agree		0.001	-0.004
		(0.006)	(0.009)
Agree		-0.005	0.006
		(0.004)	(0.006)
Disagree		-0.005	-0.009
		(0.004)	(0.006)
Strongly disagree		0.001	0.005
		(0.004)	(0.006)
Health status: Excellent		-0.022	-0.017
		(0.002)***	(0.002)***
Very good		-0.015	-0.010
		(0.002)***	(0.002)***
Fair		0.032	0.030
		(0.004)***	(0.004)***
Poor		0.080	0.065
		(0.008)***	(0.008)***
R^2	0.522	0.523	0.655

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A3: Full results for "Table 3 – Fatality risk" Model

Variables	Base model	Covariate model	Full model
Boxed warning × fatality risk	0.000	0.000	-0.000
	(0.001)	(0.001)	(0.002)
Fatality risk	-0.003	-0.003	-0.003
	(0.002)	(0.002)	(0.003)
Weekly wage ($ thousands)		-0.013	-0.012
		(0.006)**	(0.006)*
Weekly wage ($ thousands) squared		0.004	0.004
		(0.002)**	(0.002)*
Prescription drug insurance		0.010	0.013
		(0.003)***	(0.004)***
Riskier than average: Strongly agree		0.001	-0.005
		(0.006)	(0.010)
Agree		-0.004	0.006
		(0.004)	(0.006)
Disagree		-0.005	-0.009
		(0.004)	(0.006)
Strongly disagree		0.001	0.006
		(0.004)	(0.006)
Health status: Excellent		-0.023	-0.021
		(0.002)***	(0.002)***
Very good		-0.016	-0.013
		(0.002)***	(0.002)***
Fair		0.032	0.031
		(0.004)***	(0.004)***
Poor		0.081	0.066
		(0.008)***	(0.008)***
R^2	0.517	0.518	0.650

Note: N = 2,000,734. Standard errors robust and clustered on respondent. "Neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A4: Full results for "Table 3 – Specifically targeted" model

Variables	Base model	Covariate model	Full model
Boxed warning × specifically targeted	-0.000	-0.001	0.003
	(0.003)	(0.003)	(0.004)
Specifically targeted	0.055	0.056	0.065
	(0.006)***	(0.006)***	(0.008)***
Married		-0.003	-0.006
		(0.007)	(0.009)
Weekly wage ($ thousands)		-0.011	-0.011
		(0.006)**	(0.006)*
Weekly wage ($ thousands) squared		0.003	0.003
		(0.002)*	(0.002)
Prescription drug insurance		0.011	0.013
		(0.003)***	(0.004)***
Age: 14 years or younger		0.002	0.004
		(0.011)	(0.016)
15 to 24 years		0.016	0.013
		(0.010)	(0.014)
25 to 34 years		0.003	-0.003
		(0.007)	(0.011)
45 to 54 years		-0.006	-0.026
		(0.007)	(0.012)**
55 to 64 years		0.002	-0.030
		(0.011)	(0.018)*
65 years or older		0.032	0.010
		(0.015)**	(0.024)
Census region: South		0.003	-0.010
		(0.015)	(0.024)
Midwest		0.003	-0.011
		(0.017)	(0.026)
West		0.008	-0.010
		(0.016)	(0.023)
Riskier than average: Strongly agree		0.001	-0.005
		(0.006)	(0.010)
Agree		-0.004	0.005
		(0.004)	(0.006)
Disagree		-0.005	-0.009
		(0.004)	(0.006)
Strongly disagree		0.001	0.006
		(0.004)	(0.006)
Health status: Excellent		-0.024	-0.021
		(0.002)***	(0.002)***
Very good		-0.015	-0.013
		(0.002)***	(0.002)***
Fair		0.032	0.031
		(0.004)***	(0.004)***
Poor		0.081	0.066
		(0.008)***	(0.008)***
R^2	0.518	0.519	0.650

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A5: Full results for "Table 3 – Pregnancy" Model

Variables	Base model	Covariate model	Full model
Boxed warning × pregnancy	0.021	0.021	0.038
	(0.016)	(0.016)	(0.020)*
Pregnancy	0.081	0.081	0.077
	(0.011)***	(0.011)***	(0.014)***
Married		-0.004	-0.007
		(0.007)	(0.009)
Weekly wage ($ thousands)		-0.012	-0.011
		(0.006)**	(0.006)*
Weekly wage ($ thousands) squared		0.003	0.003
		(0.002)*	(0.002)
Prescription drug insurance		0.011	0.013
		(0.003)***	(0.004)***
Age: 14 years or younger		0.000	0.004
		(0.011)	(0.016)
15 to 24 years		0.015	0.014
		(0.010)	(0.014)
25 to 34 years		0.002	-0.003
		(0.007)	(0.011)
45 to 54 years		-0.005	-0.026
		(0.007)	(0.012)**
55 to 64 years		0.004	-0.030
		(0.011)	(0.018)*
65 years or older		0.035	0.010
		(0.015)**	(0.024)
Census region: South		0.003	-0.010
		(0.015)	(0.024)
Midwest		0.003	-0.011
		(0.017)	(0.026)
West		0.008	-0.011
		(0.016)	(0.023)
Riskier than average: Strongly agree		0.001	-0.005
		(0.006)	(0.010)
Agree		-0.004	0.005
		(0.004)	(0.006)
Disagree		-0.005	-0.009
		(0.004)	(0.006)
Strongly disagree		0.000	0.006
		(0.004)	(0.006)
Health status: Excellent		-0.023	-0.021
		(0.002)***	(0.002)***
Very good		-0.015	-0.013
		(0.002)***	(0.002)***
Fair		0.032	0.031
		(0.004)***	(0.004)***
Poor		0.081	0.066
		(0.008)***	(0.008)***
R^2	0.518	0.519	0.650

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A6: Full results for "Table 3 – Children" model

Variables	Base model	Covariate model	Full model
Boxed warning × child	-0.004	-0.004	-0.003
	(0.003)	(0.003)	(0.004)
Child	0.005	0.004	0.008
	(0.007)	(0.007)	(0.010)
Married		-0.002	-0.006
		(0.007)	(0.009)
Weekly wage ($ thousands)		-0.012	-0.012
		(0.006)**	(0.006)*
Weekly wage ($ thousands) squared		0.004	0.003
		(0.002)**	(0.002)*
Prescription drug insurance		0.011	0.013
		(0.003)***	(0.004)***
Age: 14 years or younger		-0.001	0.003
		(0.011)	(0.016)
15 to 24 years		0.014	0.013
		(0.010)	(0.015)
25 to 34 years		0.003	-0.002
		(0.007)	(0.011)
45 to 54 years		-0.006	-0.026
		(0.007)	(0.012)**
55 to 64 years		0.003	-0.030
		(0.011)	(0.018)*
65 years or older		0.034	0.010
		(0.015)**	(0.024)
Census region: South		0.003	-0.011
		(0.015)	(0.024)
Midwest		0.003	-0.012
		(0.017)	(0.026)
West		0.009	-0.010
		(0.016)	(0.023)
Riskier than average: Strongly agree		0.001	-0.005
		(0.006)	(0.010)
Agree		-0.004	0.006
		(0.004)	(0.006)
Disagree		-0.005	-0.009
		(0.004)	(0.006)
Strongly disagree		0.001	0.006
		(0.004)	(0.006)
Health status: Excellent		-0.023	-0.021
		(0.002)***	(0.002)***
Very good		-0.015	-0.013
		(0.002)***	(0.002)***
Fair		0.032	0.031
		(0.004)***	(0.004)***
Poor		0.081	0.066
		(0.008)***	(0.008)***
R^2	0.517	0.518	0.650

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A7: Full results for "Table 4 – Previous prescriptions" model

Variables	Base model	Covariate model	Full model
Boxed warning × previous opioid prescription	-0.967	-0.966	-0.317
	(0.166)***	(0.168)***	(0.251)
Previous opioid prescription	0.879	0.881	-0.740
	(0.166)***	(0.161)***	(0.163)***
Married		-0.245	-0.259
		(0.149)	(0.280)
Weekly wage ($ thousands)		-0.090	-0.102
		(0.085)	(0.081)
Weekly wage ($ thousands) squared		0.028	0.016
		(0.024)	(0.021)
Prescription drug insurance		-0.024	-0.004
		(0.058)	(0.071)
Age: 14 years or younger		-0.816	-0.272
		(0.952)	(0.303)
15 to 24 years		-0.777	-0.208
		(0.944)	(0.295)
25 to 34 years		0.093	-0.050
		(0.095)	(0.103)
45 to 54 years		-0.097	-0.098
		(0.102)	(0.151)
55 to 64 years		-0.018	0.056
		(0.158)	(0.268)
65 years or older		0.427	0.603
		(0.224)*	(0.346)*
Census region: South		-0.176	-0.108
		(0.141)	(0.244)
Midwest		-0.143	-0.402
		(0.154)	(0.291)
West		-0.342	-0.346
		(0.158)**	(0.262)
Riskier than average: Strongly agree		0.143	-0.073
		(0.145)	(0.176)
Agree		0.147	-0.168
		(0.171)	(0.190)
Disagree		0.022	-0.196
		(0.093)	(0.116)*
Strongly disagree		0.066	-0.089
		(0.101)	(0.127)
Health status: Excellent		-0.169	-0.080
		(0.035)***	(0.033)**
Very good		-0.115	-0.026
		(0.039)***	(0.036)
Fair		0.239	0.201
		(0.059)***	(0.071)***
Poor		0.871	0.725
		(0.159)***	(0.163)***
R^2	0.529	0.529	0.720

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A8: Full results for "Table 4 – Fatality risk" model

Variables	Base model	Covariate model	Full model
Boxed warning × fatality risk	0.076	0.077	0.007
	(0.047)	(0.047)	(0.026)
Fatality risk	0.109	0.108	0.047
	(0.130)	(0.131)	(0.078)
Weekly wage ($ thousands)		-0.097	-0.085
		(0.081)	(0.081)
Weekly wage ($ thousands) squared		0.028	0.018
		(0.023)	(0.021)
Prescription drug insurance		-0.024	-0.010
		(0.058)	(0.071)
Riskier than average: Strongly agree		0.140	-0.072
		(0.144)	(0.175)
Agree		0.148	-0.174
		(0.168)	(0.191)
Disagree		0.025	-0.201
		(0.094)	(0.115)*
Strongly disagree		0.065	-0.079
		(0.101)	(0.126)
Health status: Excellent		-0.163	-0.106
		(0.032)***	(0.033)***
Very good		-0.111	-0.041
		(0.037)***	(0.036)
Fair		0.239	0.205
		(0.059)***	(0.071)***
Poor		0.872	0.734
		(0.159)***	(0.163)***
R^2	0.528	0.529	0.719

Note: N = 2,000,734. Standard errors robust and clustered on respondent. "Neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A9: Full results for "Table 4 – Specifically targeted" model

Variables	Base model	Covariate model	Full model
Boxed warning × specifically targeted	-0.097	-0.084	0.133
	(0.058)*	(0.052)	(0.061)**
Specifically targeted	0.266	0.249	0.174
	(0.081)***	(0.078)***	(0.083)**
Married		-0.240	-0.284
		(0.149)	(0.278)
Weekly wage ($ thousands)		-0.089	-0.079
		(0.082)	(0.081)
Weekly wage ($ thousands) squared		0.025	0.017
		(0.024)	(0.021)
Prescription drug insurance		-0.018	-0.010
		(0.058)	(0.071)
Age: 14 years or younger		-0.830	-0.254
		(0.952)	(0.303)
15 to 24 years		-0.799	-0.145
		(0.952)	(0.297)
25 to 34 years		0.083	-0.029
		(0.095)	(0.103)
45 to 54 years		-0.097	-0.131
		(0.102)	(0.151)
55 to 64 years		-0.003	-0.016
		(0.157)	(0.267)
65 years or older		0.448	0.508
		(0.223)**	(0.346)
Census region: South		-0.197	-0.061
		(0.142)	(0.248)
Midwest		-0.176	-0.328
		(0.154)	(0.294)
West		-0.355	-0.331
		(0.161)**	(0.266)
Riskier than average: Strongly agree		0.138	-0.073
		(0.144)	(0.176)
Agree		0.152	-0.174
		(0.172)	(0.190)
Disagree		0.024	-0.200
		(0.094)	(0.116)*
Strongly disagree		0.064	-0.079
		(0.100)	(0.127)
Health status: Excellent		-0.163	-0.106
		(0.033)***	(0.033)***
Very good		-0.111	-0.041
		(0.037)***	(0.036)
Fair		0.240	0.204
		(0.059)***	(0.071)***
Poor		0.873	0.735
		(0.159)***	(0.163)***
R^2	0.528	0.529	0.720

