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ABSTRACT

The Economics behind the Epidemic: Afghan Opium Price and Prescription Opioids in the US*

We investigate the effect of variations in the price of opium in Afghanistan on per capita dispensation of prescription opioids in the US. Quarterly county-level data for 2003-2016 indicate that reductions in opium prices significantly increase the quantity of opioids prescribed. The increase involves natural and semi-synthetic but not fully synthetics opioids, therefore suggesting that the effect is moderated by the amount of opium contained in the products. While this evidence could suggest a pass-through of lower production costs to retail prices, boosting patients' demand for opioids, we fail to detect significant effects of changes in retail prices on per capita dispensation. Moreover, firm-level analysis reveals that advertising expenses of opioid producers increase following opium price declines and so do their stock prices and profits. Overall, our findings suggest that supply-side economic incentives might have played an important role in the opioid epidemic.

JEL Classification: I11, I12, I18, L65

Keywords: prescription opioids, drugs, opium price, supply-side economic incentives

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1 Introduction

The United States is experiencing its most devastating health crisis since the height of the HIV/AIDS pandemic in 1995. In 2016 alone, Centers for Disease Control and Prevention (CDC) recorded more than 63,600 drug overdose deaths nationwide, up five-fold since 1999. And two-thirds of these fatalities involved opioids. Over the years, opioid-analgesic poisoning death rates have increased for all age groups and especially for non-Hispanic white men and women (Chen et al., 2014; Case and Deaton, 2015). Currently, the International Narcotics Control Board estimates that the US is the leading consumer of opioid-based drugs, accounting for 50% of the worldwide use of morphine, and 72.9% of oxycodone and other derivatives (United Nations, 2018). One of the most striking aspects of the current epidemic is that even if the users later go over to illicit or illegal opioids, most of the abuse starts with opioids prescribed legally by physicians (Okie, 2010).[1]

US pain specialists and advocacy organizations began to debate pain management practices in the 1990s. The American Pain Society pressed for recognition of pain as the "fifth vital sign" along with blood pressure, heart rate, respiratory rate and body temperature, while growing numbers of professional and consumer groups urged greater use of opioid-based pain therapies (Tompkins et al., 2017; Rosenblum et al., 2008). Pharmaceutical companies promoted opioids heavily as a treatment option, often hiring consultants to emphasize the safety and benefits of their opioid-based drugs and investing in major marketing campaigns (Van Zee, 2009; Jones et al., 2018). For many years now physicians have been prescribing these drugs to more and more patients, including people not suffering from a terminal illness; and this notwithstanding the absence of any increase in patients' reported pain and the strong evidence of the risk of addiction and abuse associated with their prolonged use.[2] In 2017, New York Special Narcotics Prosecutor Bridget G. Brennan stated: "We did not develop an opioid epidemic until there was a huge surplus of opioids, which started with pharmaceutical drugs."[3] More recently, Hadland et al. (2019) and Nguyen et al. (2019b) show that opioid mortality rates and opioid prescription rates are positively associated with physicians receiving marketing payments from the pharma industry on opioid products.

In this paper, we assess the extent to which the economic incentives of opioid manufacturers, stemming from variations in the world price of opium (i.e., the raw material for producing opioid-based drugs), have contributed to the rapid growth in the use of prescription opioids (POs) in the United States over the last few decades. According to estimates of the United Nations, 10 kilograms of opium are needed to produce around 1 kilogram of morphine base, which implies a yield of about 10%.[4] We use opium price in Afghanistan as a proxy for the world price of

[1] Evans et al. (2019) and Alpert et al. (2018) analyse the effect of the reformulation of OxyContin in 2010 on heroin and opioid deaths, offering evidence of a consumer substitution response.

[2] This prompts suspicions about the reasons underlying this crisis (Chang et al., 2014). The National Institutes of Health, the federal agency responsible for biomedical and public health research, holds the pharmaceutical industry and other stakeholders (e.g. insurance companies) partly responsible. See details at `https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis`.

[3] Council on Foreign Relations, December 2017.

[4] However, higher morphine content in raw opium and/or higher extraction technologies may determine a

opium. In fact, according to the UN, in 2007 Afghanistan produced 93% of the world total production of opium. We therefore seek to determine whether shocks to the price of opium in Afghanistan, by altering opioid producers' markup, affect per capita dispensation of POs in the US.[5]

We use quarterly data at county level for the years 2003-2016 and measure price shocks by interacting the log-change in the quarterly price of opium in Afghanistan with US counties' *ex-ante* demand for opioid-based analgesics.[6] This formulation captures the larger effect of opium price shocks in counties where the initial demand for POs is greater, as the incentives for pharmaceutical companies to promote opioid painkillers should be stronger where the initial demand for analgesics is higher (Alpert et al., 2019; Nguyen et al., 2019a). In fact, the marginal rate of success in marketing POs is likely to be higher where the pool of people suffering from chronic pain is larger. To measure *ex-ante* county-level demand for POs, we use the number of mining sites per capita in 1983, since in counties with a greater concentration of mining sites the workforce is more likely to suffer from chronic pain. Given that it depends on a county's geomorphological features, this measure exploits variation in subsoil characteristics in 1983, making endogenous sorting in the demand for analgesics less likely. Indeed, most manual occupations in mining and construction, in fact, are by nature exposed to the risk of chronic pain, often associated with more use of painkillers to allow speedier return to the job (Leukefeld et al., 2007).[7]

We find that a reduction in the price of opium in Afghanistan increases per capita PO dispensation in the US significantly, and the estimated effect increases with the initial level of demand for opioids in the county. In our data, a 1-standard-deviation decrease in opium price growth (i.e., a fall by 20 percentage points) increases per capita dispensation of POs by 5 doses in counties at the 12th percentile of the mining site distribution, and by around 6 doses in those at the 76th percentile. This result is robust to a battery of tests, including the addition of both county-year and state-quarter fixed effects, a placebo test with various lead times for the price change, and alternative proxies for the *ex-ante* county demand for opioids, namely the share of miners, the share of veterans and the share of workers in the heavy manufacturing sector. Moreover, since the evolution in the price of opium is determined by the instability in Afghanistan, we provide further evidence that the results hold when using variation in conflict intensity, as measured by the number of Western casualties per quarter in Afghanistan, to capture variation in the price of opium (Lind et al., 2014).

We show that the effect varies with some socio-economic characteristics. In particular, in

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lower ratio. See DEA (1992) and United Nations (2003).

[5] We discuss that the relative size of Afghan production creates incentives to the diversion of opium to the illegal market that are likely to make the supply of licit opium destined to the pharmaceutical industry vary accordingly (Section 3.2).

[6] This recalls the approach of Bruckner et al. (2012) in studying the effect of oil price shocks on democratization.

[7] Furthermore, mining is a particularly dangerous industry. According to the 1994 Census of Fatal Occupational Injuries, the mining sector had the highest fatality rate (27 per 100,000 workers employed, compared with 24 in agriculture, forestry and fishing and 15 in construction), as well as above-average rates of severe injury (i.e., cases involving lost work days and restricted work activity).

line with the findings of previous studies (Case and Deaton, 2015; Krueger, 2017; Baker et al., 2018), it is smaller in counties with higher initial levels of income, education, urbanization or health insurance coverage. Conversely, the effect is stronger in areas with a higher initial share of health care workers in the population. This is consistent both with the thesis that a greater supply of health care services might imply easier access to POs *per se* and with the idea that prescription rates might rise where competition for customers among health care suppliers is more intense (West, 2013).

Remarkably, we find that negative changes in opium prices are significantly correlated with increases in per capita opioid abuse death rates. This suggests that the increase in POs distribution, possibly due to over-prescription, might lead the fatal abuse of pharmaceuticals, which is at the root of the current epidemic (Okie, 2010). Moreover, we show that per capita drug-related crimes, either sale or possession, increase significantly following a drop in the price of opium. This indicates spillover effects on the illegal drug market (Mallatt, 2017; Meinhofer, 2017).

Further, the evidence indicates that the change in POs distributed is influenced by economic incentives to opioid producers. Our hypothesis is that a fall in the price of opium, i.e., the cost of the raw material, might widen the markup and so prompts an increase in the quantity of opioid-based drugs dispensed. Thus, we expect the mechanism to be stronger for the drugs whose production requires positive amounts of opium. The price shocks have an asymmetric effect on the quantity of opioids prescribed, depending on the importance of opium in the manufacturing process. Specifically, we find that most of the effect on per capita dispensation of POs relates to natural and semi-synthetic drugs, which are produced either by natural processes or by chemical modifications to opium, while for fully-synthetic opioids, in which raw opium is not an input, we find no correlation with price changes.

While this evidence supports our claim, another possible explanation would be changes in demand from patients. This would be the case if a fall in the price of opium led to a decline in the market price of POs and in turn an increase in patients' demand for opioids. We test this alternative mechanism by replacing the price of opium with the average retail price of generic opioid-based painkillers. We fail to detect that decreases in the market price of opioids significantly increase per capita PO dispensation. Albeit the inclusion of different fixed effects in the model, the relation might still suffer from a residual endogeneity concern. Nevertheless, this result seems not supporting the existence of solely channel of change in patient demand. This is in line with the findings of a recent study by Cutler et al. (2019), who show that patient demand is relatively unimportant, compared with supply-side factors, in explaining variations in health care spending.

Our hypothesis is supported by a firm-level analysis where we assess how opium price changes affect the advertising expenses of US pharmaceutical companies. Importantly, we find that opioid manufacturers, pharmaceutical companies that have obtained FDA approval for opioid painkillers, significantly react to declines in opium prices by increasing advertising expenses. This might suggest that opioid producers have reacted to the drop in raw material costs by using promotions as a strategy to expand demand at a time in which their markup has increased (Zejcirovic and Fernandez, 2018). What is more, our firm-level estimates reveal that both the stock market prices and profits of opioid producers benefits from a decline in the price of opium. By contrast, the stock price of companies producing a substitute analgesic drug, ibuprofen, is unaffected, even though their profits decline following an opium price drop. Overall, these results indicate that a negative shock to the price of opium in Afghanistan is associated with higher expected future profits for PO manufacturers in the US. This apparently confirms that investors perceive opioid-producing companies as factoring fluctuations in the price of opium into their business strategies.

Taken together, our results suggest that the rapid increase in the use of POs in the US in recent decades has been to a significant extent supply-driven. This finding is particularly important in the context of an epidemic opioid crisis, which public health officials have called the worst drug emergency in America's history, and at a time when excessively high prescription rates are universally recognized as the root cause of the surge in overdose mortality (Okie, 2010; Case and Deaton, 2015; Kolodny et al., 2015; Schnell, 2017). The rise in the use of opioid-based drugs has produced a number of other adverse public health outcomes, such as emergency room visits and neonatal abstinence syndrome (Patrick et al., 2012; Chen et al., 2014; Dart et al., 2015), while the total economic burden of opioid-related overdoses, abuse and clinical practices was calculated at about USD 80 billion in 2013 alone (Pollack, 2016).[8] Other adverse effects of the opioid crisis, especially socio-economic outcomes, are also increasingly studied. Case and Deaton (2015, 2018) document that worsening labour market conditions and lack of access to health care have fuelled a rise in drug, alcohol and suicide deaths, or "deaths of despair", especially among less educated, middle-aged, non-Hispanic white Americans. With reference to opioid deaths, Ruhm (2019) highlights the importance of "drug environment" factors, such as differential drug risks for different population subgroups. Other studies focus specifically on the relationship between opioids and such other variables as employment (Carpenter et al., 2017; Harris et al., 2017; Krueger, 2017; Currie et al., 2018), crime (Mallatt, 2017; Meinhofer, 2017; Doleac and Mukherjee, 2019), duration of disability benefits (Savych et al., 2018) and child removals (Gihleb et al., 2018). Unlike these studies, our paper investigates the supply-side drivers of opioid use.[9] In line with some of these studies, we provide further evidence on the socio-economic repercussions of the rise in opioid use in terms of both deaths and drug-related crimes.

The present paper also contributes to two other strands of research. First, we add to the supplier-induced demand literature by examining the economic incentives behind the dramatic increase in PO use (Rice, 1983; Rice and Labelle, 1989; Iizuka, 2007; Liu et al., 2009; Currie et al., 2011; Iizuka, 2012; Currie et al., 2014; Lu, 2014; Shigeoka and Fushimi, 2014; Sekimoto and Ii, 2015). Second, our analysis builds on the literature on the effects of international commodity price shocks. Earlier studies have shown that commodity price shocks matter for conflict (Brückner and Ciccone, 2010; Dube and Vargas, 2013; Bazzi and Blattman, 2014; Berman and

[8] There is a vast literature on drug overdose and mortality rates. See Paulozzi (2012) for a review.
[9] Dasgupta et al. (2018) review the social and economic determinants of increased use of opioids.

Couttenier, 2015; Berman et al., 2017), democracy (Bruckner et al., 2012), mental health (Adhvaryu et al., 2014) and schooling (Brückner and Gradstein, 2013); we show that they also have an impact on the dispensation of prescription drugs. To our knowledge, this is the first contributions to explore how supply-side incentives affect the per capita dispensation of opioid-based drugs, documenting the first link in the causal chain that triggered the opioid crisis in the US.

The paper is organized as follows. Section 2 describes the development of the opioid crisis in the US. Section 3 presents the data and our empirical strategy. Section 4 discusses the results, robustness checks and the heterogeneity analysis. Section 5 interprets our findings in the light of supply-side economic incentives. Section 6 concludes.

2 The US opioid crisis

Since the late 1990s, the US has seen an unprecedented escalation in the abuse and diversion of prescription opioids that has been labelled "opioid crisis". According to the CDC (2017), in the period 1999-2016 more than 630,000 people died from drug overdoses. At first used primarily to treat cancer-related pain, opioids have increasingly been prescribed for other symptoms, such as back pain and osteoarthritis.

In the mid-1990s, the American Pain Society strongly advocated the concept of pain as an essential aspect of health, to be monitored and managed (Max et al., 1995). The aim was to promote awareness that patients in pain were generally under-treated, largely because pain was not assessed regularly during physician and GP appointments or in hospital post-surgery. Pain level was considered a subjective measure, unlike temperature, blood pressure, respiratory rate and heart rate. Within five years the Joint Commission on Accreditation of Healthcare Organizations and other US health experts had begun to emphasize the importance of regularly assessing pain in all patients.[10] Pain began to be accepted as a standard health check, and physicians started to recognize self-reported pain as a the "fifth vital sign" to be assessed in checking the body's life-sustaining functions (Walid et al., 2008). The Department of Veterans Affairs also proposed a toolkit including guidelines for comprehensive pain assessments.[11]

As prescription rates for opioid pain relievers rose, so did their misuse (Okie, 2010). Abuse and diversion of prescription opioids spread rapidly across the country. Opioid abusers learned that crushing the pills and injecting, inhaling or swallowing the resulting powder gave them a morphine-like "high" and this created a market for the diversion of prescription (Evans et al., 2019; Alpert et al., 2018). According to the Department of Health and Human Services, the consequences have been devastating: not only an increasing number of deaths directly ascribed to the abuse of these drugs but also the rising incidence of neonatal abstinence syndrome due to opioid misuse during pregnancy and a surge in infectious diseases such as HIV and hepatitis

[10] The Joint Commission accredits more than 21,000 US health care organizations and programmes. In most US states Joint Commission accreditation is a condition for eligibility for Medicaid and Medicare reimbursements.

[11] This concept is highlighted in the "Pain as the 5^{th} Vital Sign" Toolkit (VA, 2000). For further details, see `https://www.va.gov/painmanagement/docs/toolkit.pdf`. Wyse et al. (2018) report a slow but steady increase in the use of medication for opioid disorders among veterans.

C among the abusers. The Department estimates that 11.5 million people in the US misused opioids in 2016 and more than 100 people died every day from opioid overdose. However, this spectacular rise in the use of POs did not follow from any increase in patients' reported pain (Chang et al., 2014), which raises questions about the real drivers of the epidemic.

Perhaps one of the main determinants may have been the strategy adopted by some pharmaceutical companies, and related stakeholders, to promote their opioid-based products. One of the best known cases is the marketing campaign for OxyContin, an oxycodone-based drug introduced by Purdue Pharma in 1996. The amount invested in its launch and marketing was unprecedented, especially considering that it is a controlled drug. According to a 2002 Senate hearing, Purdue Pharma invested over USD 200 million in promoting OxyContin in 2001 alone.[12] In that year OxyContin accounted for more than two-thirds of all oxycodone sales in the US. As Van Zee (2009) documents, the producer's marketing practices were unusually aggressive.[13] In particular, these massive campaigns targeted the physicians profiled as the highest prescribers of opioids, and focused on convincing primary care physicians that opioids entailed very little risk of addiction and could be used safely to alleviate pain not associated with cancer. As a result, between 1997 and 2002 OxyContin prescriptions for cancer patients increased fourfold, while those for non-cancer-related pain, which accounted for 86% of the total opioid market in 1999, increased tenfold (General Accounting Office, 2003). Indeed, because of its misleading promotion campaigns and, especially, the misrepresentation of addiction risk, Purdue Pharma and some of its executives were fined over USD 600 million in 2007, and other opioid manufacturers and distributors are now also facing lawsuits on similar grounds.[14]

The policy response to the opioid crisis came primarily at state level. The targets of the policies varied (patients, physicians, pharmacists) and the types of limitation differed. The impact of state policies on this dramatic epidemic is being investigated in both the medical and the economic literature, but so far there is no clear consensus on whether these laws have effectively limited abuse or reduced mortality (Meara et al., 2016; Popovici et al., 2017; Rees et al., 2017; Buchmueller and Carey, 2018; Deiana and Giua, 2018; Doleac and Mukherjee, 2019).

[12] See "OxyContin: Balancing Risks and Benefits", Hearing of the Committee on Health, Education, Labor and Pensions, S. HRG. 107-287, US Senate, Feb 2002.

[13] They comprised the profiling of physicians, distribution of complimentary merchandising, and all-expenses-paid conferences for health professionals to be trained in pain management. By the end of 2000, Purdue had a total call list of more than 70,000 physicians across the US and had distributed patient starter coupons for free prescriptions of the drug for 7 or 30 days. By 2001, 34,000 of the coupons had been redeemed nationwide. See Van Zee (2009).

[14] For instance, the founder of Insys Therapeutics was convicted in a case linked to the US opioid crisis, where he was found guilty of conspiring to fuelling sales of addictive painkillers. Recently, Oklahoma's judge ruled that Johnson & Johnson had intentionally downplayed the dangers of using opioid drugs, forcing the company to pay 572 million dollars in compensation to the state for false, misleading and dangerous marketing campaigns for opioids. Interestingly, the fine landed well below the expected amount and trading investors responded immediately, making Johnson & Johnson's stock market price rise by more than 5% in the following hours.

3 Data and Empirical Strategy

Here we describe how the various sources have been combined to build our main dataset, provide some descriptive evidence on the relationship between the price of opium in Afghanistan and the prescription of opioids in the US, and describe our empirical strategy for investigating the effect of these price changes on the dispensation of opioid-based drugs.

3.1 Dataset Construction

The data on POs come from the Automation of Reports and Consolidated Orders System (ARCOS), maintained by the US Drug Enforcement Administration's Office of Diversion Control. Since the Controlled Substances Act of 1970, manufacturers of controlled substances are required to report on the amount of drugs produced and sold in the US. The annual ARCOS reports record the quantities (in grams) of every controlled active ingredient sold in the US. The data are disaggregated at the 3-digit zip code level across the United States and are available quarterly. We gather the data for the period 2003-2016. We also draw zip code level information on the number of mining sites in 1983 from the Mine Safety and Health Administration (MSHA).[15]

As the rest of our data are disaggregated at the county level, we transpose the prescription drug and mining site zip codes to county level using the 2000 and 2010 zip-to-county crosswalks produced by the MABLE/Geocorr Application of the Missouri Census Data Center. To account for demographic differences between counties, we use the official intercensus population estimates (total population counts and counts by sex, age band, race and ethnicity). The 1980 and 1990 population counts and the variables employed in robustness checks and heterogeneity analysis come from the US Census Bureau. The quarterly time series of average prices of dry opium in Afghanistan come from the Ministry of Counter Narcotics of the Islamic Republic of Afghanistan, in partnership with the United Nations Office for Drug Control and Crime Prevention (UNODCCP).[16]

Our final sample comprises 3,109 (out of 3,142) US counties and quarterly data for 14 years (2003q1-2016q4). We also exploit the CDC WONDER Database, which provides detailed yearly data on drug fatalities at county level.[17] Moreover, we employ the Uniform Crime Reporting (UCR) Program Data provided by the FBI, which gives the number of arrests by county and by

[15] Mining sites refer to the extraction of coal (40%), metals (6%), non-metals (6%), stone (17.5%), and sand and gravel (30.25%). The first year available is 1983. Taking instead the number of people employed in mining sites as a robustness check, our findings stand confirmed.

[16] The main analysis uses the average price (in US dollars per kilogram) drawn from traders in Nangarhar and Kandahar provinces; the empirical checks are based on the average farm-gate price, which is available only from 2004q3.

[17] We count the following underlying or contributing causes of death: mental and behavioral disorders due to use of opioids (F11) or due to multiple drug use and use of other psychoactive substances (F19); newborns affected by maternal use of addictive drugs (P04.4) or by neonatal withdrawal symptoms (P96.1); identification of opiate drugs or other drugs with addictive potential in blood (R78.1 and R78.4); abnormal levels of other drugs, medicaments and biological substances (R82.5, R83.2, R84.2 and R85.2); accidental or intentional poisoning by and exposure to drugs (X40-X44, X60-X64, Y10-Y14 and Y45); and assault by drugs, medicaments and biological substances (X85).

type of drug-related crime. According to the UCR, drug abuse violations are defined as state and/or local offenses relating to the unlawful possession, sale, use, growing, manufacturing, or making of narcotic drugs including opium, cocaine and their derivatives, marijuana, synthetic narcotics, and dangerous non-narcotic drugs such as barbiturates. Furthermore, we use data on the number of conflict fatalities in Afghanistan during the considered time period, which are provided by the web site *iCasualties.org*. The data, which we aggregate quarterly, contains information on name, cause of death, location and date of every casualty (Lind et al., 2014).

In the last part of the analysis, we use the Wharton Research Data Services (WRDS) Compustat database, which includes financial, statistical and market data on active and inactive companies throughout the world. It covers 99% of the world's total market capitalization with quarterly company data history. We focus on three main variables: stock prices, profits and advertising expenses.

3.2 Preliminaries

In the last few decades Afghanistan has been the world's leading producer of illicit opium, ahead of the "Golden Triangle" (Myanmar, Laos and Thailand) and Latin America, reaching 90% of global production in 2007.

Under Taliban rule in the 1990s, poppy cultivation increased spectacularly, from under 22,000 hectares in 1995 to over 38,000 in 1999, when Afghanistan supplied around 70% of illicit opium worldwide.[18] Cultivation plummeted to just over 3,200 hectares in July 2000, when the Taliban leader Mullah Omar declared opium to be un-Islamic, in hopes of concessions by the United Nations. With the start of military operations after 11 September 2001, however, the Taliban broke the deal with the UN, allowing farmers to grow poppies again, and the land under opium went back up to over 34,000 hectares in 2002 and 190,000 in 2007.[19] Today, Afghanistan is indisputably the world's leading opium producer: according to the UN, in 2007 it produced 8,200 tons of opium, or 93% of the world total.

After peaking in the early 2000s owing to the ban on opium production, the average price fell steadily as output soared. Figure 1 plots opium prices and the land area of opium poppy cultivation in Afghanistan over time. The solid line shows traders' prices, the dashed line farm-gate prices. Predictably, the traders' price is always a bit higher, but the two series are closely correlated and inversely related to the number of hectares under opium poppies in Afghanistan (grey bars).[20] While opium prices were very volatile during our sample period, a good part of this was due to the violent conflict in Afghanistan, which rules out the possible problem of reverse causality for our analysis (Lind et al., 2014).[21]

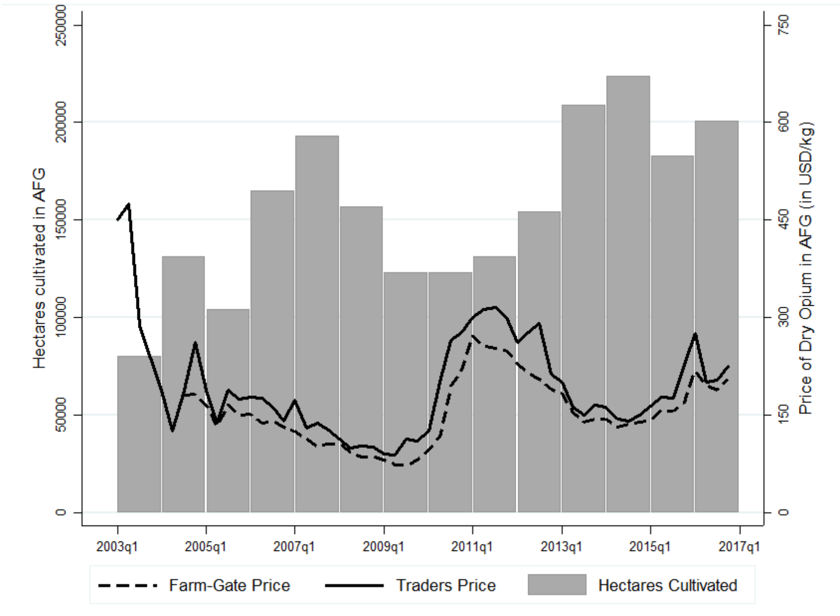
[18] The United Nations Office for Drug Control and Crime Prevention (UNODCCP) has been monitoring Afghan opium poppy production since 1994.

[19] See news reports: `https://www.theguardian.com/world/2001/apr/01/internationalcrime.drugstrade` and `https://www.theglobeandmail.com/news/world/kabul-may-be-lifting-opium-ban/article4153970/`.

[20] The peak in 2009-2011 reflects the rapid deployment of 100,000 US troops to the region, whose strengthened oversight disrupted poppy production: the total area cultivated dropped to 123,000 hectares and the price of opium jumped by 220% in a single year.