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A10: Full results for "Table 4 – Pregnancy" model

Variables	Base model	Covariate model	Full model
Boxed warning × pregnancy	0.323	0.318	0.470
	(0.192)*	(0.193)*	(0.170)***
Pregnancy	0.120	0.121	0.111
	(0.184)	(0.184)	(0.150)
Married		-0.245	-0.285
		(0.149)	(0.278)
Weekly wage ($ thousands)		-0.092	-0.080
		(0.081)	(0.080)
Weekly wage ($ thousands) squared		0.026	0.017
		(0.024)	(0.021)
Prescription drug insurance		-0.017	-0.010
		(0.058)	(0.071)
Age: 14 years or younger		-0.828	-0.252
		(0.949)	(0.303)
15 to 24 years		-0.807	-0.142
		(0.954)	(0.297)
25 to 34 years		0.078	-0.029
		(0.095)	(0.103)
45 to 54 years		-0.089	-0.132
		(0.102)	(0.151)
55 to 64 years		0.014	-0.016
		(0.157)	(0.267)
65 years or older		0.472	0.507
		(0.222)**	(0.346)
Census region: South		-0.193	-0.058
		(0.142)	(0.249)
Midwest		-0.173	-0.324
		(0.154)	(0.295)
West		-0.353	-0.330
		(0.161)**	(0.266)
Riskier than average: Strongly agree		0.137	-0.073
		(0.144)	(0.176)
Agree		0.151	-0.175
		(0.172)	(0.190)
Disagree		0.024	-0.200
		(0.094)	(0.116)*
Strongly disagree		0.064	-0.080
		(0.100)	(0.127)
Health status: Excellent		-0.163	-0.106
		(0.033)***	(0.033)***
Very good		-0.111	-0.041
		(0.038)***	(0.036)
Fair		0.241	0.204
		(0.059)***	(0.071)***
Poor		0.873	0.734
		(0.159)***	(0.163)***
R^2	0.528	0.529	0.720

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A11: Full results for “Table 4 – Child” model

Variables	Base model	Covariate model	Full model
Boxed warning × child	-0.148	-0.134	0.067
	(0.056)***	(0.047)***	(0.060)
Child	0.178	0.152	-0.012
	(0.074)**	(0.067)**	(0.082)
Married		-0.235	-0.282
		(0.149)	(0.278)
Weekly wage ($ thousands)		-0.091	-0.082
		(0.082)	(0.081)
Weekly wage ($ thousands) squared		0.026	0.018
		(0.024)	(0.021)
Prescription drug insurance		-0.018	-0.010
		(0.058)	(0.071)
Age: 14 years or younger		-0.840	-0.257
		(0.951)	(0.303)
15 to 24 years		-0.798	-0.148
		(0.951)	(0.297)
25 to 34 years		0.085	-0.028
		(0.095)	(0.103)
45 to 54 years		-0.098	-0.132
		(0.102)	(0.151)
55 to 64 years		-0.004	-0.016
		(0.157)	(0.267)
65 years or older		0.447	0.507
		(0.223)**	(0.346)
Census region: South		-0.194	-0.064
		(0.142)	(0.249)
Midwest		-0.176	-0.331
		(0.154)	(0.294)
West		-0.353	-0.327
		(0.161)**	(0.266)
Riskier than average: Strongly agree		0.138	-0.073
		(0.144)	(0.176)
Agree		0.152	-0.174
		(0.172)	(0.190)
Disagree		0.025	-0.200
		(0.094)	(0.116)*
Strongly disagree		0.065	-0.079
		(0.100)	(0.127)
Health status: Excellent		-0.163	-0.106
		(0.033)***	(0.033)***
Very good		-0.111	-0.041
		(0.037)***	(0.036)
Fair		0.240	0.204
		(0.059)***	(0.071)***
Poor		0.873	0.735
		(0.159)***	(0.163)***
R^2	0.528	0.529	0.719

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group “35 to 44 years” is omitted, “northeast” is the omitted census region, “high school” is the omitted education category, “neutral” is the omitted riskiness response, and “good” is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A12: Full results for "Table 5 – Previous prescriptions" model

Variables	Base model	Covariate model
Boxed warning × previous opioid prescription	-0.323	-0.309
	(0.124)***	(0.123)**
Previous opioid prescription	0.470	0.462
	(0.100)***	(0.099)***
Married		0.102
		(0.098)
Weekly wage ($ thousands)		-0.014
		(0.004)***
Weekly wage ($ thousands) squared		0.000
		(0.000)***
Prescription drug insurance		0.161
		(0.047)***
Age: 14 years or younger		-0.019
		(0.200)
15 to 24 years		0.145
		(0.171)
25 to 34 years		0.121
		(0.129)
45 to 54 years		-0.004
		(0.111)
55 to 64 years		0.074
		(0.165)
65 years or older		0.137
		(0.227)
Census region: South		0.127
		(0.332)
Midwest		0.096
		(0.353)
West		0.171
		(0.347)
Riskier than average: Strongly agree		0.021
		(0.065)
Agree		-0.054
		(0.039)
Disagree		0.027
		(0.037)
Strongly disagree		0.052
		(0.036)
Health status: Excellent		-0.307
		(0.044)***
Very good		-0.169
		(0.036)***
Fair		0.355
		(0.060)***
Poor		0.959
		(0.157)***
R^2	0.762	0.764

Note: N = 142,230. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A13: Full results for "Table 5 – Fatality risk" model

Variables	Base model	Covariate model
Boxed warning × fatality risk	0.001	0.001
	(0.002)	(0.002)
Fatality risk	-0.003	-0.003
	(0.003)	(0.003)
Weekly wage ($ thousands)		-0.014
		(0.004)***
Weekly wage ($ thousands) squared		0.000
		(0.000)***
Prescription drug insurance		0.162
		(0.047)***
Riskier than average: Strongly agree		0.023
		(0.066)
Agree		-0.052
		(0.040)
Disagree		0.045
		(0.038)
Strongly disagree		0.074
		(0.036)**
Health status: Excellent		-0.372
		(0.035)***
Very good		-0.221
		(0.031)***
Fair		0.416
		(0.054)***
Poor		1.057
		(0.130)***
R^2	0.762	0.764

Note: N = 2,000,734. Standard errors robust and clustered on respondent. "Neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A14: Full results for "Table 5 – Specifically targeted" model

Variables	Base model	Covariate model
Boxed warning × specifically targeted	-0.004	-0.020
	(0.080)	(0.081)
Specifically targeted	1.893	1.892
	(0.112)***	(0.113)***
Married		0.062
		(0.095)
Weekly wage ($ thousands)		-0.012
		(0.004)***
Weekly wage ($ thousands) squared		0.000
		(0.000)***
Prescription drug insurance		0.158
		(0.046)***
Age: 14 years or younger		0.040
		(0.193)
15 to 24 years		0.171
		(0.162)
25 to 34 years		0.118
		(0.119)
45 to 54 years		-0.031
		(0.111)
55 to 64 years		0.037
		(0.165)
65 years or older		0.089
		(0.227)
Census region: South		-0.297
		(0.338)
Midwest		-0.204
		(0.337)
West		-0.298
		(0.312)
Riskier than average: Strongly agree		0.022
		(0.065)
Agree		-0.053
		(0.040)
Disagree		0.036
		(0.037)
Strongly disagree		0.064
		(0.036)*
Health status: Excellent		-0.367
		(0.034)***
Very good		-0.214
		(0.030)***
Fair		0.425
		(0.054)***
Poor		1.054
		(0.129)***
R^2	0.760	0.763

Note: N = 142,230. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A15: Full results for "Table 5 – Pregnancy" model

Variables	Base model	Covariate model
Boxed warning × pregnancy	0.384	0.366
	(0.355)	(0.356)
Pregnancy	2.409	2.427
	(0.242)***	(0.242)***
Married		0.031
		(0.101)
Weekly wage ($ thousands)		-0.010
		(0.004)***
Weekly wage ($ thousands) squared		0.000
		(0.000)**
Prescription drug insurance		0.138
		(0.056)**
Age: 15 to 24 years		0.146
		(0.161)
25 to 34 years		0.081
		(0.121)
45 to 54 years		-0.103
		(0.113)
55 to 64 years		-0.152
		(0.169)
65 years or older		-0.145
		(0.236)
Census region: South		0.091
		(0.331)
Midwest		0.129
		(0.346)
West		0.150
		(0.352)
Riskier than average: Strongly agree		0.012
		(0.064)
Agree		-0.060
		(0.039)
Disagree		0.013
		(0.037)
Strongly disagree		0.036
		(0.036)
Health status: Excellent		-0.300
		(0.043)***
Very good		-0.160
		(0.035)***
Fair		0.371
		(0.060)***
Poor		0.965
		(0.156)***
R^2	0.768	0.770

Note: N = 142,230. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A16: Full results for "Table 6 – Previous prescriptions" model

Variables	Base model	Covariate model	Full model
Boxed warning × previous opioid prescription	0.009	0.009	0.009
	(0.005)*	(0.005)**	(0.005)*
Previous opioid prescription	-0.009	-0.009	0.001
	(0.004)**	(0.004)**	(0.004)
Married		0.006	0.004
		(0.005)	(0.007)
Weekly wage ($ thousands)		0.004	0.003
		(0.004)	(0.005)
Weekly wage ($ thousands) squared		-0.001	0.000
		(0.001)	(0.002)
Prescription drug insurance		0.004	0.005
		(0.002)*	(0.003)
Age: 14 years or younger		0.008	0.007
		(0.008)	(0.012)
15 to 24 years		0.002	-0.002
		(0.008)	(0.011)
25 to 34 years		0.001	0.001
		(0.006)	(0.008)
45 to 54 years		0.002	0.006
		(0.007)	(0.009)
55 to 64 years		0.007	0.013
		(0.009)	(0.013)
65 years or older		0.005	0.009
		(0.012)	(0.017)
Census region: South		0.001	0.010
		(0.010)	(0.016)
Midwest		-0.003	-0.001
		(0.012)	(0.020)
West		0.004	0.022
		(0.011)	(0.015)
Riskier than average: Strongly agree		-0.004	-0.006
		(0.004)	(0.007)
Agree		0.001	-0.003
		(0.003)	(0.005)
Disagree		0.002	0.003
		(0.003)	(0.004)
Strongly disagree		0.000	0.001
		(0.003)	(0.004)
Health status: Excellent		-0.015	-0.016
		(0.002)***	(0.002)***
Very good		-0.008	-0.009
		(0.001)***	(0.002)***
Fair		0.010	0.008
		(0.003)***	(0.003)***
Poor		0.000	-0.002
		(0.005)	(0.006)
R^2	0.490	0.491	0.633

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A17: Full results for "Table 6 – Fatality risk" model

Variables	Base model	Covariate model	Full model
Boxed warning × fatality risk	0.001	0.001	0.000
	(0.001)	(0.001)	(0.001)
Fatality risk	-0.003	-0.002	-0.001
	(0.002)*	(0.002)	(0.002)
Weekly wage ($ thousands)		0.004	0.003
		(0.004)	(0.005)
Weekly wage ($ thousands) squared		-0.001	0.000
		(0.001)	(0.002)
Prescription drug insurance		0.004	0.005
		(0.002)*	(0.003)
Riskier than average: Strongly agree		0.000	0.001
		(0.003)	(0.004)
Agree		0.002	0.003
		(0.003)	(0.004)
Disagree		0.001	-0.003
		(0.003)	(0.005)
Strongly disagree		-0.004	-0.006
		(0.004)	(0.007)
Health status: Excellent		-0.015	-0.016
		(0.002)***	(0.002)***
Very good		-0.008	-0.009
		(0.001)***	(0.002)***
Fair		0.010	0.008
		(0.003)***	(0.003)***
Poor		0.000	-0.002
		(0.005)	(0.006)
R^2	0.490	0.491	0.633