[21] To provide further evidence that the variation in opium price affecting the changes in prescription rates is exogenously determined by conflicts in Afghanistan, in Table 3 we implement a robustness test where we replace

Figure 1: Hectares Cultivated with Poppies and Price of Opium in Afghanistan



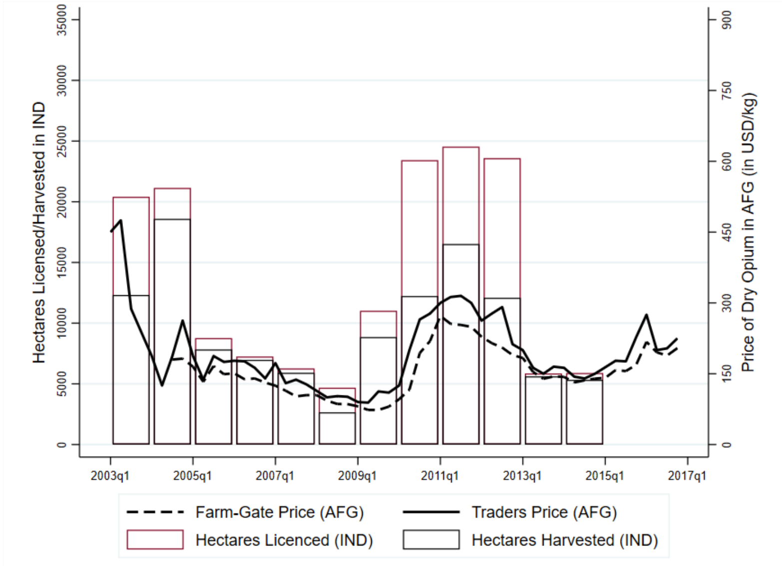
Note: The grey bars are the number of hectares cultivated with opium in Afghanistan annually. The solid line plots the average quarterly traders' price of dry opium in Afghanistan; the dashed line, the farm-gate price.

We take the price of opium in Afghanistan as a proxy for the world opium prices. In fact, while we are not claiming that pharmaceutical companies make use of raw opium sourced illicitly, we provide suggestive evidence that the trends in opium price in the legal market are likely to be correlated with those in opium price as measured in Afghanistan. According to the International Narcotics Control Board (United Nations, 2018), in 2016 India was the main legal producer of raw opium, at 23.3 tons (or, 2.5 tons in morphine equivalent). In the same year, the UNODCCP estimated Afghan opium production at 4,800 tons. Figure 2 reports information on the production and diversion of opium in India, the main producing country of licit opium.[22] The graph shows the price of illicit opium in Afghanistan, the number of hectares licensed to cultivation of licit opium in India and those actually harvested. Paoli et al. (2009) consider the share of hectares not harvested over the total area licensed to cultivation as a proxy for diversion of licit opium. Also the UN has repeatedly reported the existence of leakages into the illicit market (United Nations, 2005). As Figure 2 shows, this ratio for diversion of licit opium is positively correlated with the price of opium in Afghanistan, as the difference between hectares licensed and harvested is larger the higher the price of opium in Afghanistan. This signals the existence of a stronger incentive for diversion from licit production when the price of opium in the illegal market is higher. While actual production of licit opium in India is positively correlated with the amount of opium diverted, the fact that both are also positively

our measure of price shock (i.e. the log-change in quarterly opium price) with conflict intensity as proxied by (the log-change in) the number of Western casualties by quarter.

[22] Data on India comes from the Indian Central Bureau of Narcotics (`http://cbn.nic.in/html/operationscbn.htm`). See also Paoli et al. (2009) for contextual information.

Figure 2: Price of Opium in Afghanistan vs Production of Opium in India



Note: The bars are the number of hectares licensed to opium cultivation (red) and those actually harvested (black) in India annually. The solid line plots the average quarterly traders' price of dry opium in Afghanistan; the dashed line, the farm-gate price.

correlated with the price of opium in Afghanistan suggests that, *ceteris paribus*, the quantity of licit opium destined to the pharmaceutical industry decreases more than proportionally at high levels of the Afghan opium price and vice versa. Thus, this would make licit opium relatively more costly when opium price in Afghanistan is high and relatively less costly when incentives for diversion are very low, i.e. opium price in Afghanistan is low.

Over the same period, pharmaceutical firms in the US invest billions of dollars annually in advertising of drugs and medical equipment. While promotion of prescription drugs includes direct-to-consumer advertising (DTCA) on broadcast and print media, the bulk of promotional spending is targeted to physicians and other health care professionals through office visits by company representatives (i.e., detailing), product sampling, and advertising in professional journals (Zejcirovic and Fernandez, 2018; Cegedim, 2013).[23] Over the years, the growth in the share of prescription drugs expenditures coincided with the growth in pharmaceutical promotion, which increased from \$11.4 billion in 1996 to \$29.9 billion in 2005 (Datta and Dave, 2017) and \$32.3 billion in 2008 (Cegedim, 2013).[24] Notably, these are the years in which, as shown above in Figure 1, the price of opium fell sharply. Consistent with this, in Section 5 we show that declines in the price of opium are positively associated with advertising expenses by firms

[23] Together with New Zealand, the United States is the only country where advertising for prescription drugs is legal. According to Cegedim (2013), detailing and free sampling accounted for about 83% of the US pharmaceutical promotional budget in 2011.

[24] Based on a representative survey, Campbell et al. (2007) show that in 2004 a good fraction of US physicians received gifts from pharmaceutical sales representatives. Further, Mizik and Jacobson (2004), find that detailing and free drug samples have positive and statistically significant effects on the number of new prescriptions issued by a physician.

that produce FDA-approved opioid-based drugs. This provides support to the hypothesis that supply-side economic incentives played a role in the onset of the opioid epidemic.[25] Recently, Hadland et al. (2019) and Nguyen et al. (2019b) find that marketing payments on opioid products received by physicians are positively correlated with opioid mortality rates and opioid prescription rates, respectively. At the same time, Figure A.1 indicates that the retail prices of generic POs and the substitute analgesic, ibuprofen, remained relatively flat throughout the period 2000-2015, offering presumptive evidence that demand-driven effects are unlikely to have played a significant role in the rapid expansion of PO use.[26]

3.3 Empirical Strategy

Our analysis serves to gauge the extent to which change in dispensation of opioid-based drugs in the US, which in principle should respond only to medical needs, is instead driven by economic incentives. Specifically, we investigate whether changes in the sales of prescription opioids in the US are driven by those in the price of dry opium produced in Afghanistan.

If the change in the quantity of opioids dispensed in the US is determined by economic incentives to suppliers based on the price of the raw material, this mechanism can be expected to be stronger in areas (in our study, counties) with higher *ex-ante* demand for opioids, as proxied by (the log of) the per capita number of mining sites in 1983.[27] These counties would represent the most fertile local markets for analgesics, where PO promotion campaigns presumably had the greatest chances of success. Accordingly, we estimate the following model:

$$\Delta \ln MGEpc_{ct} = \alpha + \beta(\ln Mines1983pc_c * \Delta \ln OpiumP_t) + \delta_t + \gamma_c + t\theta_c + \epsilon_{ct}, \qquad (1)$$

where $\Delta \ln MGEpc_{ct}$ is the log-change in the per capita amount of Morphine Gram Equivalent (MGE) dispensed in county c between quarter $t-1$ and quarter t, $\Delta \ln OpiumP_t$ is the log-change in the average price of dry opium in Afghanistan between quarter $t-1$ and quarter t and $\ln Mines1983pc_c$ is the log of the number of mining sites in 1983 (over the population in 1980).[28] We include county and quarter dummies and county-specific linear trends, which should capture any changes in institutional or demographic factors during the period. The errors are clustered at county level.[29]

[25] David et al. (2010) find a positive correlation between different types of promotion of pharmaceuticals and adverse drug events, such as overdoses and allergic reactions, in the US. See Morton and Kyle (2011, ch.12) for a description of the market for pharmaceutical products.

[26] The average prices are computed from the full sample of the Medical Expenditure Panel Survey (MEPS) as the average full price for each dose (tablet or patch) of the generic drug in a given year. Only the price of hydrocodone decreased in the period, by around half.

[27] The robustness analysis uses alternative proxies for *ex-ante* county demand for painkillers.

[28] $Mines1983pc$ is rescaled by 100,000 residents to ease the interpretation. We use the log rather than the simple number of mining sites per capita in 1983 because the distribution of sites across US counties is strongly positively skewed. Using the number of mines per capita yields comparable results when excluding counties above the 99th percentile (32 counties).

[29] Clustering the errors at state level does not alter the results. The regressions are weighted by the county's share of the national population in 2000. Unweighted estimates are identical.

Our dependent variable is a measure that accounts for changes in the total per capita dispensation of opioid-based analgesics in a given county. These drugs come in different forms and have different active ingredients. Here, we focus on the most commonly used substances: morphine, hydrocodone, hydromorphone, oxycodone, fentanyl, meperidine and methadone, which are all classified as Schedule II or Schedule III.[30] We rescale the quantity of each substance to account for relative potency and construct a single MGE indicator.[31] Table A.1 reports the descriptive statistics for the main outcome and control variables. Figure A.2 describes the geographical distribution of average MGE in 2003 and 2016, i.e. at the beginning and the end of our sample period. We observe substantial variation across counties and years. The darker the area, the higher the dispensation of POs. The lighter areas, indicating lower levels of MGE per capita, are found predominantly in the central regions. The two maps also reveal the remarkable nationwide increase in opioid use that marked our period.

Our explanatory variable measures shocks to the price of opium in Afghanistan. The analysis exploits price changes between two consecutive quarters to capture time variation. The fluctuations during the period 2003q1-2016q4 are highly persistent, with an autoregression coefficient of 0.99. The augmented Dickey-Fuller test does not reject the hypothesis of a unit root in opium price levels at the 90% confidence level, but it does reject the hypothesis of a unit root in the first-differenced opium price at the 99% confidence level. Thus, we use the first-differenced series of the (log) price of opium, which is stationary (as shown in Figure A.3), to identify local shocks to the time series, as a proxy for changes in the cost of the raw material for opioid-based drugs. Moreover, as observed above, opium price changes depend essentially on the violent conflicts in Afghanistan, ruling out potential reverse causality problems (Lind et al., 2014).

The geographical variation in local demand for prescription opioids in the US is proxied by the number of mining sites per capita in a county in 1983. The distribution of mining sites across the US is shown in Figure A.4. We use this as a measure for *ex-ante* demand for opioids at the local level, given the common use of analgesics among workers employed in jobs marked by physical strain and risk of injury (Leukefeld et al., 2007). A simple cross-sectional regression between the log of mines per capita in 1983 and the log of opioid dispensation rate over the period 2003-2016 produces an elasticity equal to 0.08, controlling for state-level unobserved heterogeneity. This evidence goes together with Figure A.5, which shows a positive link between our measure for the *ex-ante* demand of painkillers, i.e. mines, and the incidence of unintentional injury rates at work. Moreover, as additional suggestive evidence we show that mines positively correlates with payments or transfers of value to physicians or hospital recipients in 2016 (Figure A.6). This provides empirical support to the claim that the presence

[30] The lower the schedule order, the greater the drug's abuse potential. For instance, heroin is a Schedule I substance, while cough medicines with less than 200 mg of codeine per 100 ml. are Schedule V. Schedule II and Schedule III substances are those that have respectively high and moderate potential for abuse and are known to lead to psychological or physical dependence.

[31] Our choice of multipliers for conversion into MGE units conforms to Gammaitoni et al. (2003), Paulozzi et al. (2011) and Brady et al. (2014). We rescale the substances as follows: morphine by 1, hydrocodone by 1, hydromorphone by 4, oxycodone by 1, fentanyl by 75, meperidine by 0.1 and methadone by 7.5.

of mining sites is a good proxy for the *ex-ante* local demand for opioid analgesics. At the same time, this measure is reasonably exogenous to the current quantity of opioids prescribed by physicians, as it is predetermined by geographic morphology and measured in 1983, well before the onset of the opioid crisis (in the late 1990s).

The coefficient β in Equation 1 is meant to capture the impact of opium price shocks on per capita MGE units dispensed in US counties. In other words, if opioids were dispensed independently of the price of opium and strictly on the basis of the actual medical needs of the population, β would not be statistically different from zero. Yet, the unfolding of the opioid crisis and the proliferation of newspaper articles and academic papers instead suggest that we should expect the coefficient β to be negative. This would imply that, where dependence on painkillers is greater, a fall in the price of opium should trigger a larger increase in per capita dispensation of POs. In this case the underlying mechanism would be purely economic; that is, drug manufacturers react to changes in the cost of the raw material (the price of dry opium) by promoting their drugs so as to obtain a greater increase in profits.

4 Results

In this section we present our main result, namely the estimate of the effect of opium price shocks on per capita dispensation of MGE units. We test for robustness to a battery of checks and placebos. Then, we discuss heterogeneous effects and compare them with the results in the literature. Finally, we give evidence of the effect of opium price shocks on opioid-related mortality rates and drug-related crime rates.

4.1 The Effect of Opium Price Shocks on Prescription Opioids Dispensation

Table 1 shows the main results of the estimation of Equation 1. Column 1 reports the unconditional estimate of the effect. This coefficient is negative and strongly significant at the 1% level, indicating that an increase in the price of opium in Afghanistan is closely correlated with a reduction in opioid prescriptions in the US. Our interaction term implies that the impact of opium price changes should be larger in counties with higher initial demand for analgesics (i.e., heavier dependence on opioids), proxied by mining sites. Indeed, we expect pharmaceutical companies to have a higher marginal rate of success in promoting opioids in areas where relatively more people suffer from chronic pain and are therefore in need of analgesics.

Column 2 includes county and quarter dummies to control, respectively, for time-invariant local heterogeneity and for time effects that might possibly confound the main effect. We find that the coefficient doubles and remains statistically significant at the 1% level, which suggests considerable heterogeneity in opioid use across quarters and counties. Column 3 evaluates our main specification as in Equation 1, where we also add county-specific linear time trends to purge the effect of other unobserved time-varying characteristics at county level. This should rule out the possibility that counties with different initial demand for POs were already on differential growth trajectories of opioid dispensation, so that the change in use would have

Table 1: Effects on MGE

	(1)	(2)	(3)
Dep. variable	Δ lnMGEpc	Δ lnMGEpc	Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0025***	-0.0056***	-0.0064***
	(0.0003)	(0.0021)	(0.0023)
Observations	174,104	174,104	174,104
R-squared	0.0074	0.3279	0.3329
County Dummies		✓	✓
Quarter Dummies		✓	✓
County-Specific Linear Trends			✓

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of MGE per capita dispensed. OpiumP is the average trader price of opium. Mines1983pc is the number of mining sites per capita in 1983. Clustered-robust standard errors at county level in parenthesis.

occurred even in the absence of opium price shocks. The magnitude of the coefficient is slightly greater than in column 2. The results are statistically significant at the 1% level, indicating a clear inverse relationship between the change in raw material cost and the change in per capita dispensation.[32]

Our estimate suggests that, in the case of counties at the 12th percentile of the (log) mining site distribution (e.g., Forsyth County, GA, with 2.72 mining sites per 100,000 inhabitants), a 1-standard deviation decrease in opium price growth (i.e., a fall by around 20 percentage points) increases per capita MGE growth by 0.0013, that is by 0.13 percentage points.[33] This translates into an increase of 0.1525 MGE units per capita, which is equivalent, given the standard morphine dose of around 30 milligrams, to 5 doses per capita in a quarter.[34] For counties at the 40th percentile (e.g., Maverick County, TX, with 7.39 mining sites per 100,000 inhabitants) the effect amounts to 5.5 doses per capita, and for counties at the 76th percentile (e.g., Marinetti County, WI, with 20.10 mining sites per 100,000 inhabitants) to roughly 6 doses per capita.

We conduct a series of tests to ensure that these results are robust and well-identified. First, we run a placebo test similar to that proposed by Autor et al. (2013), adding different leads of our main interaction term in order to check whether the results effectively capture the impact of change in the price of opium and not some other factor common to the change in POs and in the opium price. That is, we analyse whether subsequent changes in the price may not be affecting current changes in the amount of POs being prescribed. The results are reported in Table A.2. Column 1 shows the first lead, column 2 the second, third and fourth. Reassuringly, both columns demonstrate that there is no statistically significant correlation between future opium price changes and current per capita dispensation of POs. Moreover, in columns 3 and

[32] If we compute the dependent variable (MGE units per capita) excluding methadone, which is used both in treatment of pain and for rehabilitation from opioid misuse, the results are identical.

[33] $\ln Mines1983pc$ is equal to 1, 2 and 3 at the 12th, 40th and 76th percentile of the (log) mining sites per capita distribution, respectively.

[34] At the average, the growth of per capita MGE units is 0.0082. An increment by 0.0013 implies that the growth of MGE units becomes 0.0095. Thus, given that at the average $\overline{MGEpc} = 8.5965$ and that $\Delta(\%\Delta MGEpc) = \frac{\widehat{MGEpc}-\widetilde{MGEpc}}{\widetilde{MGEpc}} - \frac{\widetilde{MGEpc}-\overline{MGEpc}}{\overline{MGEpc}} = 0.0095 - 0.0082 = 0.0013$, it follows that $\Delta MGEpc = \widehat{MGEpc} - \overline{MGEpc} = 0.1525$.

4 of Table A.2 we add 1-quarter and up to 1-year lags, respectively, to our main specification. The coefficients associated with the lags suggest that there are no delayed effects, while the coefficient of interest remains stable in both magnitude and significance.[35]

We also run a battery of additional placebo tests. First we generate new interaction terms that exploit quarterly changes in other time series: international oil prices, the Consumer Price Index (CPI) and the international prices of copper, sugar, coffee, cocoa, wheat and palm oil. Table A.3 shows no impact of these interaction terms on changes in per capita use of POs. This eliminates the danger that our results might be capturing spurious correlations. Second, we check whether opium price shocks are systematically associated with changes in the sales of other drugs, namely amphetamines, methamphetamines and cocaine. The results in Table A.4 support our thesis.

Table 2 presents a set of robustness checks on our main specification. Column 1 includes county-specific quadratic and cubic time trends to purge the effect from possible non-linear, unobserved time-varying characteristics at county level. The coefficient β remains stable and statistically significant at the 1% level. Column 2 includes state-quarter fixed effects to account for potential unobserved time-varying factors, such as changes to the institutional set-up at state level, during the period. This is an important check in view of the policies recently introduced in various states to counter the opioid crisis. In this case the magnitude of the effect diminishes, but it remains statistically significant at the 5% level. Next, in column 3, we include county-year fixed effects to account for yearly heterogeneity at county level. Here, we exploit only the residual quarterly variation of the phenomenon, as the fixed effects absorb any changes in local characteristics that may vary from year to year (such as average education or income) and

Table 2: Effects on MGE: Robustness checks I

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc	(4) Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0065***	-0.0039**	-0.0083**	-0.0054**
	(0.0024)	(0.0019)	(0.0034)	(0.0025)
Observations	174,048	174,104	174,104	174,048
R-squared	0.3367	0.5942	0.4349	0.6545
County-Specific Quadratic Trends	✓			
County-Specific Cubic Trends	✓			
State-Quarter FE		✓		✓
County-Year FE			✓	✓

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of MGE dispensed per capita. OpiumP is the average trader price of opium. Mines1983pc is the number of mining sites per capita in 1983. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

[35] The absence of delayed effects would suggest that our results are not aligned to the theory of rational addictive behavior (Becker and Murphy, 1988; Becker et al., 1994). This might be due to the following reasons. First, differently from other addictive substances such as tobacco or alcohol, opioids are obtained via regular medical prescriptions, which somehow limits the patients' freedom to acquire them. Second, previous works have found some evidence of substitution to illicit drugs such as heroin for users that have become addicted to prescription opioids (Okie, 2010; Evans et al., 2019; Alpert et al., 2018). In such cases, however, we would not await to capture the increase in the amount of drugs consumed, as our dependent variable only refers to legally dispensed drugs.

confound our estimate. In this specification the coefficient is higher and remains statistically significant at the 5% level. Finally, in column 4, we almost saturate the model by including both state-quarter and county-year fixed effects. Remarkably, the coefficient remains strongly negative and statistically significant at the 5% level.[36]

Then, we consider whether the results may not be driven by the way in which the explanatory variable is measured. Throughout the analysis we use the traders price of opium in Afghanistan, but it could be contended that this price itself depends on trends in demand for opium-based products in the US. Accordingly, we re-estimate our main specification, replacing the traders price with the farm-gate price (Table 3, column 1), which is known to depend mainly on changes in local conditions (conflict events or weather) and is unlikely to be affected by changes in the prescribing rates of opioids in the US. Since the farm-gate price is available only after 2004, column 2 also reports the estimate using the trader price, but with the restricted farm-gate sample. Reading across columns 1 and 2 indicates that our main result is robust not only to an alternative measure of opium prices but also to restriction of the sample to more recent periods.

Moreover, we test the robustness of our results by exploiting changes in conflict intensity in Afghanistan as an alternative measure to capture opium price shocks. As discussed above, variation in the price of opium produced in Afghanistan is mainly determined by conflict. In our setting, warfare destroys physical infrastructure, cultivated hectares and human capital, which should trigger a drop in the production of opium and a subsequent increase in its price.[37]

Table 3: Effects on MGE: Robustness checks II

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc	(4) Δ lnMGEpc	(5) Δ lnMGEpc	(6) Δ lnMGEpc	(7) Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0083**	-0.0053***					
	(0.0032)	(0.0019)					
lnMines1983pc * Δ lnCasualties			-0.0019**				
			(0.0010)				
I(Mines1983pc > Median) * Δ lnOpiumP				-0.0107***			
				(0.0039)			
lnMiners1983pc * Δ lnOpiumP					-0.0046***		
					(0.0014)		
lnVeterans1999pc * Δ lnOpiumP						-0.0400***	
						(0.0137)	
lnHeavyManuf1999pc * Δ lnOpiumP							-0.0040*
							(0.0021)
Observations	152,341	152,341	174,104	174,104	173,880	173,936	96,880
R-squared	0.3557	0.3557	0.3339	0.3325	0.3323	0.3319	0.3443
Opium Price	Farm	Trader		Trader	Trader	Trader	Trader

Note: * p<.10 ** p<.05 *** p<.01. Sample: post 2004q3 (columns 1-2), 2003q1-2016q4 (columns 3-7). MGEpc is the quantity of MGE dispensed per capita. OpiumP is the average farm-gate (column 1) and trader (columns 2,5-8) prices of opium. Mines1983pc is the number of mining sites per capita in 1983. Casualties are the number of Western casualties in Afghanistan. Miners1983pc is the share of the population employed at mining sites in 1983 (the sample is reduced to 173,880, as four counties present zero value). Veterans1999pc is the number of veterans per capita in 1999 (the sample is reduced to 173,936 because three counties have zero value). HeavyManuf1990pc is the number of workers in heavy manufacturing per capita in 1990 (the sample drops to 96,880 because the data covers only 1,730 counties). All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

[36] We also run a specification controlling for observed yearly time-varying demographic characteristics (population, share of 16-65 year olds, share of those aged 65+, share of females, share of whites, share of blacks); the point estimate is unchanged with respect to our main specification (Pei et al., 2018).

[37] Our data show indeed that conflict intensity, as measured by the number of Western casualties, is negatively correlated with the number of hectares with opium poppy cultivation.

Thus, we replace the log-change in opium price with the log-change in the number of Western casualties in Afghanistan (see Lind et al., 2014). The estimates in column 3 confirm our main result. This lends further credibility to our empirical strategy as it rules out any residual concern on the endogeneity of opium price shocks.

Next, we construct four alternative measures of initial opioid exposure. In column 4 of Table 3, instead of a continuous variable for initial exposure we use a binary indicator for the most highly exposed counties, i.e. those above the median in number of mines per capita. In column 5, we replace the number of mining sites per capita with the number of people employed in mines in 1983 over the population in 1980 (Miners1983pc). Since mines might also capture levels of urbanization, education or poverty, columns 6 and 7 of Table 3 use two alternative proxies for the initial demand for opioids to address this concern. Column 6 uses the population share of war veterans in 1999. Veterans are another population group making greater use of opioid-based medications (Edlund et al., 2007; Banerjee et al., 2016), and they are more or less evenly distributed across rural and urban counties. Column 7 takes the per capita number of heavy manufacturing workers in 1990, as this sector, like mining, is characterized by high rates of work-related injury but is typically concentrated in cities and towns. Reassuringly, the estimated coefficients in these alternative specifications are all negative and statistically significant, strengthening confidence in our main results.[38]

4.2 Heterogeneity Analysis

We check for heterogeneous effects of opium price shocks on the per capita dispensation of POs according to counties' socio-economic characteristics.

In Table 4 we define dummy variables equal to 1 for above-median values of income per capita, share of graduates, urbanization, share of people with health insurance, and share of elderly (over 65) at the beginning of the period (1990 or 2000, depending on data availability). Interacting these indicators with our variable of interest, we find empirically that factors such as education mitigate the effect of opium price shocks on PO dispensation, in line with the findings reported by Case and Deaton (2015). Also, wealthier and urbanized areas, which typically feature a higher share of residents with health insurance, display lower impact of opium price changes on the dispensation of opioid-based drugs, in line with the empirical evidence provided by Krueger (2017). This result also confirms the recent findings on the effect of Medicare expansion on opioid use by Baker et al. (2018), namely that enrolment in the Medicare plan that combines drug coverage with other medical benefits significantly reduces the probability of requests for opioid prescriptions, by comparison with other (stand-alone) drug plans.

We also explore the possibility of heterogeneous effects driven by the initial availability of health services in a county. Specifically, we interact our variable of interest with the share of

[38] When including different proxies for the *ex-ante* demand for opioids (mines, veterans and employment in the manufacturing sector) in a "horse-race" regression, we find a robust and statistically significant negative impact on opioids dispensation associated with any of them. Since the effects are separately identified, we confidently exclude that the different proxies are possibly capturing similar geographical variations (if anything, we are estimating different sub-population margins). All the specifications are also robust to the inclusion of county-year fixed effects, thus exploiting within-year variation.