Note: N = 2,000,734. Standard errors robust and clustered on respondent. "Neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A18: Full results for "Table 6 – Specifically targeted" model

Variables	Base model	Covariate model	Full model
Boxed warning × specifically targeted	-0.000	-0.000	0.002
	(0.002)	(0.002)	(0.003)
Specifically targeted	0.019	0.019	0.014
	(0.004)***	(0.004)***	(0.005)***
Married		0.005	0.004
		(0.005)	(0.007)
Weekly wage ($ thousands)		0.005	0.004
		(0.004)	(0.005)
Weekly wage ($ thousands) squared		-0.001	-0.000
		(0.001)	(0.002)
Prescription drug insurance		0.004	0.005
		(0.002)*	(0.003)
Age: 14 years or younger		0.009	0.007
		(0.008)	(0.012)
15 to 24 years		0.004	-0.002
		(0.007)	(0.011)
25 to 34 years		0.001	0.001
		(0.006)	(0.008)
45 to 54 years		0.002	0.006
		(0.007)	(0.009)
55 to 64 years		0.006	0.014
		(0.009)	(0.013)
65 years or older		0.004	0.009
		(0.012)	(0.017)
Census region: South		0.001	0.010
		(0.010)	(0.016)
Midwest		-0.002	-0.001
		(0.012)	(0.020)
West		0.004	0.022
		(0.011)	(0.015)
Riskier than average: Strongly agree		-0.004	-0.006
		(0.004)	(0.007)
Agree		0.001	-0.003
		(0.003)	(0.005)
Disagree		0.002	0.003
		(0.003)	(0.004)
Strongly disagree		0.000	0.001
		(0.003)	(0.004)
Health status: Excellent		-0.015	-0.016
		(0.002)***	(0.002)***
Very good		-0.008	-0.009
		(0.001)***	(0.002)***
Fair		0.010	0.008
		(0.003)***	(0.003)***
Poor		0.000	-0.002
		(0.005)	(0.006)
R^2	0.490	0.491	0.633

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A19: Full results for "Table 6 – Pregnancy" model

Variables	Base model	Covariate model	Full model
Boxed warning × pregnancy	0.005	0.005	0.012
	(0.010)	(0.010)	(0.012)
Pregnancy	0.027	0.027	0.022
	(0.008)***	(0.008)***	(0.010)**
Married		0.005	0.004
		(0.005)	(0.007)
Weekly wage ($ thousands)		0.004	0.004
		(0.004)	(0.005)
Weekly wage ($ thousands) squared		-0.001	-0.000
		(0.001)	(0.002)
Prescription drug insurance		0.004	0.005
		(0.002)*	(0.003)
Age: 14 years or younger		0.008	0.007
		(0.008)	(0.012)
15 to 24 years		0.003	-0.002
		(0.007)	(0.011)
25 to 34 years		0.001	0.001
		(0.006)	(0.008)
45 to 54 years		0.002	0.006
		(0.007)	(0.009)
55 to 64 years		0.006	0.014
		(0.009)	(0.013)
65 years or older		0.005	0.009
		(0.012)	(0.017)
Census region: South		0.000	0.010
		(0.010)	(0.016)
Midwest		-0.002	-0.001
		(0.012)	(0.020)
West		0.004	0.022
		(0.011)	(0.015)
Riskier than average: Strongly agree		-0.004	-0.006
		(0.004)	(0.007)
Agree		0.001	-0.003
		(0.003)	(0.005)
Disagree		0.002	0.003
		(0.003)	(0.004)
Strongly disagree		0.000	0.001
		(0.003)	(0.004)
Health status: Excellent		-0.015	-0.016
		(0.002)***	(0.002)***
Very good		-0.008	-0.009
		(0.001)***	(0.002)***
Fair		0.010	0.008
		(0.003)***	(0.003)***
Poor		0.000	-0.002
		(0.005)	(0.006)
R^2	0.490	0.491	0.633

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table A20: Full results for "Table 6 – Children" model

Variables	Base model	Covariate model	Full model
Boxed warning × child	-0.001	-0.001	0.000
	(0.002)	(0.002)	(0.003)
Child	0.005	0.005	-0.010
	(0.004)	(0.004)	(0.007)
Married		0.006	0.004
		(0.005)	(0.007)
Weekly wage ($ thousands)		0.004	0.003
		(0.004)	(0.005)
Weekly wage ($ thousands) squared		-0.001	0.000
		(0.001)	(0.002)
Prescription drug insurance		0.004	0.005
		(0.002)*	(0.003)
Age: 14 years or younger		0.008	0.007
		(0.008)	(0.012)
15 to 24 years		0.003	-0.002
		(0.008)	(0.011)
25 to 34 years		0.001	0.001
		(0.006)	(0.008)
45 to 54 years		0.002	0.006
		(0.007)	(0.009)
55 to 64 years		0.006	0.014
		(0.009)	(0.013)
65 years or older		0.005	0.009
		(0.012)	(0.017)
Census region: South		0.001	0.010
		(0.010)	(0.016)
Midwest		-0.002	-0.001
		(0.012)	(0.020)
West		0.004	0.022
		(0.011)	(0.015)
Riskier than average: Strongly agree		-0.004	-0.006
		(0.004)	(0.007)
Agree		0.001	-0.003
		(0.003)	(0.005)
Disagree		0.002	0.003
		(0.003)	(0.004)
Strongly disagree		0.000	0.001
		(0.003)	(0.004)
Health status: Excellent		-0.015	-0.016
		(0.002)***	(0.002)***
Very good		-0.008	-0.009
		(0.001)***	(0.002)***
Fair		0.010	0.008
		(0.003)***	(0.003)***
Poor		0.000	-0.002
		(0.005)	(0.006)
R^2	0.490	0.491	0.633

Note: N = 2,000,734. Standard errors robust and clustered on respondent. The age group "35 to 44 years" is omitted, "northeast" is the omitted census region, "high school" is the omitted education category, "neutral" is the omitted riskiness response, and "good" is the omitted health status. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Chapter 3: The Effect of Opioid Abuse on Fatal Workplace Injuries

I. Introduction

Policy responses to the ongoing opioid epidemic have generally focused on making prescription opioids less available and abusable and on decreasing deaths from opioid overdoses. Examples include the naloxone access laws and opioid boxed warnings that the first two chapters of this dissertation studied, as well as prescription drug monitoring programs (Buchmueller and Carey 2017; Dave et al. 2017), abuse deterrent reformulations of prescription opioids (Alpert et al. 2016), and pain clinic regulations (Popovici et al. 2017). Overdose fatalities are the most widely discussed consequence of the opioid epidemic—from 2006 to 2016, more than 280,000 individuals in the United States overdosed on opioids. The White House Council of Economic Advisers (2016) estimated that the economic costs attributable to overdose fatalities in 2015 alone reached approximately $430 billion. But, focusing on overdose fatalities ignores the many other social costs of opioid abuse that researchers have identified, including increased health care costs (Johnston et al. 2016; Kirson et al. 2017), labor market effects, and criminal enforcement costs (Hansen et al. 2011).

In this chapter, I identify a category of collateral consequences to the opioid epidemic that remains unidentified in the literature: increases in fatal occupational injuries. Opioid use can impair individuals' ability to perform fine motor tasks and operate machinery (Hegmann et al. 2014); as a result, it is possible that rising opioid abuse increases workplace injury risks. In particularly dangerous industries and occupations opioid abuse could even increase the probability that workers suffer fatal injuries. If opioid abuse in a geographic area increases fatality rates from nominally unrelated causes such as worker fatalities, policymakers will underestimate the true cost of the epidemic. Moreover, policymakers could misdiagnose a spike in worker injuries and misallocate resources as a result.

I estimate the effect of opioid abuse on fatal worker injuries using two-way fixed effects models and county-level vital statistics data. My ordinary least squares results demonstrate that counties with relatively higher rates of opioid overdoses exhibit higher rates of fatal worker injuries. A 1% increase in opioid overdose rates is associated with a 0.05% percent increase in worker injury rates. In other words, from 2006 to 2016 the opioid epidemic has been associated with approximately 2,827 excess worker fatalities. The effect is concentrated in rural and suburban areas with relatively higher pain medication overdose rates.

To ensure that simultaneity bias is not driving the positive relationship between fatal overdoses and fatal worker injuries, I augment my ordinary least squares models with instrumental variables ("IV") estimates of the effect of overdoses on worker injuries. Opioid prescriptions are a common medical treatment for individuals who are injured at work (Bernacki et al. 2012), and a growing body of evidence suggests that prescriptions for acute injuries often result in a person using opioids long after the individual has recovered from the injury (Shah et al. 2017; Mierch et al. 2015). It is therefore plausible that opioid abuse is not increasing worker injuries, but rather, worker injuries are causing an increase in opioid overdoses as individuals receiving repeat opioid prescriptions for acute injuries become opioid dependent and begin misusing. To address potential endogeneity attributable to such reverse causation, I instrument for county-level opioid overdose rates using naloxone access laws and prescription drug monitoring program laws. These state policies influence opioid overdose rates and abuse rates but have no direct impact on the conditions that workers face in the workplace. Previous research demonstrates that after controlling for state and county characteristics, these policies are plausibly exogenous shocks to opioid overdose and use rates (Rees et al. 2019; Buchmueller and

Carey 2017).[1] The IV models demonstrate that the opioid epidemic is fueling a sizeable increase in workplace fatalities—increases in opioid abuse yielding a 1% increase in overdose deaths result in a 0.31–0.46% increase in worker fatalities. As further evidence, I estimate IV models examining whether higher fatal worker injury rates cause higher opioid overdose rates, instrumenting for worker fatality rates using worker fatality rates in border counties. Border county fatal injury rates correlate with fatal injury rates in the county of interest because of shared industry and occupation characteristics. Neighbor county labor market characteristics have been applied as an instrument for county-of-interest characteristics in a variety of previous studies, such as the use of neighboring county unemployment rates in Mahershri and Winston (2016) and border county minimum wages in Dube et al. (2010). The second set of instrumental variables models provide no evidence of the reverse causal effects that motivated the IV models.

II. Background

The most salient result of the opioid epidemic is the large number of overdose fatalities that have occurred in the United States in recent years. Figure 1 presents the evolution of opioid overdose fatality rates from 1999 to 2016 for the entire United States. Figure 1 demonstrates that opioid fatality rates grew every year from 1999 to 2016. In 2006, approximately 3.5 individuals died of an opioid overdose for every 100,000 individuals in the U.S. population. The amount steadily increased until 2013, when it began to sharply rise. The rate of overdose fatalities in 2016 was approximately 16 fatalities per 100,000 individuals, more than quadruple the rate in 1999.

But, the staggering number of overdose fatalities is not the only consequence of opioid abuse. Researchers have identified several other categories of social costs attributable to opioid

[1] Chapter 1, Appendix Table 1 and 2 provides further evidence that naloxone access laws are exogenous with respect to overdose deaths.

abuse, including increased health care costs, increased criminal enforcement costs, decreased labor force participation, and increased unemployment. Opioid users utilize more health care resources than non-users, including direct medical care and drug costs, as well as substance abuse treatment and additional public health research (Birnbaum et al. 2011; Kirson et al. 2017). Criminal enforcement costs arise because opioid abuse can be associated with illegal activity such as property damage and theft that requires the use of police and adjudicatory resources and results in incarceration of some users (Birnbaum et al. 2011; Florence et al. 2016). Labor market effects are extensive as well, including disability, lost wages, and premature death of workers (Birnbaum et al. 2011; Harris et al. 2018).