Table 4: Heterogeneous Effects by Socio-Economic Characteristics

	(1)	(2)	(3)	(4)	(5)
Dep. variable	Δ lnMGEpc	Δ lnMGEpc	Δ lnMGEpc	Δ lnMGEpc	Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0081***	-0.0081***	-0.0080***	-0.0079***	-0.0061***
	(0.0023)	(0.0024)	(0.0024)	(0.0024)	(0.0023)
lnMines1983pc * Δ lnOpiumP *	0.0013***				
I(Income1990pc > median)	(0.0003)				
lnMines1983pc * Δ lnOpiumP *		0.0014***			
I(Graduates1990pc > median)		(0.0003)			
lnMines1983pc * Δ lnOpiumP *			0.0012***		
I(Urban2000)			(0.0003)		
lnMines1983pc * Δ lnOpiumP *				0.0012***	
I(Insurance2000pc > median)				(0.0003)	
lnMines1983pc * Δ lnOpiumP *					0.0009
I(Over65yo2000pc > median)					(0.0006)
Observations	174,104	174,104	174,104	174,104	174,104
R-squared	0.3330	0.3329	0.3329	0.3329	0.3329

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of MGE dispensed per capita. OpiumP is the average trader price of opium. Mines1983pc is the number of mining sites per capita in 1983. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

people employed in various types of health facility in 1998. The results, reported in Table A.5, show that the main effect on per capita dispensation of POs is stronger in counties with a larger share of workers in outpatient care centers and home health care facilities, or in hospitals that treat mental health and substance abuse problems.[39] This result would appear to indicate that a larger number of health care professionals implies easier access to prescription drugs *per se*. However, it could also be interpreted as evidence that areas with a greater concentration of such facilities feature sharper competition among health care suppliers, inducing laxer prescription practices designed to retain customers.

4.3 The Effect of Opium Price Shocks on Opioid-Related Deaths and Drug-Related Crimes

In this section, we seek to determine whether drops in the price of opium, by contributing to the escalation in PO use, had negative socio-economic spillover effects. In particular, we look at two key outcomes: opioid-related deaths and drug-related crimes. Table 5 shows the extent to which our interaction term affects both the rate of increase in opioid-related deaths per capita and in drug-related crimes per capita.[40] In fact, the counties more exposed to opium price shocks exhibit higher rates of opioid-related deaths. This is consistent with our finding that the more highly exposed counties experience a greater increase in prescription rates following an exogenous decline in the price of opium. Column 1 of Table 5 replicates our main result when

[39] Outpatient care refers to ambulatory surgical and emergency centers; home health care centers typically deal with terminally ill patients. Because the data are aggregated at the NAICS 4-digit level, it is not possible to distinguish people employed in psychiatric hospitals from those in substance abuse clinics.

[40] Data are available at county-month level. However, counts below 9 are suppressed for confidentiality, which results in a large number of suppressed entries. We therefore aggregate at year level.

Table 5: Effects on Opioid-Related Deaths and Drug-Related Crimes

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnDeathspc	(3) Δ lnDrugTotpc	(4) Δ lnDrugSalepc	(5) Δ lnDrugPosspc
lnMines1983pc * Δ lnOpiumP	-0.0075***	-0.0120*	-0.2095**	-0.1431**	-0.2056**
	(0.0027)	(0.0063)	(0.0908)	(0.0659)	(0.0905)
Observations	40,404	40,404	40,404	40,404	40,404
R-squared	0.5783	0.0787	0.7636	0.7027	0.7570

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003-2016). MGEpc is the quantity of MGE dispensed per capita. Deathspc is the number of opioid-related deaths per capita. DrugTotpc is the total number of drug-related crimes per capita. DrugSalepc and DrugPosspc stand for per capita arrests for sale and possession of drugs, respectively. OpiumP is the average trader price of opium. Mines1983pc is the number of mining sites per capita in 1983. All columns include year and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

both the outcome variable, i.e. the log-change in per capita MGE, and the fluctuations in opium prices are defined yearly. As in the main specification, the coefficient is negative and statistically significant at the 1% level. It is slightly higher because of the greater yearly variations in the price of opium.

Columns 2-5 analyse the impact on the relevant socio-economic outcomes. Column 2 shows an inverse correlation between opium price changes and opioid-related deaths. Our estimate is that for counties at the 40th percentile of the (log) mining site distribution, a 1-standard deviation diminution in opium prices (i.e. a price fall by around 34 percentage points) is associated with a 0.81 percentage-point rise in the rate of increase in deaths per capita. This corresponds to an increase of roughly 0.118 deaths per 100,000 inhabitants.[41] We also analyse negative spillovers on the illegal drug market at the local level. Here the estimates indicate that a 1-standard-deviation decline in the growth in the opium price causes an increase in the growth in drug-related crimes per capita by 14 percentage points. This translates into an increase of 360 arrests per 100,000 inhabitants (column 3), reflecting both possession (column 4) and sale of illicit substances (column 5).[42] The results are consistent with the thesis that drug diversion depends on the overall amount of POs distributed in a given area.[43]

5 The Role of Supply-Side Economic Incentives

This section provides additional evidence for the hypothesis that economic incentives for producers have contributed to driving the effects presented above. First, we investigate whether impacts differ according to the opium intensity of the various types of opioids, in order to bring out potentially asymmetric effects related to the cost of the raw material used in producing each type of drug. Second, we explore the role of changes in patient demand by looking at the effect of changes in the relative retail price of opioids on the per capita dispensation of

[41] Average opioid death rate in the sample is 4,5 per 100,000 inhabitants.
[42] Average drug-related arrest rate in the sample is 100 per 100,000 inhabitants.
[43] Among recent contributions on opioid abuse and criminal activities, Meinhofer (2017), Mallatt (2017) and Doleac and Mukherjee (2019) study how state laws restricting opioid use affect heroin crimes, drug theft, homicides and assaults.

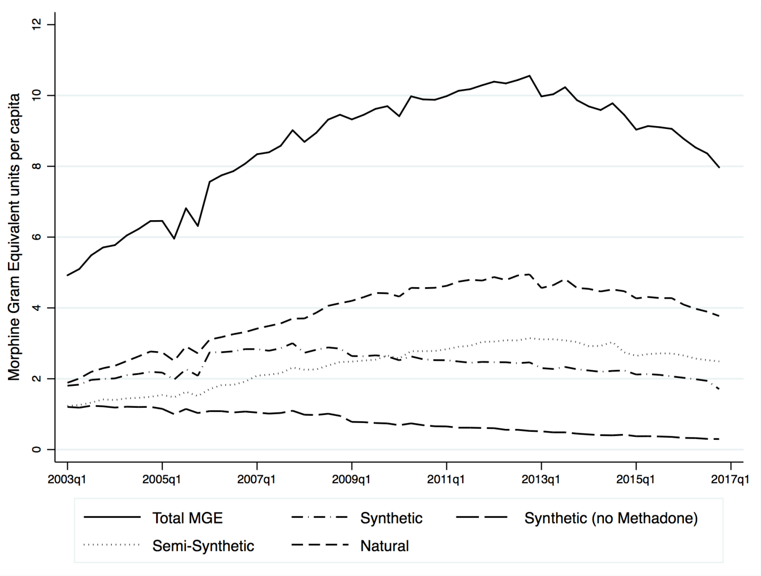
POs. Finally, we confirm the evidence set out above in an examination of the impact of changes in opium prices on the expenditure for advertising, stock prices and profit indicators of US pharmaceutical companies that sell opioids.

5.1 The Asymmetric Effect of Opium Price Shocks Across Opioid-Based Drug Types

The analysis presented so far highlights a significant and robust negative relationship between changes in the price of opium and changes in the quantity of POs dispensed per capita. The hypothesis is that decreases in the cost of the raw material induce an increase in the quantity of drugs prescribed. Clearly, we expect this mechanism to be stronger for drugs that require more raw opium.

Opioids can be classified according to how they are manufactured.[44] Natural opiates are alkaloids contained in the resin of the opium poppy (e.g. morphine). Semi-synthetic opioids (e.g. oxycodone) are obtained from natural opiates or morphine esters through synthesis of natural substances. Synthetic opioids are synthesized in laboratories and contain no natural ingredients. One of the most potent synthetic opioids is fentanyl, which recently overtook oxycodone as the main cause of overdose death in the United States. Thus, we can divide the drugs studied here into three groups according to active ingredient: natural (morphine), semi-synthetic (hydrocodone, hydromorphone and oxycodone) and fully synthetic opioids (fentanyl,

Figure 3: Trends in the Prescription of MGE Opioids Per Capita



Note: Natural opioids: morphine; semi-synthetic opioids: hydrocodone, hydromorphone and oxycodone; synthetic opioids: fentanyl, meperidine and methadone. All quantities are in MGE units.

[44] Technically, all opioids are synthetic, while opiates refer to all types of opium-derived drugs. The term "opioid" is used currently to designate the entire family of opiates (natural, semi-synthetic and synthetic).

meperidine and methadone).[45]

If the agents and stakeholders in this market are interested only in profit maximization, we would expect to find different responses to opium price changes depending on the type of opioid manufactured, since natural and semi-synthetic should logically be more responsive than fully synthetic opioids to variations in the price of the raw material. If raw opium is relatively more expensive, it is costlier to manufacture natural and semi-synthetic opioids, so firms might prefer to increase the use of cheaper substitute synthetics.

Figure 3 shows that when we distinguish between natural, semi-synthetic and fully synthetic opioids, the increase in the total quantity (solid line) is determined mainly by the natural and semi-synthetic opioids (dashed and dotted lines, respectively), while the volume of synthetic opioids (long-dashed line) is fairly flat and tends to decline over time. These trends continue during periods when the price of the raw material is decreasing (see Figure 1).

In Table 6, we test whether the quantities of natural and semi-synthetic and synthetic POs respond differently to opium price shocks, given that the former category requires the use of raw opium to be manufactured, while the latter does not. Column 1 considers only natural and semi-synthetic opioids. Here, the effect of price shocks persists. Column 2 takes as dependent variable the per capita dispensation of fully synthetic opioids: in this case the coefficient drops to zero and loses its statistical significance, as expected. Overall, the coefficients in columns 1 and 2 support the hypothesis that the quantity of opioid-based drugs dispensed in the US increases as the price of dry opium in Afghanistan falls, and that this increase mainly involves drugs that require at least some input of raw opium. By contrast, fully synthetic opioids do not react to changes in the price of opium.[46]

Moreover, consistent with the fact that up to 2010 most overdose deaths had involved natural and semi-synthetic prescription opioids, we split the sample accordingly. We find a larger effect in the period of maximum expansion of medical POs (column 3), which is three times larger in

Table 6: Effects by Type of Drug

Dep. variable	(1) Δ lnMGEpc (Natural/ Semi-synthetic)	(2) Δ lnMGEpc (Synthetic)	(3) Δ lnMGEpc (Natural/ Semi-synthetic)	(4) Δ lnMGEpc (Natural/ Semi-synthetic)	(5) Δ lnMGEpc (Synthetic)	(6) Δ lnMGEpc (Synthetic)
lnMines1983pc * Δ lnOpiumP	-0.0063***	-0.0001	-0.0096***	-0.0024*	-0.0027	0.0041
	(0.0022)	(0.0023)	(0.0037)	(0.0013)	(0.0038)	(0.0046)
Observations	174,104	174,104	87,052	87,052	87,052	87,052
R-squared	0.2523	0.1033	0.2191	0.2638	0.1466	0.0710
Period	Full	Full	<2010	≥2010	<2010	≥2010

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of MGE dispensed per capita. OpiumP is the average trader price of opium. Mines1983pc is the number of mining sites per capita in 1983. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis. Fully-synthetic MGEs excluding methadone.

[45] Although methadone is a synthetic opioid with high risk of abuse and addiction, we exclude it from this part of the analysis because it is used extensively not only to treat pain but also to treat opioid abusers. This means that the higher the share of drug abusers in an area, the more methadone will be used, both as medication and for drug rehabilitation. Methadone use is therefore likely to confound the effects we are interested in. Excluding fentanyl also produces identical results.

[46] These findings are confirmed in Table A.6, where results by active ingredient are shown.

magnitude than the coefficient for the post-2010 sample. Conversely, we do not find statistically significant coefficients for the fully-synthetic opioids (column 5 and 6). Interestingly, the sign of the coefficient for the fully-synthetic opioids in the post-2010 period (column 6) becomes positive. This is a period characterized by a remarkable increase in overdose deaths involving synthetic opioids, particularly fentanyl.[47] These results suggest the existence of a substitution effect across opioid types, as upturns in the price of the raw material (opium) are associated with higher dispensation of fully-synthetic opioids.

5.2 Exploring the Role of Changes in Patient Demand

The foregoing findings support the hypothesis that supply-side economic incentives have played a role in the soaring use of POs in recent decades. A possible alternative hypothesis is that it was the consequence of change in the demand from patients. This would hold if decreases in the price of opium were associated with declines in the relative price of opioids. Such a pattern would suggest the pass-through of lower production costs to retail prices, boosting patients' demand for opioids.

To test this alternative hypothesis directly, we use the time series of retail prices of opioid-based drugs from 2003 to 2015.[48] That is, we replace our main explanatory variable, the log-change in the price of opium, with the log-change in the retail price of opioids expressed in terms of MGE units. The coefficients reported in Table 7 corroborate the earlier findings and significantly attenuate the concerns set out above. While we do find a negative coefficient associated with the log-change in retail price of opioids on the quantity of drug substances prescribed, we fail to detect a statistically significant effect. This might suggest that it is unlikely that our main results are entirely driven by a change in patient's demand. On the contrary, this evidence is consistent with the idea that US pharmaceutical companies used

Table 7: Effects of Fluctuations in Opioid Retail Prices on MGE

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0075***		-0.0102***
	(0.0027)		(0.0038)
lnMines1983pc * Δ lnOpioidsP		-0.0038	-0.0104
		(0.0049)	(0.0065)
Observations	40,404	40,404	40,404
R-squared	0.5783	0.5774	0.5790

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,108 counties, 2003-2016). MGEpc is the quantity of MGE dispensed per capita. OpiumP is the average trader price of opium. OpioidsP measures the average retail price of opioids per MGE. Mines1983pc is the number of mining sites per capita in 1983. All columns include year and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

[47] For details of the distinct opioid overdose death waves, see `https://www.cdc.gov/drugoverdose/epidemic/index.html`.

[48] Retail prices are computed from the total cost per pill or per patch of generic opioids, as described in Section 3.3 and in the note to Figure A.1, then standardized to account for their potency relative to morphine. Here we just focus on natural and semi-synthetic opioids given the evidence shown above in Section 5.1.

marketing campaigns strategically to promote opioids when the price of opium was declining, i.e. when their markup was increasing (Zejcirovic and Fernandez, 2018).

5.3 The Effect of Opium Price Shocks on Advertising Expenses, Stock Market Prices and Profits

In this final part of the study, we explore: i) how fluctuations in the price of opium affect firms' advertising expenses, and ii) whether pharmaceutical companies are seen by investors as exploiting opium price variations in their business strategies. In fact, if changes in the price of opium are perceived as persistent – and they are, as the existence of a unit root confirms (see Section 3.3) –, then investors can expect opioid producers to factor such changes into their production and distribution decisions.

We rely on quarterly firm-level data from Compustat, which gives balance-sheet data and other financial indicators for a sizeable sample of firms operating in the US. We focus on three main outcomes, namely advertising expenses, stock prices and profits. The idea is to determine the extent to which variations in the price of opium affect the advertising expenses as well as the stock prices and profits of firms in this sector. The sample includes all manufacturing firms operating in the US during the period 2003q1-2016q4. Our causal variable is the interaction between the log-change in the quarterly price of opium in Afghanistan and a dummy for listed companies with FDA opioid-based drug approval.[49] Our baseline model includes quarter dummies, firm fixed effects, NAICS-quarter dummies and firm-specific linear trends, to allow for time and firm heterogeneity and potential time-varying sectoral shocks.

Column 1 of Table 8, Panel A, shows that declines in the price of opium significantly boost the advertising expenses of opioid producers relative to other manufacturing firms. To corroborate these findings, in column 2 we include as additional covariate a dummy that takes value 1 if the company has obtained FDA approval to market an ibuprofen-based drug. Ibuprofen, in fact, can be seen as a partial substitute for opioids, given its pain-relief properties, but its production and sale should not be affected by the price of raw opium, which is not one of its components. The estimated coefficient slightly increases with respect to the one in column 2. In addition, the positive and significant effect of upturns in opium prices on the advertising expenses of ibuprofen-producing firms suggests a substitution effect between ibuprofen- and opioid-based drugs. Column 3 presents a placebo exercise in which we assign drug approvals randomly to the listed companies in the sample.[50] Given substantial heterogeneity in trends between opioid manufacturers and other companies, the placebo test should show an effect comparable to our baseline coefficients. Here, the lack of statistical significance supports our conclusions (Bertrand et al., 2004; Abadie and Gardeazabal, 2003).

[49] We retrieve information on approvals from the FDA's so-called "Orange Book," i.e. "Approved Drug Products with Therapeutic Equivalence Evaluations". This proxies for companies with a specific interest in the opioid market. We cannot exclude the possibility that other actors, such as insurance companies, may also have an interest in this market, relying on the assumption of well-informed investors. Since we are considering only listed companies, it is possible that some control firms may operate in the opioids market even without specific drug approval.

[50] We run 200 replications.

Table 8: Firm Level Estimates

Panel A	(1)	(2)	(3)
Dep. variable	Δ lnAdExpense	Δ lnAdExpense	Δ lnAdExpense
Δ lnOpiumP * I(Opioid Approval)	-0.060***	-0.080***	
	(0.006)	(0.007)	
Δ lnOpiumP * I(Ibuprofen Approval)		0.051***	
		(0.004)	
Δ lnOpiumP * I(Placebo Approval)			-0.027
			(0.091)
Observations	10,442	10,442	10,442
R-squared	0.148	0.148	

Panel B	(1)	(2)	(3)
Dep. variable	Δ lnStockP	Δ lnStockP	Δ lnStockP
Δ lnOpiumP * I(Opioid Approval)	-0.025***	-0.024***	
	(0.001)	(0.006)	
Δ lnOpiumP * I(Ibuprofen Approval)		-0.005	
		(0.027)	
Δ lnOpiumP * I(Placebo Approval)			0.000
			(0.082)
Observations	48,030	48,030	48,030
R-squared	0.165	0.165	

Panel C	(1)	(2)	(3)
Dep. variable	Δ lnProfit	Δ lnProfit	Δ lnProfit
Δ lnOpiumP * I(Opioid Approval)	-0.107***	-0.124***	
	(0.008)	(0.009)	
Δ lnOpiumP * I(Ibuprofen Approval)		0.070***	
		(0.003)	
Δ lnOpiumP * I(Placebo Approval)			-0.016
			(0.134)
Observations	29,062	29,062	29,062
R-squared	0.205	0.205	

Note: * p<.10 ** p<.05 *** p<.01. Full sample of firms operating in NAICS sector 32. OpiumP is the average traders price of opium. The dummies for opioid approval and ibuprofen approval take value 1 if the firm has FDA approval for opioid-based or ibuprofen-based drugs. All regressions include quarter, firm and NAICS-quarter fixed effects and firm-specific linear trends. Clustered-robust standard errors at NAICS level in parenthesis.

Taken together, the estimates in Panel A show that declines in the cost of the raw material are associated with increases in advertising expenses by firms who have an FDA approval for opioid-based drugs, therefore confirming our hypothesis that opioid-producing companies use promotions as a strategy to expand demand at a time in which their markup is increasing. It is worth noticing that the advertising expenses of pharmaceutical companies are mostly directed to physicians through detailing, product sampling, and advertising in professional journals (Zejcirovic and Fernandez, 2018; Cegedim, 2013).

Next, we address the extent to which firms' stock prices react to opium price shocks. Reading across the columns in Panel B shows that opioid producers' stock market performance significantly benefits from declines in the price of opium with respect to the stock market performance of other manufacturing firms. This provides a clear picture that also investors expect opioid manufacturers to exploit opium price fluctuations in their production and distribution strategies.

Finally, as a robustness check, we examine the association between opium price changes and firms' profits.[51] The estimated coefficients in Panel C point to conclusions analogous to those obtained from Panel B. The positive and significant effect of upturns in opium prices on the profits of ibuprofen-producing firms (Panel C, column 2) confirms the existence of a potential substitution effect between ibuprofen- and opioid-based drugs.

To our knowledge, this is the first empirical study offering evidence that the dispensation of opioids could stem from an economic rather than a purely medical rationale. Tracking changes to the price of opium, we observe a clear inverse correlation with three important measures of firms' performance, namely advertising expenses, stock prices and profits. The performance of opioid manufacturers, i.e. firms with FDA approval to produce them, improves in response to reductions in the price of opium. That is, opium price changes in Afghanistan are associated with changes in the expected future profits of the pharmaceutical companies that produce opioid-based drugs, and hence with the economic incentive to promote and sell them.

6 Conclusions

The United States is in the throes of an opioid epidemic, with more than 2 million Americans addicted to or abusing prescription opioid painkillers.

This paper explores the role of supply-side economic incentives in the course of the US opioid crisis, testing whether the quantity of POs dispensed per capita responds to variations in the international price of opium. The empirical analysis reveals a significant positive effect of declines in the price of opium on the quantity of POs dispensed: a 20 percentage point decrease in opium price growth generates an increase in the quantity of POs dispensed of about 5.5 medical doses of morphine per capita in counties at the 40th percentile of the distribution of mining sites. Interestingly, while opium price shocks significantly affect the quantity of natural and semi-synthetic opioids dispensed, they have no effect on prescriptions for fully synthetic opioids, which do not require opium as a production input. Moreover, opium price changes are correlated with increases in opioid-related deaths per capita and in the arrest rates for possession and sale of illicit substances. Finally, firm-level analysis suggests that advertising expenses of opioids manufacturers respond significantly to opium price shocks and do so their stock prices and profits. This supports the hypothesis that supply-side economic incentives might have driven to a significant extent the distribution of opioids in the US.

While the medical literature acknowledges that opioids are unquestionably effective in treating certain severe conditions, the risks involved in the excessive use of these drugs are far from negligible, as the opioid epidemic has made clear. Our work adds to the previous inquiries into the mechanisms underlying the opioid crisis, pointing to the presence of a plausible relationship between economic incentives and the spread of these drugs in the US. This strongly implies that policy makers should seriously reconsider the impact of the regulations on the marketing and promotion of these substances. A step in this direction has recently been made, as some opioid manufacturers have announced that they will limit their marketing activities for opioid-based

[51] We restrict the sample to the observations for which we have full information for the dependent variable.

products. Additionally, our analysis offers indications for an effective strategy to counter the opioid crisis: we observe weaker effects in wealthier and urban areas with a better educated population. The clear implication is that a greater effort should be made to improve access to alternative treatments and to promote better public understanding of the danger of prescription opioids abuse through more effective public health surveillance, especially in remote areas.

References

Abadie, A. and J. Gardeazabal (2003): "The Economic Costs of Conflict: a Case Study of the Basque Country," *American Economic Review*, 93, 113–132.

Adhvaryu, A., J. Fenske, and A. Nyshadham (2014): "Early Life Circumstance and Adult Mental Health," *University of Oxford Department of Economics Discussion Paper Series*, 1471–0498.

Alpert, A., D. Powell, and R. L. Pacula (2018): "Supply-Side Drug Policy in the Presence of Substitutes: Evidence From the Introduction of Abuse-Deterrent Opioids," *American Economic Journal: Economic Policy*, 10, 1–35.

Alpert, A. E., W. N. Evans, E. M. Lieber, and D. Powell (2019): "Origins of the Opioid Crisis and Its Enduring Impacts," *NBER Working Paper Series*, 26500.

Autor, D., D. Dorn, and G. Hanson (2013): "The China Syndrome: Local Labor Market Effects of Import Competition in the United States," *American Economic Review*, 103, 2121–68.

Baker, L. C., K. Bundorf, and D. Kessler (2018): "The Effects of Medicare Advantage on Opioid Use," *NBER Working Paper Series*, 25327.

Banerjee, G., E. J. Edelman, D. T. Barry, W. C. Becker, M. Cerdá, S. Crystal, J. R. Gaither, A. J. Gordon, K. S. Gordon, R. D. Kerns, S. S. Martins, D. A. Fiellin, and B. D. L. Marshall (2016): "Non-Medical Use of Prescription Opioids is Associated with Heroin Initiation Among US Veterans: a Prospective Cohort Study," *Addiction*, 111, 2021–2031.

Bazzi, S. and C. Blattman (2014): "Economic Shocks and Conflict: Evidence from Commodity Prices," *American Economic Journal: Macroeconomics*, 6, 1–38.

Becker, G. S., M. Grossman, and K. M. Murphy (1994): "An Empirical Analysis of Cigarette Addiction," *American Economic Review*, 84, 396–418.

Becker, G. S. and K. M. Murphy (1988): "A theory of rational addiction," *Journal of political Economy*, 96, 675–700.

Berman, N. and M. Couttenier (2015): "External Shocks, Internal Shots: the Geography of Civil Conflicts," *Review of Economics and Statistics*, 97, 758–776.

Berman, N., M. Couttenier, D. Rohner, and M. Thoenig (2017): "This Mine is Mine! How Minerals Fuel Conflicts in Africa," *American Economic Review*, 107, 1564–1610.

Bertrand, M., E. Duflo, and S. Mullainathan (2004): "How Much Should We Trust Differences-in-Differences Estimates?" *The Quarterly Journal of Economics*, 119, 249–275.

Brady, J. E., H. Wunsch, C. DiMaggio, B. H. Lang, J. Giglio, and G. Li (2014): "Prescription Drug Monitoring and Dispensing of Prescription Opioids." *Public Health Reports*, 129, 139–47.

Brückner, M. and A. Ciccone (2010): "International Commodity Prices, Growth and the Outbreak of Civil War in Sub-Saharan Africa," *The Economic Journal*, 120, 519–534.

Bruckner, M., A. Ciccone, and A. Tesei (2012): "Oil Price Shocks, Income, and Democracy," *The Review of Economics and Statistics*, 94, 389–399.

Brückner, M. and M. Gradstein (2013): "Exogenous Volatility and the Size of Government in Developing Countries," *Journal of Development Economics*, 105, 254–266.

Buchmueller, T. C. and C. Carey (2018): "The Effect of Prescription Drug Monitoring Programs on Opioid Utilization in Medicare," *American Economic Journal: Economic Policy*, 10, 77–112.

Campbell, E. G., R. L. Gruen, J. Mountford, L. G. Miller, P. D. Cleary, and D. Blumenthal (2007): "A National Survey of Physician–Industry Relationships," *New England Journal of Medicine*, 356, 1742–1750.

Carpenter, C. S., C. B. McClellan, and D. I. Rees (2017): "Economic Conditions, Illicit Drug Use, and Substance Use Disorders in the United States," *Journal of Health Economics*, 52, 63–73.

Case, A. and A. Deaton (2015): "Rising Morbidity and Mortality in Midlife among White Non-Hispanic Americans in the 21st Century," *Proceedings of the National Academy of Sciences*, 112, 15078–15083.

——— (2018): "Deaths of Despair Redux: a Response to Christopher Ruhm," *Mimeo.*

Cegedim (2013): "2012 U.S. Pharmaceutical Company Promotion Spending," Tech. rep.