These collateral consequences of the opioid epidemic are substantial. Birnbaum et al. (2011) estimated that the total social cost of opioid abuse, including each of the above components, was $61.5 billion in 2007. Florence et al. (2016) estimated that in 2013, opioid overdoses, abuse, and dependence cost the United States approximately $57 billion in economic costs not attributable to fatalities. The White House Council of Economic Advisers (2016) drew on Florence et al. (2016)'s estimate to calculate that the costs of opioid abuse not attributable to fatalities in 2015 reached $72.3 billion. This chapter contributes to the ongoing effort to catalogue the costs of opioid abuse by demonstrating that opioid abuse causes a significant increase in the rate of fatal worker injuries.

Worker safety has been the subject of several other strands of the health and labor economics literature. National worker injury rates have followed a very different pattern from opioid overdose fatalities. Figure 2 presents the evolution of fatal worker injury rates in the United States from 1999 to 2016. In 1999, approximately 4.5 individuals per 100,000 workers suffered a fatal on-the-job injury per year. There was a sharp jump in 2001 as a result of the approximately 3,000 victims of the terrorist attacks of September 11, 2001. Following 2001, the rate of worker fatalities was relatively constant at the 1999 level until 2006. From 2006 to 2009, the rate of fatal worker injuries fell by approximately 25% to 3.6 fatalities per 100,000 workers. The rate plateaued in 2009; while the cause is not clear, it is noteworthy that the change occurred as the Great Recession began. The rate remained relatively steady until 2015 and showed a small but significant increase from 2015 to 2016.

The most salient determinant of workplace safety is the nature of the workplace that an individual works in; in particular, workplace fatality rates are strongly associated with industry and occupation. For example, the rate of fatal on-the-job injuries for mining machine operators is more than ten times as large as manufacturing executives and managers (Viscusi 2004). A variety of demographic characteristics correlate with worker safety, including race, union membership, immigration status, and whether an individual is a smoker (Leeth and Ruser 2003; Viscusi and Hersch 2008; Viscusi and Hersch 2010). Worker injuries may be positively correlated with macroeconomic conditions, though evidence of this may be a function of increased reporting of worker injuries when the economy is thriving (Farris 1998; Boone et al. 2011). This chapter demonstrates that opioid abuse is an additional determinant of workplace safety that remains overlooked in the literature.

III. Methods

A. Data Sources

This chapter demonstrates that opioid abuse most likely causes an increase in worker fatalities, rather than worker injuries causing more opioid overdoses. As such, the key variables in this project are measures of opioid overdoses and worker fatal injuries, which I draw from the National Vital Statistics System's ("NVSS") multiple cause of death all county micro data files. The data contain detailed information on each individual death certificate issued in the United

States, including the decedent's date of death, the location of death at the state and county level, the decedent's education, sex, race, age, and marital status, whether the decedent died of an injury at work, and the decedent's causes of death indexed by International Classification of Diseases (Tenth Revision) ("ICD-10") code. The ICD-10 coding system is the standard method for classifying causes of death in U.S. government data (CDC 2018). As in Chapter 1, I count fatalities based on the county an individual died in, rather than their county of residence.[2] My sample utilizes NVSS data covering the period from 2006–2016.

From the fatality counts in the vital statistics data, I construct monthly counts of fatalities due to any opioid; additionally, I disaggregate the data into non-mutually exclusive counts of fatalities associated with heroin, pain medications, synthetic opioids, and other opioids.[3] I also construct a count of the quantity of individuals who died of a work-related injury. The work-related injury classification is separate from the ICD-10 cause of death; all injuries that occur while an individual is on the job that result in death are classified as a work injury fatality. I transform all fatality counts into monthly fatality rates. For opioid fatalities, I calculate fatalities rates per 100,000 county residents by dividing each count by the population of the relevant county and multiplying by 100,000. For fatal work injuries, I analogously calculate fatalities per 100,000 individuals employed in a county. The monthly rates of fatal work injuries constitute the primary dependent variables in my analyses that follow, while the opioid overdose fatality rates are my primary explanatory variable of interest.

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[2] The vast majority of overdose fatalities (86%) occur in the decedent's county of residence. I use the county of death in this research because it is likely a better measure of where opioid use is occurring, which will likely relate more strongly to additional risks from opioid abuse at work.

[3] The ICD-10 codes associated with fatal overdoses from opiates are T40.0 (opium), T40.1 (heroin), T40.2 (other opioids), T40.3 (methadone), T40.4 (other synthetic narcotics), and T40.6 (other/unspecified narcotics). I classify any fatality with an ICD-10 code of T40.2 and T40.3 as pain medication fatalities, T40.4 deaths are classified as synthetic opioid fatalities, and T40.6 are classified as other opioid fatalities. This classification scheme is consistent with other work documenting opioid fatalities (Rudd et al. 2016).

The fatal occupational injury data in the NVSS is often subject to measurement error, but I mitigate such measurement error to the extent possible using the Bureau of Labor Statistics' Census of Fatal Occupational Injuries ("CFOI"). Because the NVSS data are coded using death certificates and not all certifiers record whether a fatality occurred as a result of an occupational injury, approximately 80% of the observations in the data are missing an entry for whether an individual died of an occupational fatality. Cross-referencing with the Census of Fatal Occupational Injuries, a full census of all individuals who died of occupational injuries, demonstrates that the Vital Statistics data accurately identify approximately 90% of occupational fatalities within states. For the individuals for whom data is missing, I use publicly available state level data from the CFOI to identify the residual probability that each fatality marked as "unknown" actually occurred on the job.[4] I impute these probabilities when I construct worker fatality counts and rates to reduce the measurement error in my worker fatality data.

I combine the vital statistics data with several other data sources containing state and county time-variant characteristics. I gather data on county-level macroeconomic characteristics from the Bureau of Labor Statistics' Quarterly Census of Employment and Wages. The Quarterly Census on Employment and Wages publishes quarterly reports on employment and wages at the county level. Controlling for local macroeconomic conditions is important given that several papers have demonstrated that substance abuse is positively associated with macroeconomic conditions (Carpenter et al. 2017), although opioid-specific studies have found the opposite effect (Hollingsworth et al. 2017). I use county-level demographic information from the Census

[4] The difference between the CFOI fatality count and the NVSS data for a given state and year provides the quantity of "residual" workplace fatalities that the NVSS data fail to identify. I estimate the quantity of unknown fatalities in a county and month that are actually workplace fatalities as the number of unknown fatalities in the relevant county and month divided by the annual unknown fatalities in the relevant state, multiplied by the number of residual fatalities in the state.

Bureau, including county population, the percentage of the county population that is white, and the average age of county residents.

I also draw on the National Provider Identifier ("NPI") database to construct counts of various medical providers and facilities at the county level from 2006 to 2016. The availability of medical services is plausibly associated with both fatal worker injuries as well as opioid overdoses. For example, Bertoli and Grembi (2017) demonstrated greater distances to the nearest hospital increases car accident fatality rates. Similarly, quick access to emergency medical care can increase the probability that an individual who is injured at work or who is overdosing survives. All medical providers who are required to comply with the Health Insurance Portability and Accountability Act of 1996 (more commonly referred to by its acronym, "HIPAA") or who bill Medicare for services must obtain an NPI. The information associated with any given NPI is publicly available in the National Plan and Provider Enumeration System's NPI Registry. The NPI Registry provides the taxonomy of the provider as well as the provider's street address. I collapse the NPI registry's data into a count of pharmacies, hospitals, and emergency medical technicians in each county in the United States for each month that my data cover. The NPI data will not capture *every* such medical provider or facility, as some may choose not to accept Medicare. EMTs are relatively more likely to be undercounted in the data as they will not generally be required to register individually. To better capture how many first responders are available to respond to either a fatal workplace injury or an overdose, I also gather an annual count of the amount of police officers in each county in the United States from the 2006 to 2016 FBI Crime in the United States Publications.

Finally, I gather data on several state statutes that are relevant to opioid overdose fatalities. I gather information on whether each state in my data had a naloxone access law, a medical marijuana law permitting marijuana to be dispensed to treat pain, a recreational marijuana law, any prescription drug monitoring program, ("PDMP") and whether prescribers are required to access the PDMP before prescribing. Information on each of these statutes are from the Prescription Drug Abuse Policy System's database. PDMPs require or permit dispensers to record prescriptions of controlled substances in a database that medical providers can access (Paulozzi et al. 2011). Such programs provide more information to clinicians, enabling them to provide better care. State PDMPs have been an effective tool in reducing concurrent opioid prescriptions (Griggs 2015; Johnson et al. 2014). Some studies have found that medical marijuana laws are associated with opioid fatalities, although the results are inconclusive and have varied greatly depending on the exact provisions in such statutes (Buchmueller and Carey 2018; Powell et al. 2018).

Table 1 provides summary statistics for each of the variables I utilize in this chapter. The average county exhibits an opioid fatality rate of 0.82 fatal overdoses from any opioid per 100,000 residents per month, just under 10 fatalities per 100,000 residents annually. The average rates mask a large amount of county-level heterogeneity; counties at the 95th percentile exhibited 2.9 fatalities per 100,000 county residents per month, while the majority of county-months in my sample actually exhibited no overdose fatalities.[5] The average rate of opioid overdoses exceeds the rate of fatal worker injuries.[6] In the average county, 0.37 workers per 100,000 workers per month experience a fatal injury on the job—about 4.4 workers annually per 100,000 individuals employed. Like the overdose rates, individual counties differed substantially from the mean rate. County-months at the 95th percentile exhibited 1.2 fatal worker injuries per 100,000 individuals

[5] Of the 414,498 county-months included in my analysis, 319,602 exhibited 0 opioid overdose fatalities. After weighting each county-month by its population as I do in my regression analysis, the 0 overdose counties account for 34.1% of the weighted observations.
[6] The number of opioid overdose fatalities exceeds the number of worker fatalities in 79.9% of county-months exhibiting at least one opioid overdose fatality or worker fatality.

employed in the county, and most county-months exhibited no workplace fatalities.[7] The mean weekly wage in the average county is $890 and the average age is 38 years old. When weighting by county population, the average county has an employment-to-population ratio of 0.50, though the unweighted average is substantially smaller at 0.35, indicating that high-population areas exhibit better macroeconomic conditions generally across the U.S.

B. Empirical Methodology

I estimate the relationship between fatal opioid overdoses and fatal injuries using a two-way fixed effects model and ordinary least squares.[8] My initial empirical specification regresses the rate of fatal worker injuries, W_{ct}, on the rate of fatal opioid overdoses, O_{ct}, and county opioid prescriptions per capita, Rx_{ct}. The estimating equation is as follows, where c indexes counties and t indexes months:

$$W_{ct} = \alpha + \beta_1 O_{ct} + \beta_2 Rx_{ct} + X_{ct}\beta + \gamma_c + \delta_t + e_{ct} \tag{1}$$

The vector of variables X_{ct} includes the mean weekly wage in the county, the employment to population ratio, the county population, the percent of the population which is white, the average age in the county, the number of pharmacies, hospitals, and EMTs per 1,000 residents in the county, and the number of police officers per 1,000 county residents. The final variables, γ_c and δ_t are fixed effects for each county and month in my sample. Including these fixed effects controls for time-invariant characteristics of counties or time that may be correlated with opioid fatalities, such as national macroeconomic trends or the rural character of a county.

[7] Before adding the residual fatality probability to each county-month as described in footnote 30, 378,989 of 414,498 county-months exhibited no worker fatalities. After weighting each county-month by its population as I do in my regression analysis, the zero worker fatality county-months account for 68.0 % of the weighted observations. In the instrumental variable models of Section V, 311,838 county-months had no worker fatalities in neighboring counties. After weighting each observation by its population, the zero border fatality county-months account for 57.6% of the weighted observations.

[8] I utilize the reghdfe Stata package to perform the ordinary least squares estimation, as it is dramatically faster than the default package in Stata (Correia 2017).

Upon first glance, measuring the relationship between opioid abuse and job dangerousness using fatality rates may seem peculiar. Generally, if an individual is fatally injured at work they did not fatally overdose on opioids (and the reverse is true as well).[9] Opioid fatality rates serve as a proxy for underlying opioid abuse, though it is a noisy measure in circumstances where increases in opioid abuse do not increase fatal opioid overdoses. Including county-level prescription rates in equation 1 controls for some, but not all, of the opioid use that would lead to a divergence between opioid fatality rates and opioid abuse rates.