Centers for Disease Control and Prevention (2017): "Annual Surveillance Drug-Related Risks and Outcomes," Tech. rep., United States.

Chang, H.-Y., M. Daubresse, S. P. Kruszewski, and G. C. Alexander (2014): "Prevalence and Treatment of Pain in EDs in the United States, 2000 to 2010," *The American Journal of Emergency Medicine*, 32, 421–431.

Chen, L. H., H. Hedegaard, and M. Warner (2014): "Drug-Poisoning Deaths Involving Opioid Analgesics: United States, 1999-2011," *National Center for Health Statistics Data Brief*, 166, 1–8.

Currie, J., J. Y. Jin, and M. Schnell (2018): "US Employment and Opioids: is There a Connection?" *NBER Working Paper Series*, 24440.

Currie, J., W. Lin, and J. Meng (2014): "Addressing Antibiotic Abuse in China: an Experimental Audit Study," *Journal of Development Economics*, 110, 39–51.

Currie, J., W. Lin, and W. Zhang (2011): "Patient Knowledge and Antibiotic Abuse: Evidence from an Audit Study in China," *Journal of Health Economics*, 30, 933–949.

Cutler, D., J. S. Skinner, A. D. Stern, and D. Wennberg (2019): "Physician Beliefs and Patient Preferences: A New Look at Regional Variation in Health Care Spending," *American Economic Journal: Economic Policy*, 11, 192–221.

Dart, R. C., H. L. Surratt, T. J. Cicero, M. W. Parrino, S. G. Severtson, B. Bucher-Bartelson, and J. L. Green (2015): "Trends in Opioid Analgesic Abuse and Mortality in the United States," *New England Journal of Medicine*, 372, 241–248.

Dasgupta, N., L. Beletsky, and D. Ciccarone (2018): "Opioid Crisis: No Easy Fix to its Social and Economic Determinants," *American Journal of Public Health*, 108, 182–186.

Datta, A. and D. Dave (2017): "Effects of physician-directed pharmaceutical promotion on prescription behaviors: Longitudinal evidence," *Health economics*, 26, 450–468.

David, G., S. Markowitz, and S. Richards-Shubik (2010): "The Effects of Pharmaceutical Marketing and Promotion on Adverse Drug Events and Regulation," *American Economic Journal: Economic Policy*, 2, 1–25.

DEA (1992): "Opium Poppy Cultivation and Heroin Processing in Southeast Asia," Tech. rep., US Department of Justice: Drug Enforcement Administration.

Deiana, C. and L. Giua (2018): "The US Opidemic: Prescription Opioids, Labour Market Conditions and Crime," *MPRA Working Paper Series*, 85712.

Doleac, J. L. and A. Mukherjee (2019): "The Moral Hazard of Lifesaving Innovations: Naloxone Access, Opioid Abuse, and Crime," *Mimeo.*

Dube, O. and J. F. Vargas (2013): "Commodity Price Shocks and Civil Conflict: Evidence from Colombia," *The Review of Economic Studies*, 80, 1384–1421.

Edlund, M. J., D. Steffick, T. Hudson, K. M. Harris, and M. Sullivan (2007): "Risk Factors for Clinically Recognized Opioid Abuse and Dependence among Veterans using Opioids for Chronic Non-Cancer Pain," *Pain*, 129, 355–362.

Evans, W. N., E. M. Lieber, and P. Power (2019): "How the Reformulation of OxyContin Ignited the Heroin Epidemic," *Review of Economics and Statistics*, 101, 1–15.

Gammaitoni, A. R., P. Fine, N. Alvarez, M. L. McPherson, and S. Bergmark (2003): "Clinical Application of Opioid Equianalgesic Data," *The Clinical Journal of Pain*, 19, 286–297.

General Accounting Office (2003): “Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem,” Tech. rep., United States.

Gihleb, R., O. Giuntella, and N. Zhang (2018): “The Effects of Mandatory Prescription Drug Monitoring Programs on Foster Care Admissions,” *IZA Discussion Paper Series*.

Hadland, S. E., A. Rivera-Aguirre, B. D. Marshall, and M. Cerdá (2019): “Association of Pharmaceutical Industry Marketing of Opioid Products with Mortality from Opioid-Related Overdoses,” *JAMA network open*, 2, 1–12.

Harris, M. C., L. M. Kessler, M. N. Murray, and M. E. Glenn (2017): “Prescription Opioids and Labor Market Pains: The Effect of Schedule II Opioids on Labor Force Participation and Unemployment,” *MPRA Paper Working Paper Series*.

Iizuka, T. (2007): “Experts’ Agency Problems: Evidence from the Prescription Drug Market in Japan,” *The Rand Journal of Economics*, 38, 844–862.

——— (2012): “Physician Agency and Adoption of Generic Pharmaceuticals,” *American Economic Review*, 102, 2826–58.

Jones, M. R., O. Viswanath, J. Peck, A. D. Kaye, J. S. Gill, and T. T. Simopoulos (2018): “A Brief History of the Opioid Epidemic and Strategies for Pain Medicine,” *Pain and Therapy*, 7, 13–21.

Kolodny, A., D. T. Courtwright, C. S. Hwang, P. Kreiner, J. L. Eadie, T. W. Clark, and G. C. Alexander (2015): “The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction,” *Annual Review of Public Health*, 36, 559–574.

Krueger, A. (2017): “Where Have All the Workers Gone: an Inquiry into the Decline of the U.S. Labor Force Participation Rate,” *Brookings Papers on Economic Activity Fall*.

Leukefeld, C., R. Walker, J. Havens, C. A. Leedham, and V. Tolbert (2007): “What Does the Community Say: Key Informant Perceptions of Rural Prescription Drug Use,” *Journal of Drug Issues*, 37, 503–524.

Lind, J. T., K. O. Moene, and F. Willumsen (2014): “Opium for the Masses? Conflict-Induced Narcotics Production in Afghanistan,” *The Review of Economics and Statistics*, 96, 949–966.

Liu, Y.-M., Y.-H. K. Yang, and C.-R. Hsieh (2009): “Financial Incentives and Physicians’ Prescription Decisions on the Choice Between Brand-Name and Generic Drugs: Evidence from Taiwan,” *Journal of Health Economics*, 28, 341–349.

Lu, F. (2014): “Insurance Coverage and Agency Problems in Doctor Prescriptions: Evidence from a Field Experiment in China,” *Journal of Development Economics*, 106, 156–167.

Mallatt, J. (2017): "The Effect of Prescription Drug Monitoring Programs on Opioid Prescriptions and Heroin Crime Rates," *Mimeo.*

Max, M. B., M. Donovan, C. A. Miaskowski, S. E. Ward, D. Gordon, M. Bookbinder, C. S. Cleeland, N. Coyle, M. Kiss, H. T. Thaler, et al. (1995): "Quality Improvement Guidelines for the Treatment of Acute Pain and Cancer Pain," *Jama*, 274, 1874–1880.

Meara, E., J. R. Horwitz, W. Powell, L. McClelland, W. Zhou, A. J. O'Malley, and N. E. Morden (2016): "State Legal Restrictions and Prescription-Opioid Use among Disabled Adults," *New England Journal of Medicine*, 44–53.

Meinhofer, A. (2017): "The War on Drugs: Estimating the Effect of Prescription Drug Supply-Side Interventions," *Mimeo.*

Mizik, N. and R. Jacobson (2004): "Are Physicians "Easy Marks"? Quantifying the Effects of Detailing and Sampling on New Prescriptions," *Management Science*, 50, 1704–1715.

Morton, F. S. and M. Kyle (2011): "Markets for Pharmaceutical Products," in *Handbook of Health Economics*, Elsevier, vol. 2, 763–823.

Nguyen, T. D., W. D. Bradford, and K. I. Simon (2019a): "How do Opioid Prescribing Restrictions Affect Pharmaceutical Promotion? Lessons from the Mandatory Access Prescription Drug Monitoring Programs," *NBER Working Paper Series*, 26356.

——— (2019b): "Pharmaceutical Payments to Physicians May Increase Prescribing for Opioids," *Addiction*, 114, 1051–1059.

Okie, S. (2010): "A Flood of Opioids, a Rising Tide of Deaths," *New England Journal of Medicine*, 363, 1981–1985.

Paoli, L., V. A. Greenfield, M. Charles, and P. Reuter (2009): "The Global Diversion of Pharmaceutical Drugs: India: the Third Largest Illicit Opium Producer?" *Addiction*, 104, 347–354.

Patrick, S. W., R. E. Schumacher, B. D. Benneyworth, E. E. Krans, J. M. McAllister, and M. M. Davis (2012): "Neonatal Abstinence Syndrome and Associated Health Care Expenditures: United States, 2000-2009," *Journal of American Medical Association*, 307, 1934–1940.

Paulozzi, L. J. (2012): "Prescription Drug Overdoses: a Review," *Journal of Safety Research*, 43, 283–289.

Paulozzi, L. J., E. M. Kilbourne, and H. A. Desai (2011): "Prescription Drug Monitoring Programs and Death Rates from Drug Overdose," *Pain Medicine*, 12, 747–754.

Pei, Z., J.-S. Pischke, and H. Schwandt (2018): "Poorly Measured Confounders Are more Useful on the Left than on the Right," *Journal of Business and Economic Statistics*, 1–34.

Pollack, H. A. (2016): "Commentary on the Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence," *Medical Care*, 54(10), 899–900.

Popovici, I., J. C. Maclean, B. Hijazi, and S. Radakrishnan (2017): "The Effect of State Laws Designed to Prevent Nonmedical Prescription Opioid Use on Overdose Deaths and Treatment," *Health Economics*, 1–12.

Rees, D., J. Sabia, L. Argys, J. Latshaw, and D. Dave (2017): "With a Little Help from My Friends: The Effects of Naloxone Access and Good Samaritan Laws on Opioid-Related Deaths," *NBER Working Paper Series*, 23171.

Rice, T. H. (1983): "The Impact of Changing Medicare Reimbursement Rates on Physician-Induced Demand," *Medical Care*, 803–815.

Rice, T. H. and R. J. Labelle (1989): "Do Physicians Induce Demand for Medical Services?" *Journal of Health Politics, Policy and Law*, 14, 587–600.

Rosenblum, A., L. A. Marsch, H. Joseph, and R. K. Portenoy (2008): "Opioids and the Treatment of Chronic Pain: Controversies, Current Status, and Future Directions." *Experimental and Clinical Psychopharmacology*, 16, 405.

Ruhm, C. J. (2019): "Drivers of the Fatal Drug Epidemic," *Journal of Health Economics*, 25–42.

Savych, B., D. Neumark, and R. Lea (2018): "Do Opioids Help Injured Workers Recover and Get Back to Work? The Impact of Opioid Prescriptions on Duration of Temporary Disability," *NBER Working Paper Series*, 24528.

Schnell, M. (2017): "Physician Behavior in the Presence of a Secondary Market: The Case of Prescription Opioids," *Mimeo.*

Sekimoto, M. and M. Ii (2015): "Supplier-Induced Demand for Chronic Disease Care in Japan: Multilevel Analysis of the Association Between Physician Density and Physician-Patient Encounter Frequency," *Value in Health Regional Issues*, 6, 103–110.

Shigeoka, H. and K. Fushimi (2014): "Supplier-Induced Demand for Newborn Treatment: Evidence from Japan," *Journal of Health Economics*, 35, 162–178.

Tompkins, D. A., J. G. Hobelmann, and P. Compton (2017): "Providing Chronic Pain Management in the "Fifth Vital Sign" Era: Historical and Treatment Perspectives on a Modern-Day Medical Dilemma," *Drug and Alcohol Dependence*, 173, S11–S21.

United Nations (2003): "Limited Opium Yield Assessment Surveys," Tech. rep., United Nations: Office of Drugs and Crime.

——— (2005): "Report of the International Narcotics Control Board for 2005," Tech. rep., United Nations: International Narcotics Control Board.

——— (2018): "Narcotic Drugs: Estimated World Requirements for 2018; Statistics for 2016," Tech. rep., United Nations: International Narcotics Control Board.

VA (2000): "Pain as the 5^{th} Vital Sign Toolkit," *The United States Department of Veterans Affairs Toolkit.*

Van Zee, A. (2009): "The promotion and marketing of oxycontin: Commercial triumph, public health tragedy," *American Journal of Public Health*, 99, 221–227.

Walid, M. S., S. N. Donahue, D. M. Darmohray, L. A. Hyer Jr, and J. S. Robinson Jr (2008): "The Fifth Vital Sign: What Does it Mean?" *Pain Practice*, 8, 417–422.

West, R. (2013): "EMCDDA Insights: Models of addiction," *Publications Office of the European Union. Luxemburg.*

Wyse, J. J., A. J. Gordon, S. K. Dobscha, B. J. Morasco, E. Tiffany, K. Drexler, F. Sandbrink, and T. I. Lovejoy (2018): "Medications for Opioid Use Disorder in the Department of Veterans Affairs (VA) Health Care System: Historical Perspective, Lessons Learned and Next Steps," *Substance Abuse*, 00–00.