Fatal occupational injury rates similarly measure general job dangerousness. Fatal occupational injuries are strongly correlated with non-fatal injuries and are routinely used to measure job risks (Viscusi 2004; Viscusi and Gentry 2015). Fatal injury rates are easier to measure than non-fatal injury rates; ambiguity in injury rates can arise when individuals have different thresholds at which they consider a non-fatal workplace injury serious enough to report. Non-fatal injury data mask substantial heterogeneity in the nature of injuries that they count. Moreover, government data sources on non-fatal workplace injuries are substantially less complete[10] and reliable than comparable fatal worker injury data (Rappin et al. 2016). As a result, workplace fatality rates are more appropriately viewed as a proxy for general job dangerousness in a county rather than only measuring the worker fatalities. However, this measure will fail to capture any increases in job place risks that opioid abuse causes which does not correlate with increases in fatal injuries. My empirical estimates will fail to identify the total effect of opioid abuse on worker injuries if, for example, individuals who abuse opioids in very safe jobs have increased nonfatal injury risks, but not increased fatal injury risks. As a result, my

[9] It is theoretically possible, though quite unlikely, that a given individual could suffer a fatal workplace injury for which an opioid overdose is a cause of death. For example, an individual at work could fall upon the onset of an overdose and sustain a fatal injury as a result of the fall. Such niche cases are not my focus here.
[10] The Survey of Occupational Injuries and Illnesses from the Bureau of Labor Statistics provides data from only 41 states and Washington, D.C. at the state-year level, unlike the fatality data I use here which is at the county-month level.

estimates should be considered a lower bound on the aggregate effect of opioid abuse on worker injuries.

Additionally, my data do not provide good measures of the availability of products that may be opioid substitutes, such as marijuana. Like opioids, marijuana is used both medically to treat pain and used nonmedically (Ilgen et al. 2013). As a result, opioids and marijuana may be substitutes for opioid users, though the probability of substitution will likely be lower among individuals who are opioid-dependent. Some drugs, such as benzodiazepines, may be opioid complements (Ladapo et al. 2018), at least in the sense that changes in opioid overdose fatalities are positively correlated with prescriptions or changes in deaths associated with such drugs. If marijuana or other non-opioid drugs are substitutes for opioids and affect the probability of injury at work (and at least some studies have found an association between marijuana use and workplace injuries (Ramchan et al. 2009), their omission from the ordinary least squares model in equation 1 will bias the estimate of the relationship between opioid overdoses and worker fatality rates. If a drug is a substitute of opioids and increases the rate of worker injuries, then the results will be biased downward so that my estimate is a lower bound on the actual relationship between opioid overdoses and workplace fatalities. If a drug is an opioid compliment and increases the rate of worker injuries, then the results from equation 1 will be biased upwards.[11]

IV. Ordinary Least Squares Estimates

Table 2 provides the results of estimating equation 1 on my sample. The dependent variable is fatal worker injuries per 100,000 employees in a county. The first column corresponds to the standard two-way fixed effects model. Column 2 augments the model with state-specific time trends and column 3 augments the model with county-specific time trends. The results

[11] Further, because the passage of state level opioid policies should be unrelated to the use and abuse of opioid substitutes or compliments, the IV estimates using state laws in Section V should reduce any potential bias attributable to substitutes.

indicate that higher opioid fatality rates in a county are associated with higher worker fatality rates. A one-unit increase in opioid fatalities per 100,000 residents gives rise to a 0.02 unit increase in the worker fatality rate per 100,000 workers. In other words, fatal opioid overdoses are associated with an average of approximately 206 excess worker fatalities per year, or 2,827 total fatalities from 2006 to 2016. Expressed as an elasticity, a 1% increase in fatal opioid overdose rates is associated with a 0.05% increase in worker fatal injury rates. The estimate is remarkably stable across the three models, with a range of 0.020–0.021. An increase in opioid prescriptions per capita has a statistically significant effect only in the base model. On balance, the results indicate that the increase in worker fatality rates is due to increases in opioid abuse rather than increases in medical use of opioid prescriptions.

The other effects in Table 2 are generally consistent with expectations and previous research. The coefficients on mean weekly wages and employment-to-population ratios demonstrate that worker fatalities increase as macroeconomic conditions improve. The coefficient on population is significant and positive in the model with county-specific time trends, suggesting that increases in population marginally increase the worker fatality rate. Pharmacies are associated with a lower worker fatality rate and hospitals are associated with a higher worker fatality rate, consistent with hospitals self-sorting into health care markets with higher injury rates or possibly being more-dangerous-than-average workplaces (OSHA 2013). The remaining variables do not have a significant or consistent effect on the fatal worker injury rate.

It is plausible that there are differences in the relationship between opioid fatality rates and worker injury rates by opioid type, as there may be substantial demographic differences by type of opioid used. Individuals who work in more dangerous jobs may be more willing to tolerate risk and therefore use riskier opioids when they choose to do so.[12] Alternatively, such users may be risk averse, as dangerous jobs are often lower-paying blue-collar jobs that may leave workers less able to weather financial shocks. Heroin users are more likely to be male, nonwhite, and young (Jones et al. 2015), while individuals receiving prescription opioids are more likely to be female, white, and older.[13]

Table 3 re-estimates equation 1, replacing the unitary opioid fatality rate with four rates: the heroin, pain medication, synthetic opioids, and other opioids fatality rates. The estimates in Table 3 indicate that the increase in worker fatalities associated with opioid abuse is most strongly related to pain medication abuse, rather than heroin, synthetic, or other opioids.[14] The coefficient on the heroin rate is not statistically significant in any of the models. The pain medication rate coefficient is significant at the five percent level in all three models. The point estimate is 80% as large as the any opioid estimate from Table 2. The coefficients for the synthetic opioid rates and other opioid rates are significant at the ten percent level in the base model, but not the models that include state or county specific time trends.

The results here contrast starkly with the results in chapter 2 indicating that individuals who receive pain medication prescriptions are less likely to overdose. The significant effect on the pain medication rate would be consistent with such users exposing themselves to greater workplace risks as a result of their use. However, individuals who use counterfeit pain medications or purchase pain medications from illicit sources could also be driving the effect, and my data do not enable me to disentangle these possibilities. Nevertheless, the effects suggest that reducing employee use of pain medication opioids is likely to decrease the fatal risk identified in Tables 2 and 3.

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[12] But see Chapter 2, Table 2, indicating no relationship between self-assessed riskiness and opioid prescriptions.
[13] See chapter 2, Table 2.
[14] Because overdose fatalities by drug type are not mutually exclusive, some fatalities are included in multiple rates. Approximately 15% of opioid overdose fatalities in the NVSS data involved more than one opioid type.

Finally, Table 4 investigates whether there are substantial differences in the relationship between opioid abuse and worker injuries by county urbanization. While urban counties have the highest average rate of fatal opioid overdoses, rural counties constitute a disproportionate amount of the right tail of the distribution of fatality rates. Moreover, a disproportionate number of counties with the highest rates of opioid prescribing are rural, which Table 2's results indicate are a key factor behind the relationship between opioid overdoses and worker fatal injury rates. Combined with the fact that rural counties and suburban counties have significantly larger worker fatality rates than urban counties (0.63 and 0.38 fatalities per 100,000 workers versus 0.26 fatalities per 100,000 workers), it is plausible that worker fatalities are more likely to manifest as a consequence of the opioid epidemic in rural and suburban areas.

Table 4 breaks the sample into three subsamples: rural counties, suburban counties, and urban counties.[15] Each entry in the table corresponds to the estimated coefficient of the opioid overdose fatality rate for a different regression. As with Tables 2 and 3, the three columns of Table 4 correspond to a base model, a model including state time trends, and a model including county time trends. The first row corresponds to regressions ran on my rural county subsample, the second row corresponds to suburban counties, and the third row corresponds to urban counties. Table 4 demonstrates that the effects from Tables 2 and 3 occur predominantly in rural and suburban counties. A one unit increase in the opioid overdose fatality rate is significantly (at the ten percent level) associated with 0.03 more worker fatalities per 100,000 employees in a county. In suburban counties the effect is significant at the one percent level; the effect is smaller (by 0.01–0.02 fatalities per 100,000 individuals), but more precisely estimated. The estimate is significant in the urban county subsample only in the base model.

[15] I adapt the National Council of Health Statistics ("NCHS") Urban-Rural Classification scheme for this analysis. I classify a county as urban if the NCHS classification of a county is "Large central metro" or "Large fringe metro." I classify a county as suburban if the NCHS classification of a county is "Medium metro" or "Small metro." Finally, I classify a county as rural if the NCHS classification is "Micropolitan" or "Noncore."

V. Instrumental Variables Estimates

A. Instruments and First Stage Results

It is possible that the OLS estimates in Section 3 suffer from simultaneity bias. Injured workers may receive prescription opioids, which may lead to such workers abusing opioids, possibly increasing the fatal opioid overdose rate in a county. Alternatively, individuals who abuse opioids may have different risk preferences and sort into riskier jobs. Previous research has demonstrated that individuals who smoke sort into more dangerous jobs (Viscusi and Hersch 2008); opioid users could resemble smokers in this regard.[16] The model in equation (1) could therefore be written with opioid overdose rates and prescriptions as the dependent variables, as in the following equations:

$$O_{ct} = \alpha + \beta_1 * W_{ct} + X_{ct}\beta + \gamma_c + \delta_t + e_{ct} \tag{2}$$

$$Rx_{ct} = \alpha + \beta_1 * W_{ct} + X_{ct}\beta + \gamma_c + \delta_t + e_{ct} \tag{3}$$

I will address potential simultaneity using instrumental variables estimation. Instrumental variables estimation requires identifying an instrument that is (1) relevant (i.e., correlates sufficiently with the endogenous explanatory variable of interest), and (2) excludable (i.e, uncorrelated with the dependent variable *except* though its relationship with the endogenous explanatory variable) (Angrist and Pischke 2009). The instruments I use for fatal worker injury rates are the rate of fatal worker injuries in all neighboring counties. The instruments I use for opioid fatality rates are naloxone access laws and prescription drug monitoring program policies. Figure 3 provides a graphic illustration of the instrumental variables model.

[16] The estimates in Table 2 of chapter 2 suggest that this is unlikely, as there is little relationship between self-assessed riskiness and the probability of receiving an opioid prescription.

Neighboring county fatal worker injury rates are relevant and excludable instruments. The first stage results are detailed in Appendix Table A1. The estimates demonstrate that border county worker fatality rates are a strong instrument for worker fatality rates in the county of interest. The exclusion restriction will be satisfied as long as border county worker fatality rates are not directly related to opioid fatality rates in the county of interest. While no statistical test exists that can directly demonstrate whether the exclusion restriction is met, the data yield evidence that apparent mechanisms that would threaten the validity of the instrument do not exist.

One mechanism that could cause a violation of the exclusion restriction would be for individuals to commute across county lines to acquire and abuse opioids, but not to work. If opioid commuting is unrelated to the worker fatality rate, then it would suggest that this mechanism does not threaten the validity of my instrument. To test this relationship, I measure opioid commuting as the percent of overdose deaths in a county that represent deaths of individuals who live in another county. Regressing either the worker fatality rate or the worker fatality rate in neighboring counties on this measure of opioid commuting, controlling for county and time fixed effects, the coefficient on opioid commuting is statistically insignificant with $p > 0.75$.

Another mechanism would be for social networks among opioid users to stretch across counties, so that individuals who use opioids in a given county may cause individuals to use opioids in a neighboring county. This is particularly plausible given that communities are often not segregated across county lines. Particularly in rural counties, individuals frequently travel across county lines to socialize or work. Social networks are unlikely to threaten the validity of my instrument here, however. Previous research suggests that social networks will be a primary method of opioid distribution in isolated and rural communities (Runyon 2017). Such isolated and rural communities are the communities where border county fatalities rates are not likely to provide identification in regressions using the border-county instrument because their labor markets will likely be relatively less similar to the labor markets in neighboring counties than in less rural areas. Finally, even if the instrument is not perfectly exogenous, because the border county instrument is strong, any residual bias will likely be in the same direction as ordinary least squares and smaller in magnitude, so that the results would be biased in the direction of the OLS estimate though smaller in magnitude.

State laws regulating naloxone access and prescription drug monitoring programs ("PDMPs") are likewise relevant and excludable instruments for opioid overdose rates. The first stage results for my instrumental variables estimation are detailed in Appendix Table A2 and demonstrate that naloxone access laws combined with PDMP laws are relevant instruments for fatal opioid overdose rates and opioid prescription levels. There is no direct mechanism by which naloxone access could affect worker fatality rates, as standalone naloxone products are *only* useful for reversing an ongoing opioid overdose. Moreover, as demonstrated in the Technical Appendix to Chapter 1, the adoption of a naloxone access law is exogenous with respect to overdose fatalities. As a result, worker fatality rates cannot have some attenuated effect on the adoption of a naloxone access law, even if such rates have a reverse causal effect on overdose rates themselves. Likewise, prescription drug monitoring programs and laws requiring prescribers to consult them do not affect labor markets directly but rather change the probability that an individual is able to acquire prescription opioids or other controlled substances.

Using naloxone access laws and prescription drug monitoring programs as an instrument presents one unique challenge, however. If these policies only affect the probability that an individual suffers an opioid overdose without affecting the extent to which individuals use or abuse opioids, the statutes would not be appropriate instruments. In this case, naloxone access would merely change the probability an individual dies conditional on an overdose, without changing the probability that the population of employed individuals will be injured on the job. As a result, it is necessary to demonstrate that naloxone access laws not only affect opioid overdose rates but also opioid use rates themselves. Appendix Table A2 demonstrates that these laws are strong instruments for opioid prescribing rates as well as fatality rates alone.

B. Instrumental Variable Results

Table 5 presents my IV estimates examining whether simultaneity bias exists in the relationship between opioid use and overdose rates and fatal worker injuries. Columns 1, 2, and 3 estimate the effect of job dangerousness on overdose fatality rates, while columns 4, 5, and 6 estimate the effect of job dangerousness on opioid prescribing rates. These estimates directly test for whether simultaneity bias exists in the results from Tables 2, 3, and 4. Columns 1 and 4 correspond to the base models, columns 2 and 5 include state-specific time trends, and columns 3 and 6 augment the previous models with county-specific time trends.

The results in Table 5 demonstrate that increases in fatal worker injuries have no statistically significant relationship with opioid overdoses or prescriptions. Across all six models, the estimated coefficient on the instrumented worker fatality rate is small and insignificant. It is somewhat counterintuitive that job dangerousness does not increase opioid prescriptions per capita. The results suggest that increases in job dangerousness do not increase opioid prescriptions after controlling for fixed geographic characteristics and general time trends. In particular, prescribers nationwide have become more reluctant to prescribe opioids for injuries in recent years.[17] The national time trends combined with the null result in columns 4, 5, and 6 indicate that the relationship between acute worker injuries and opioid prescriptions may be

[17] The month fixed effects in columns 4, 5, and 6 indicate that nationwide opioid prescription rates decreased in 2015 and 2016, after controlling for all other variables in the model.

weakening. Table 5's results indicate that simultaneity bias is not likely a large concern in the OLS estimates from Tables 2, 3, and 4. Another explanation which cannot be ruled out is that border county worker fatality rates may have been too weak or too inadequate of an instrument to identify any effect if one existed. While the instrument plausibly provides exogenous variation sufficient to identify an effect, it remains possible that the instrument itself is faulty.

Table 6 provides my IV estimates of the relationship of opioid overdose rates with worker fatalities. Columns 1, 2, and 3 correspond to the base model, the model including state time trends, and the model including county time trends. The results are entirely consistent with the ordinary least squares results above: increases in the opioid overdose fatality rate yield increases in the fatal worker injury rate. However, the IV estimates are substantially larger than the OLS estimates. The opioid fatality rate coefficients indicate that an increase in the fatal opioid overdose rate of 1 per 100,000 individuals increases the worker fatal injury rate by 0.139–0.185 fatalities per 100,000 employees. In other words, an increase in opioid abuse that causes a 1% increase in the fatal opioid overdose rate is associated with a 0.30–0.41% increase in fatal work injuries. Put more concretely, the IV estimates indicate that the nationwide increase in fatal overdose rates from 2014 to 2015 led to an additional 307 worker fatalities relative to 2014. Because Table 5 demonstrated no evidence that worker injuries are fueling opioid abuse, the smaller OLS estimates in Table 2 are likely preferable to the estimates here. The reason for the substantially larger estimates is likely two-fold. First, IV estimation is less efficient than ordinary least squares, and the higher estimate may be a function of the larger variance of the estimator. Second, the F-test for instrument strength indicates that even though naloxone access and prescription drug monitoring program legal provisions are sufficient to predict opioid fatalities or opioid prescriptions, they are weak instruments for predicting both simultaneously. As a result, the estimates may suffer from a positive weak instrument bias, which pushes the estimates upward.

VI. Conclusion

The analysis in this chapter provides evidence that opioid abuse has substantially increased risks that workers in the United States face. Between 2006 and 2016, opioid abuse was associated with at least 2,800 excess worker fatalities. In 2016, approximately 8% of the 5,313 worker fatalities were likely related to opioid abuse. Identifying this new source of fatalities attributable to the opioid epidemic is the primary contribution of this chapter. This research adds to the mounting evidence that the impacts of the opioid epidemic stretch into labor markets in addition to increasing overdoses and drug use.

My results do not provide any evidence that dangerous jobs are currently fueling the opioid epidemic, however. The IV estimates provide no evidence that geographic concentration of worker injuries causes an increase in worker fatalities or opioid prescriptions per capita, at least in the years that my data cover. These findings could be because individuals who are injured on the job rarely begin abusing opioids in a manner that exposes them to higher risks of opioid overdose, even if such individuals do use opioids repeatedly. This would be consistent with my findings in chapter 2, which demonstrate that sizeable decreases in the probability of opioid prescriptions to repeat opioid users have no effect on the opioid overdose fatality rate.

The results here indicate that collateral policy responses by occupational safety agencies may be appropriate in addition to the policy responses that state and federal governments have taken so far to reduce fatalities from the opioid epidemic. The Occupational Safety and Health Administration ("OSHA") and its state-level counterparts have wide discretion to set enforcement priorities and implement strategic safety programs. Guidance from OSHA indicates that the agency focuses its inspection resources, in order of importance, in workplaces that: (1)

present imminent danger situations, (2) report a severe injury and illness, (3) are subject to worker complaints, (4) are referred from other agencies or the media, (5) are historically high-hazard industries or employers, and (6) require follow-up inspections to ensure compliance with an order of abatement (OSHA 2016). Federal law empowers the agency to shift these priorities as workplace risks evolve over time.[18] Under this authority, OSHA has previously established alliances with other federal agencies and private organizations to decrease methamphetamine abuse in the workplace and promote drug-free work environments (OSHA 2008). Prioritizing and increasing inspections in counties with particularly large concentrations of opioid overdoses could stem the flow of worker fatalities attributable to opioids. This policy shift has the added advantage of mitigating the impact of worker injuries on opioid use and abuse if such effects truly exist and the model presented here merely failed to identify them.

More broadly, the results indicate that individuals who medically use prescription opioids to treat acute injuries are not the individuals who are fueling the dramatic increase in overdose deaths that has occurred in recent years. Even though abuse of medications (or illicit substances containing the same compounds) drive the increased worker injury rate, there is no evidence that increases in job injuries increase overdoses. Efficient opioid policy must shift away from its laser-like focus on prescription supply toward reducing the availability of and the demand for these illicit drugs. Particularly because these drugs function as substitutes for one another, without a cohesive strategy for reducing fatalities from all opioids, policy efforts are likely to merely shift users from one drug to another rather than cause meaningful change.

[18] See Industrial Union Department v. American Petroleum Institute, 448 U.S. 607 (1980), which recognizes that 29 U.S.C. § 655(g) requires the Secretary of Labor, acting through OSHA, to establish priorities in setting occupational safety standards that address more serious risks first, taking into account the benefits and costs of various priorities.

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Figures

Figure 1: Opioid fatal overdose rates over time

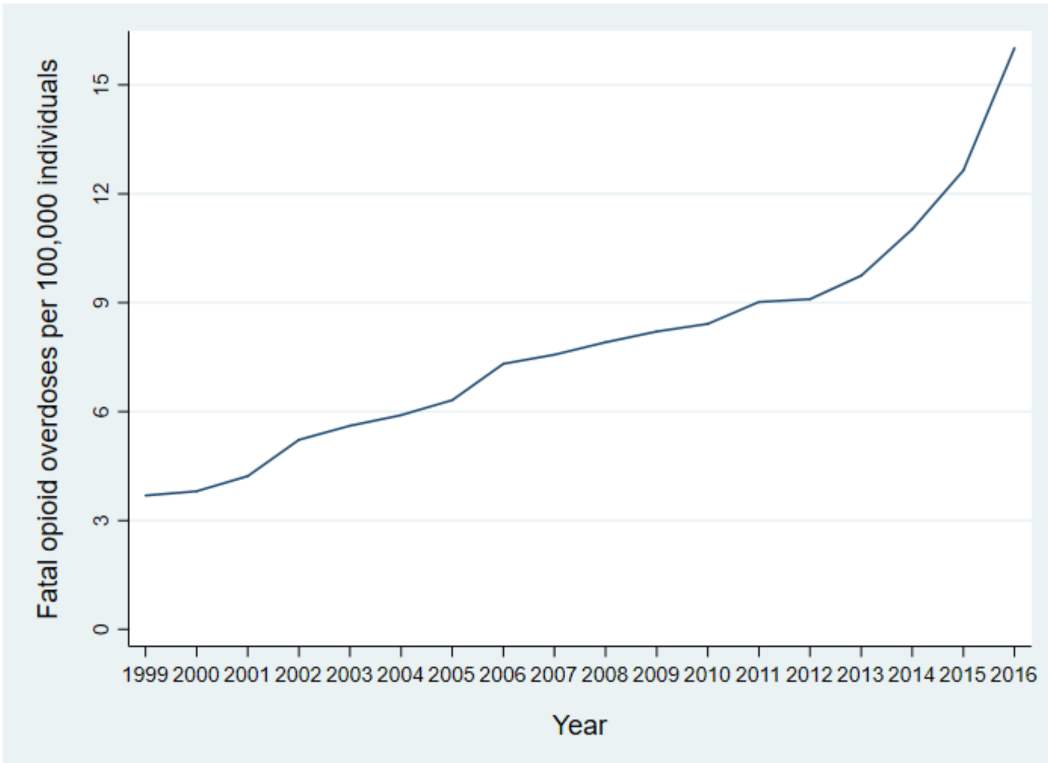


Figure 2: Worker fatal injury rates over time

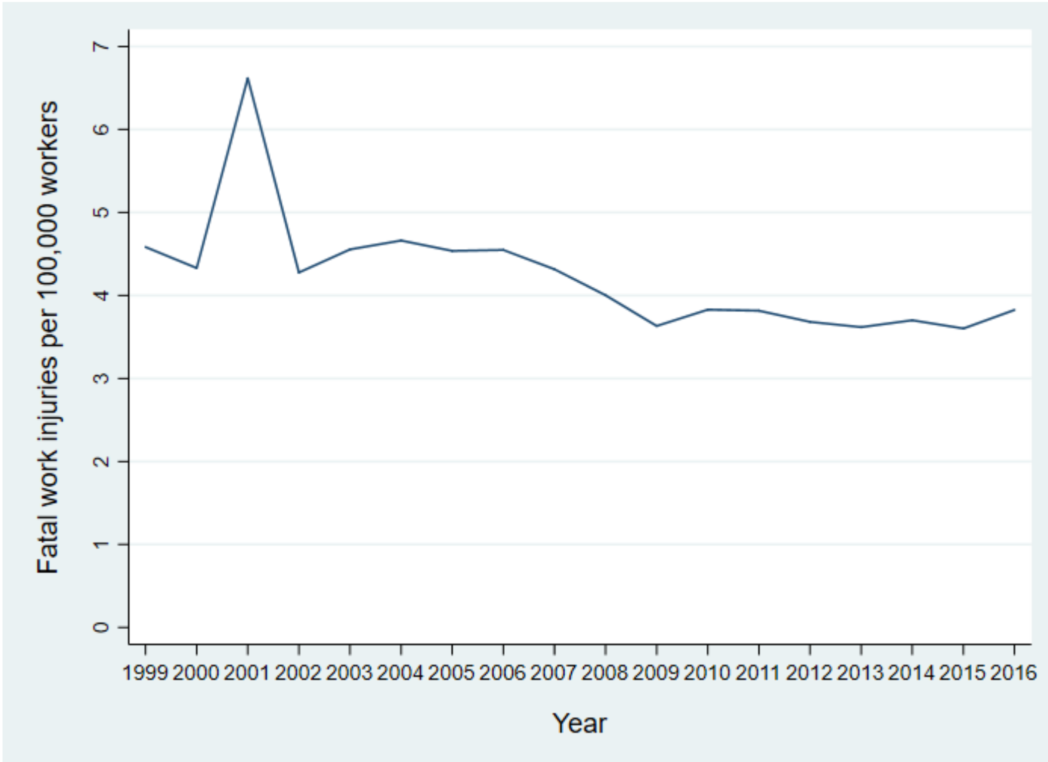
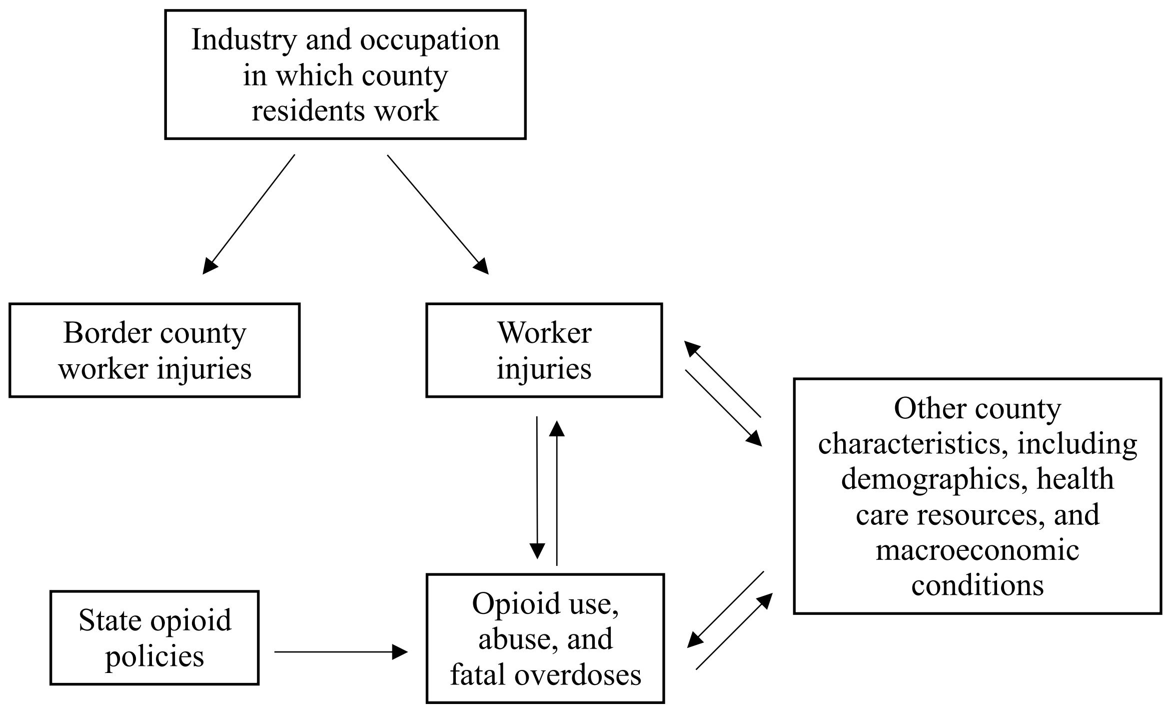


Figure 3: Graphic representation of the instrumental variable model



Tables

Table 1: Summary statistics

Variables	Mean	Median	Standard deviation
Opioid overdose fatalities per 100,000 individuals	0.815	0.486	1.174
Fatal worker injuries per 100,000 employees	0.369	0.067	1.984
County characteristics:			
Opioid prescriptions per capita	0.870	0.814	0.476
Mean weekly wage ($ 2015 thousands)	0.892	0.849	0.212
Employment to population ratio	0.498	0.413	0.434
Population (hundreds of thousands)	4.235	3.072	3.710
White population (%)	0.769	0.834	0.204
Mean age	38.101	37.901	2.964
Pharmacies	1.126	0.190	5.369
Hospitals	0.249	0.060	0.539
EMTs per 1,000 residents	0.006	0.002	0.025
Police per 1,000 residents	0.819	0.614	0.950
Opioid policies:			
Naloxone provider legal immunity	0.157	0.000	0.364
Naloxone administrator legal immunity	0.200	0.000	0.400
Third party naloxone prescribing	0.202	0.000	0.401
No patient-specific naloxone prescription req’t	0.167	0.000	0.373
PDMP	0.883	1.000	0.321
Must access PDMP	0.086	0.000	0.281
Medical marijuana	0.147	0.000	0.354
Recreational marijuana	0.013	0.000	0.114

Note: N = 414,498. Observations are at the county-month level. Summary statistics are weighted by county population.

Table 2: OLS estimates of the effect of opioid abuse on worker fatal injury rates

Variables	(1)	(2)	(3)
Opioid fatality rate	0.021	0.020	0.020
	(0.008)**	(0.008)**	(0.009)**
Opioid prescriptions per capita	0.064	0.025	-0.016
	(0.031)**	(0.034)	(0.047)
Mean weekly wage ($ 2015 thousands)	0.121	0.129	0.118
	(0.041)***	(0.042)***	(0.039)***
Employment to population ratio	-0.069	-0.124	0.021
	(0.052)	(0.057)**	(0.065)
Population (hundreds of thousands)	0.007	-0.002	0.045
	(0.014)	(0.014)	(0.019)**
White population (%)	-0.275	-0.265	-0.416
	(0.208)	(0.212)	(0.403)
Mean age	0.006	0.005	-0.003
	(0.006)	(0.005)	(0.007)
Pharmacies	-0.001	-0.002	-0.002
	(0.001)	(0.001)**	(0.001)***
Hospitals	-0.006	-0.023	0.071
	(0.012)	(0.012)*	(0.034)**
Pain clinics	-0.059	-0.034	-0.222
	(0.098)	(0.080)	(0.174)
EMTs per 1,000 residents	0.023	0.040	-0.059
	(0.168)	(0.167)	(0.315)
State specific time trends		X	X
County specific time trends			X

Note: N = 414,498. Dependent variable is fatal worker injuries per 100,000 workers. Standard errors robust and clustered on county. All regressions include county and month-by-year fixed effects and are weighted by county population. *** p<0.01, ** p<0.05, * p<0.1.

Table 3: OLS estimates of fatal worker injuries by opioid type

Variables	(1)	(2)	(3)
Heroin fatality rate	0.003	-0.000	-0.002
	(0.006)	(0.006)	(0.006)
Pain medication fatality rate	0.016	0.017	0.017
	(0.008)**	(0.008)**	(0.008)**
Synthetic opioids fatality rate	0.010	0.007	0.008
	(0.005)*	(0.006)	(0.006)
Other opioids fatality rate	0.016	0.015	0.011
	(0.009)*	(0.010)	(0.010)
Opioid prescriptions per capita	0.062	0.024	-0.016
	(0.032)**	(0.034)	(0.048)
Mean weekly wage ($ 2015 thousands)	0.118	0.129	0.119
	(0.041)***	(0.042)***	(0.039)***
Employment to population ratio	-0.074	-0.125	0.031
	(0.051)	(0.057)**	(0.062)
Population (hundreds of thousands)	0.007	-0.001	0.047
	(0.014)	(0.014)	(0.019)**
White population (%)	-0.317	-0.359	-0.513
	(0.214)	(0.215)*	(0.394)
Mean age	0.007	0.006	-0.002
	(0.006)	(0.005)	(0.007)
Pharmacies	-0.001	-0.002	-0.003
	(0.001)	(0.001)**	(0.001)***
Hospitals	-0.002	-0.019	0.066
	(0.012)	(0.013)	(0.032)**
Pain clinics	-0.063	-0.027	-0.245
	(0.098)	(0.079)	(0.175)
EMTs per 1,000 residents	0.021	0.042	-0.078
	(0.168)	(0.168)	(0.318)
State specific time trends		X	X
County specific time trends			X

Note: N = 414,498. Dependent variable is fatal worker injuries per 100,000 workers. Standard errors robust and clustered on county. All regressions include county and month-by-year fixed effects and are weighted by county population. *** p<0.01, ** p<0.05, * p<0.1.

Table 4: OLS estimates of fatal worker injuries on fatal opioid overdose rates by urbanization

Subsample	(1)	(2)	(3)
Rural counties	0.027	0.027	0.027
	(0.016)*	(0.016)*	(0.016)*
Suburban counties	0.016	0.014	0.015
	(0.005)***	(0.005)***	(0.005)***
Urban counties	0.011	0.009	0.007
	(0.005)**	(0.005)*	(0.006)
State specific time trends		X	X
County specific time trends			X

Note: N = 414,498. Each entry is the estimated coefficient of the fatal opioid overdose rate from the regression of fatal worker injury rates on fatal overdose rates. Standard errors robust and clustered on county. All regressions control for opioid prescribing rates, mean weekly wages, employment to population ratios, county population, the percent of the county population that is white, the mean age in the county, the number of pharmacies, hospitals, and pain clinics in the county, and the number of EMTs per 1,000 residents. All regressions also include county and month-by-year fixed effects and are weighted by county population. *** p<0.01, ** p<0.05, * p<0.1.

Table 5: IV Estimates of the effect of worker fatal injury rates on opioid overdoses and prescription rates

	Fatal overdose rate			Prescriptions per capita		
Variables	(1)	(2)	(3)	(4)	(5)	(6)
Worker fatality rate	0.015	-0.056	-0.071	0.021	0.007	-0.008
	(0.131)	(0.133)	(0.140)	(0.015)	(0.016)	(0.013)
Mean weekly wage	0.018	0.074	0.084	0.011	0.012	0.029
($ 2015 thousands)	(0.088)	(0.082)	(0.086)	(0.011)	(0.009)	(0.009)***
Employment to	0.547	0.764	1.604	-0.062	-0.011	0.098
population ratio	(0.379)	(0.330)**	(0.808)**	(0.055)	(0.052)	(0.044)**
Population (hundreds	-0.217	-0.145	-0.180	-0.012	-0.020	0.002
of thousands)	(0.055)***	(0.048)***	(0.164)	(0.009)	(0.008)**	(0.015)
White population (%)	1.062	-0.803	-2.928	1.000	0.870	0.451
	(1.322)	(1.025)	(1.801)	(0.153)***	(0.145)***	(0.266)*
Mean age	-0.093	-0.095	-0.020	0.001	0.000	-0.002
	(0.029)***	(0.028)***	(0.037)	(0.003)	(0.003)	(0.005)
Pharmacies	-0.000	-0.006	-0.016	-0.001	-0.000	-0.000
	(0.004)	(0.005)	(0.006)***	(0.001)**	(0.000)	(0.000)
Hospitals	0.107	0.058	-0.455	-0.003	-0.020	0.006
	(0.110)	(0.086)	(0.365)	(0.014)	(0.013)	(0.017)
Pain clinics	0.228	0.938	0.730	-0.145	-0.017	0.175
	(0.324)	(0.272)***	(1.761)	(0.131)	(0.086)	(0.334)
Police per 1,000	-0.054	-0.040	-0.025	-0.000	-0.001	-0.001
residents	(0.037)	(0.033)	(0.025)	(0.005)	(0.005)	(0.004)
EMTs per 1,000	-0.237	-0.035	-0.410	0.027	-0.004	0.004
residents	(0.110)**	(0.105)	(0.289)	(0.032)	(0.029)	(0.064)
Must access PDMP	0.198	0.074	0.073	-0.040	-0.021	-0.019
law	(0.043)***	(0.036)**	(0.035)**	(0.007)***	(0.004)***	(0.004)***
Any PDMP	-0.001	0.130	0.137	-0.004	-0.006	-0.005
	(0.030)	(0.025)***	(0.026)***	(0.004)	(0.003)*	(0.003)
Medical marijuana	0.192	0.159	0.148	0.023	0.019	0.020
	(0.049)***	(0.050)***	(0.047)***	(0.006)***	(0.004)***	(0.004)***
Recreational	-0.381	-0.133	-0.135	-0.052	0.024	0.025
marijuana	(0.084)***	(0.059)**	(0.058)**	(0.009)***	(0.010)**	(0.010)**
Noneconomic	0.024	-0.019	-0.022	-0.006	0.004	0.004
damage caps	(0.023)	(0.027)	(0.027)	(0.007)	(0.007)	(0.006)
Punitive damage caps	0.101	0.113	0.113	-0.019	0.014	0.012
	(0.042)**	(0.037)***	(0.038)***	(0.013)	(0.009)	(0.009)
Joint and several	0.363	-0.161	-0.169	0.023	-0.002	-0.003
liability reform	(0.045)***	(0.059)***	(0.059)***	(0.020)	(0.022)	(0.022)
F-test for instrument relevance	14.91	13.91	12.64	14.91	13.91	12.64
State time trends		X	X		X	X
County time trends			X			X

Note: N = 414,498. Dependent variable in columns 1–3 is the fatal opioid overdose rate. Dependent variable in columns 4–6 is opioid prescriptions per capita. Observations are at the county-month level. Worker fatality rate is instrumented using border county worker fatality rate; first stage results are in Appendix Table A1. Standard errors robust and clustered on county. All regressions include county and month-by-year fixed effects and are weighted by county population. *** p<0.01, ** p<0.05, * p<0.1.

Table 6: Estimates of the effect of opioid abuse on worker fatal injury rates

Variables	(1)	(2)	(3)
Opioid fatality rate	0.139	0.209	0.185
	(0.069)**	(0.079)***	(0.073)**
Opioid prescriptions per capita	0.583	0.279	0.099
	(0.363)	(0.415)	(0.395)
Mean weekly wage ($ 2015 thousands)	0.124	0.113	0.109
	(0.041)***	(0.040)***	(0.038)***
Employment to population ratio	-0.090	-0.198	-0.038
	(0.081)	(0.081)**	(0.125)
Population (hundreds of thousands)	0.042	0.029	0.071
	(0.025)*	(0.020)	(0.039)*
White population (%)	-0.839	-0.245	0.008
	(0.426)**	(0.355)	(0.618)
Mean age	0.016	0.021	0.001
	(0.008)**	(0.009)**	(0.011)
Pharmacies	-0.000	-0.000	0.000
	(0.001)	(0.001)	(0.002)
Hospitals	-0.020	-0.032	0.116
	(0.025)	(0.022)	(0.072)
Pain clinics	-0.008	-0.194	-0.451
	(0.102)	(0.101)*	(0.362)
Police per 1,000 residents	0.006	0.011	0.004
	(0.021)	(0.021)	(0.022)
EMTs per 1,000 residents	0.044	0.044	0.014
	(0.167)	(0.170)	(0.332)
Medical marijuana	-0.007	-0.024	-0.015
	(0.015)	(0.018)	(0.017)
Recreational marijuana	-0.004	0.016	0.017
	(0.037)	(0.032)	(0.030)
Noneconomic damage caps	0.007	-0.035	-0.035
	(0.015)	(0.021)*	(0.021)*
Punitive damage caps	-0.018	-0.062	-0.057
	(0.021)	(0.033)*	(0.032)*
Joint and several liability reform	-0.078	-0.022	-0.027
	(0.044)*	(0.051)	(0.051)
F-test for instrument relevance	2.719	6.817	6.855
State time trends		X	X
County time trends			X

Note: N = 414,498. Dependent variable is worker fatality rate. Opioid fatality rate and opioid prescriptions per capita are instrumented using naloxone access law provisions and prescription drug monitoring program provisions; first stage results are in Appendix Table A2. Standard errors robust and clustered on county. All regressions include county and month-by-year fixed effects and are weighted by county population. *** p<0.01, ** p<0.05, * p<0.1.

Appendix

This Appendix presents the results associated with my IV models. Tables A1 and A2 present the first stage estimates. In Table A1, columns 1, 2, and 3 correspond to the base model, models including state time trends, and models including county time trends. Table A1 provides direct evidence that border county worker fatality rates serve as a relevant instrument for worker fatality rates. The base model, model with state trends, and model with county time trends, yield F-statistics of 14.92, 13.90, and 12.63. Table A2 presents estimates of the effect of naloxone access laws and prescription drug monitoring programs on both opioid overdose fatality rates and opioid prescriptions per capita. Columns 1 and 4 present the base model estimates. Columns 2 and 5 augment the base models with state-level time trends, and columns 3 and 6 further augment the models with county-level time trends. The F-tests for instrument significance range from 6.96 to 18.33 across the six models. In all models except the opioid mortality models including geographic specific time trends, the instruments exceed the rule of thumb threshold that F should exceed 10. (Staiger and Stock 1997; Stock and Yogo 2005).

Appendix Tables

Table A1: Worker fatality rates and neighboring county worker fatality rates

Variables	(1)	(2)	(3)
Neighboring county worker deaths per 100,000 residents	0.007	0.007	0.006
	(0.002)***	(0.002)***	(0.002)***
Mean weekly wage ($ 2015 thousands)	0.149	0.149	0.141
	(0.053)***	(0.053)***	(0.048)***
Employment to population ratio	-0.072	-0.151	-0.024
	(0.082)	(0.094)	(0.120)
Population (hundreds of thousands)	0.003	-0.012	0.050
	(0.017)	(0.017)	(0.024)**
White population (%)	-0.280	-0.305	-0.712
	(0.252)	(0.262)	(0.518)
Mean age	0.005	0.003	-0.005
	(0.006)	(0.006)	(0.009)
Pharmacies	-0.001	-0.002	-0.003
	(0.001)*	(0.001)**	(0.001)***
Hospitals	-0.009	-0.026	0.066
	(0.014)	(0.015)*	(0.036)*
Pain clinics	-0.077	-0.031	-0.207
	(0.122)	(0.088)	(0.185)
Police per 1,000 residents	0.007	0.012	0.004
	(0.022)	(0.021)	(0.023)
EMTs per 1,000 residents	0.028	0.045	-0.009
	(0.168)	(0.167)	(0.323)
Medical marijuana	0.026	-0.002	0.001
	(0.009)***	(0.012)	(0.012)
Recreational marijuana	-0.051	-0.026	-0.025
	(0.021)**	(0.027)	(0.027)
Noneconomic damage caps	0.008	-0.035	-0.035
	(0.014)	(0.021)	(0.022)
Punitive damage caps	-0.014	-0.036	-0.036
	(0.018)	(0.030)	(0.030)
Joint and several liability reform	-0.010	-0.055	-0.057
	(0.031)	(0.049)	(0.050)
F-statistic for border county worker fatality rate significance	14.91	13.91	12.64
State specific time trends		X	X
County specific time trends			X

Note: N = 414,498. Dependent variable is the quantity of worker fatalities per 100,000 county residents. Standard errors robust and clustered on county. All regressions include county and month-by-year fixed effects. *** p<0.01, ** p<0.05, * p<0.1.

Table A2: Effect of naloxone access laws on opioid overdoses and prescriptions

Variables	Opioid fatality rate			Opioid prescriptions per capita		
	(1)	(2)	(3)	(4)	(5)	(6)
Naloxone provider legal	-0.043	0.027	0.044	0.017	-0.002	-0.002
immunity	(0.064)	(0.070)	(0.072)	(0.007)**	(0.004)	(0.004)
Lay naloxone administrator	0.141	0.087	0.088	-0.002	0.016	0.016
legal immunity	(0.055)**	(0.055)	(0.050)*	(0.007)	(0.005)***	(0.005)***
Third party naloxone	0.082	-0.031	-0.042	-0.037	-0.024	-0.024
Prescribing	(0.030)***	(0.027)	(0.026)	(0.005)***	(0.004)***	(0.004)***
Relaxed prescription	-0.161	-0.075	-0.076	0.022	0.005	0.005
requirements	(0.044)***	(0.038)**	(0.035)**	(0.005)***	(0.004)	(0.004)
Must access PDMP law	-0.048	0.063	0.034	0.007	0.011	0.023
	(0.067)	(0.059)	(0.059)	(0.009)	(0.008)	(0.007)***
PDMP	0.297	0.412	0.398	-0.008	0.010	0.088
	(0.279)	(0.267)	(0.512)	(0.046)	(0.037)	(0.030)***
Mean weekly wage	-0.225	-0.136	-0.148	-0.014	-0.020	-0.013
($ 2015 thousands)	(0.048)***	(0.039)***	(0.140)	(0.008)*	(0.007)***	(0.012)
Employment to population	0.989	-1.054	-3.259	0.858	0.676	0.469
ratio	(1.162)	(0.865)	(1.761)*	(0.143)***	(0.126)***	(0.206)**
Population	-0.078	-0.082	-0.016	-0.001	-0.002	-0.003
(hundreds of thousands)	(0.026)***	(0.024)***	(0.035)	(0.003)	(0.003)	(0.004)
White population (%)	0.000	-0.006	-0.016	-0.001	-0.000	-0.000
	(0.004)	(0.005)	(0.006)**	(0.001)*	(0.000)	(0.000)
Mean age	0.109	0.077	-0.258	-0.002	-0.017	-0.004
	(0.097)	(0.075)	(0.269)	(0.015)	(0.013)	(0.012)
Pharmacies	0.186	0.829	1.042	-0.122	0.000	0.208
	(0.332)	(0.262)***	(1.528)	(0.107)	(0.067)	(0.282)
Hospitals	-0.039	-0.026	-0.019	-0.001	-0.001	-0.003
	(0.035)	(0.030)	(0.025)	(0.005)	(0.004)	(0.004)
Pain clinics	-0.235	-0.010	-0.355	0.022	-0.001	0.009
	(0.114)**	(0.118)	(0.287)	(0.034)	(0.029)	(0.064)
Police per 1,000 residents	0.274	0.108	0.108	-0.044	-0.027	-0.026
	(0.039)***	(0.035)***	(0.035)***	(0.006)***	(0.004)***	(0.004)***
EMTs per 1,000 residents	0.029	0.107	0.106	-0.001	-0.005	-0.005
	(0.030)	(0.025)***	(0.024)***	(0.004)	(0.003)	(0.003)
Medical marijuana	0.073	0.124	0.116	0.016	0.010	0.011
	(0.043)*	(0.046)***	(0.042)***	(0.005)***	(0.003)***	(0.003)***
Recreational marijuana	-0.236	-0.067	-0.068	-0.030	0.015	0.016
	(0.064)***	(0.054)	(0.054)	(0.009)***	(0.007)**	(0.007)**
Noneconomic damage caps	0.030	-0.015	-0.017	-0.005	0.005	0.006
	(0.024)	(0.026)	(0.026)	(0.007)	(0.007)	(0.006)
Punitive damage caps	0.073	0.105	0.103	-0.015	0.016	0.015
	(0.042)*	(0.035)***	(0.036)***	(0.013)	(0.009)*	(0.009)
Joint and several liability caps	0.335	-0.157	-0.156	0.015	-0.002	-0.002
	(0.047)***	(0.058)***	(0.057)***	(0.020)	(0.022)	(0.022)
F-statistic for naloxone provisions' joint significance	12.01	7.496	6.958	18.33	14.05	14.13
State specific time trends		X	X		X	X
County specific time trends			X			X

Note: N = 414,498. Dependent variable is the quantity of worker fatalities per 100,000 county residents. Standard errors robust and clustered on county. All regressions include county and month-by-year fixed effects. *** p<0.01, ** p<0.05, * p<0.1.