Zejcirovic, D. and F. Fernandez (2018): "Can Pharmaceutical Promotion to Physicians lead to Adverse Health Outcomes? Evidence from the Opioid Epidemic in the US," *Mimeo.*

Appendix

Table A.1: Descriptive Statistics

	Obs	Mean	Std. Dev.	Min	Max
Quarterly data					
Δ lnMGEpc	174,104	0.0082	0.0862	-1.9667	2.1384
MGEpc	174,104	8.5965	54.4104	0.0195	3443.2370
lnMines1983pc	174,104	2.2644	1.2500	-14.7557	6.7565
Mines1983pc	174,104	20.3456	46.9551	3.91e-07	859.6231
Δ lnOpiumP	174,104	-0.0164	0.1963	-0.5021	0.4700
Δ lnOpiumP (farmer)	152,341	0.0026	0.1249	-0.2156	0.5097
OpiumP	174,104	196.4955	80.6617	88.7500	475.0000
OpiumP (farmer)	155,450	155.0733	50.8262	73.3333	272.3333
Population	174,104	97883.5700	314821.4000	55	10100000
lnMiners1983p	173,880	-6.9885	1.5597	-23.0431	-2.1860
lnVeterans1999pc	173,936	-2.4162	0.2481	-5.5188	-0.9163
lnHeavyManuf1999pc	96,880	-3.3728	1.2789	-9.1229	0.0522
Δ lnCasualties	174,104	0.0117	0.5971	-1.7917	1.1192
Δ lnMGEpc (Natural)	174,104	0.0115	0.2169	-12.3886	12.4359
Δ lnMGEpc (Semi-synthetic)	174,104	0.0126	0.0852	-2.0633	2.0285
Δ lnMGEpc Fully-synthetic)	174,104	-0.0265	0.1595	-4.6215	4.5491
Δ lnAmphetaminepc	174,104	0.0202	0.0945	-1.1195	1.8048
Δ lnMethamphetaminepc	174,104	-0.0082	0.4903	-5.1307	5.2815
Δ lnCocainepc	174,104	-0.0137	0.5128	-3.5239	3.1730
Δ lnFentanylpc	174,104	0.0078	0.1180	-6.7779	6.7003
Δ lnMeperidinepc	174,104	-0.0343	0.2135	-4.7482	4.5954
Δ lnMethadonepc	174,104	0.0155	0.2067	-9.1890	8.9730
Δ lnHydrocodonepc	174,104	0.0082	0.1059	-1.7097	1.9299
Δ lnHydromorphonepc	174,104	0.0245	0.2611	-3.6599	3.8499
Δ lnOxycodonepc	174,104	0.0139	0.0952	-1.8388	1.9156
Δ lnMorphinepc	174,104	0.0115	0.2169	-12.3886	12.4359
Yearly data					
Δ lnMGEpc	40,404	0.0503	0.1041	-1.0225	2.0128
Δ lnOpiumP	40,404	-0.0715	0.3442	-0.6427	0.7710
Δ lnOpioidsP	40,404	0.1213	0.5453	-0.8496	1.5896
Δ lnDeathspc	40,404	0.0091	0.1304	-1.9070	2.0889
Δ lnDrugTotpc	40,404	-0.3285	1.4058	-10.8234	7.1050
Δ lnDrugSalepc	40,404	-0.2046	1.1153	-9.0649	5.9948
Δ lnDrugPosspc	40,404	-0.3113	1.3561	-10.6343	7.0851
Firm-level data					
Δ lnStockP	48,030	-0.0065	0.5185	-9.2203	9.6158
Δ lnProfit	26,908	0.0272	0.5888	-7.3907	6.5705
Δ lnAdExpense	10,442	0.0075	0.4255	-6.9180	7.3677

Note: The main sample consists of 3,109 counties.

Table A.2: Effects on MGE: Leads and Lags

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc	(4) Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP$_{(t-4)-(t-5)}$				0.0083
				(0.0064)
lnMines1983pc * Δ lnOpiumP$_{(t-3)-(t-4))}$				0.0062*
				(0.0034)
lnMines1983pc * Δ lnOpiumP$_{(t-2)-(t-3)}$				-0.0045
				(0.0032)
lnMines1983pc * Δ lnOpiumP$_{(t-1)-(t-2)}$			0.0002	-0.0004
			(0.0022)	(0.0025)
lnMines1983pc * Δ lnOpiumP	-0.0063***	-0.0076**	-0.0064***	-0.0082***
	(0.0024)	(0.0036)	(0.0023)	(0.0027)
lnMines1983pc * Δ lnOpiumP$_{(t+1)-t}$	-0.0033	-0.0023		
	(0.0023)	(0.0029)		
lnMines1983pc * Δ lnOpiumP$_{(t+2)-(t+1)}$		0.0013		
		(0.0017)		
lnMines1983pc * Δ lnOpiumP$_{(t+3)-(t+2)}$		0.0027		
		(0.0033)		
lnMines1983pc * Δ lnOpiumP$_{(t+4)-(t+3)}$		-0.0040		
		(0.0032)		
Observations	170,995	161,668	174,104	174,104
R-squared	0.3292	0.3255	0.3329	0.3345

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of Morphine Gram Equivalent dispensed per capita. OpiumP is the average traders price of opium. Mines1983pc is the number of mining sites per capita in 1983. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

Table A.3: Effects on MGE: Placebo on Price Shocks

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc	(4) Δ lnMGEpc	(5) Δ lnMGEpc	(6) Δ lnMGEpc	(7) Δ lnMGEpc	(8) Δ lnMGEpc
lnMines1983pc * Δ lnOilP	-0.0030							
	(0.0022)							
lnMines1983pc * Δ lnCPI		0.0167						
		(0.0487)						
lnMines1983pc * Δ lnCopperP			0.0010					
			(0.0029)					
lnMines1983pc * Δ lnSugarP				0.0046				
				(0.0117)				
lnMines1983pc * Δ lnCoffeP					-0.0045			
					(0.0071)			
lnMines1983pc * Δ lnCocoaP						-0.0068		
						(0.0054)		
lnMines1983pc * Δ lnWheatP							0.0022	
							(0.0029)	
lnMines1983pc * Δ lnPalmOilP								0.0022
								(0.0038)
Observations	174,104	174,104	174,104	174,104	174,104	174,104	174,104	174,104
R-squared	0.3325	0.3324	0.3324	0.3324	0.3325	0.3325	0.3324	0.3324

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of Morphine Gram Equivalent dispensed per capita. OilP, CPI, CopperP, SugarP, CoffeP, CocoaP, WheatP, PalmOilP and OpiumP are the international oil price, the average consumer price index, and the international prices of copper, sugar, coffee, cocoa, wheat, palm oil and opium, respectively. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

Table A.4: Effects on Other Types of Drugs: Placebo

Dep. variable	(1) Δ lnAmphetaminepc	(2) Δ lnMethamphetaminepc	(3) Δ lnCocainepc
lnMines1983pc * Δ lnOpiumP	0.0011	-0.0188	-0.0021
	(0.0011)	(0.0153)	(0.0082)
Observations	174,104	174,104	174,104
R-squared	0.3334	0.4796	0.1428

Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). Drug quantities are in grams per capita. Mines1983pc is the number of mining sites per capita in 1983. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

Table A.5: Heterogeneous Effects on the Availability of Health Services

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc	(4) Δ lnMGEpc	(5) Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0064***	-0.0060***	-0.0054***	-0.0066***	-0.0044**
	(0.0023)	(0.0022)	(0.0020)	(0.0023)	(0.0017)
lnMines1983pc * Δ lnOpiumP	-0.0124	-0.1045	-0.1262*	-0.0109	-0.0524**
* HealthSector1998pc	(0.0286)	(0.0995)	(0.0668)	(0.1046)	(0.0255)
Observations	173,040	173,040	173,040	173,040	173,040
R-squared	0.3316	0.3316	0.3317	0.3316	0.3318
P-value	0.5070	0.2655	0.0495	0.8668	0.0229
Health Sector	Physicians	Dentists	Outpatient Care	Labs/Screening	Home Health Care

Dep. variable	(6) Δ lnMGEpc	(7) Δ lnMGEpc	(8) Δ lnMGEpc	(9) Δ lnMGEpc	(10) Δ lnMGEpc
lnMines1983pc * Δ lnOpiumP	-0.0074***	-0.0049**	-0.0067***	-0.0074***	-0.0064**
	(0.0024)	(0.0019)	(0.0022)	(0.0022)	(0.0025)
lnMines1983pc * Δ lnOpiumP	0.0116	-0.1477**	0.0033	0.1967***	-0.0082
* HealthSector1998pc	(0.0116)	(0.0698)	(0.0160)	(0.0464)	(0.0254)
Observations	173,040	173,040	173,040	173,040	173,040
R-squared	0.3316	0.3317	0.3316	0.3318	0.3316
P-value	0.6930	0.0283	0.8368	0.0000	0.5445
Health Sector	Hospitals	Psych/Subst Abuse	Nursing Care	Elderly Care	Social Assist

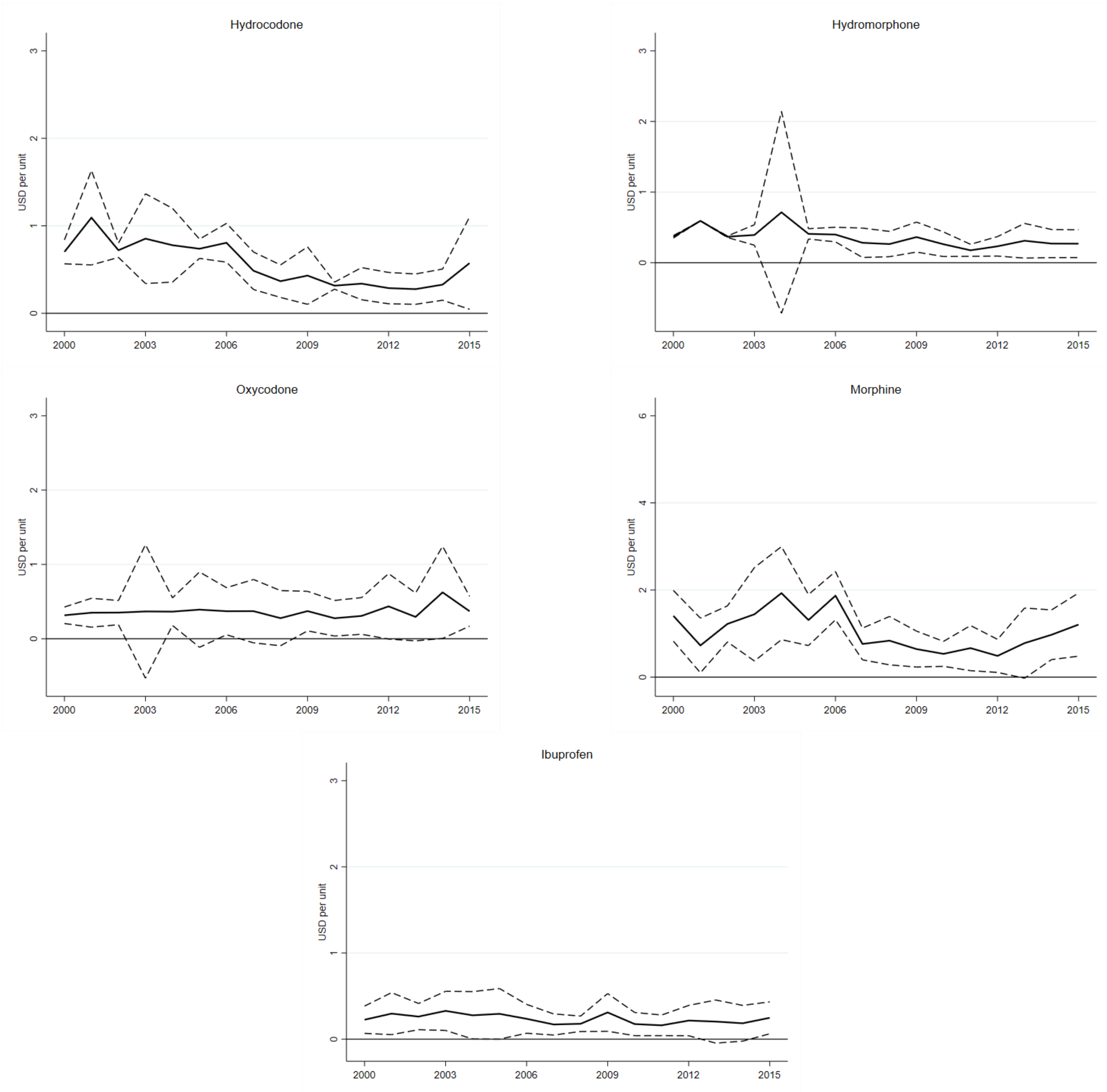
Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). MGEpc is the quantity of Morphine Gram Equivalent dispensed per capita. OpiumP is the average traders price of opium. Mines1983pc is the number of mining sites per capita in 1983. P-value refers to the sum of the two interactions being equal to zero. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

Table A.6: Effects on MGE: Drug Types

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
		Δ lnFully-syntheticpc		Δ lnNatural/Semi-synthetic			
Dep. variable	Methadone	Fentanyl	Meperidine	Hydrocodone	Hydromorphone	Oxycodone	Morphine
lnMines1983pc * Δ lnOpiumP	-0.0128***	-0.0036*	0.0022	-0.0052	-0.0083**	-0.0113***	-0.0057***
	(0.0042)	(0.0019)	(0.0033)	(0.0044)	(0.0039)	(0.0032)	(0.0021)
Observations	174,104	174,104	174,104	174,104	174,104	174,104	174,104
R-squared	0.3673	0.2164	0.0829	0.2651	0.0645	0.2611	0.0455

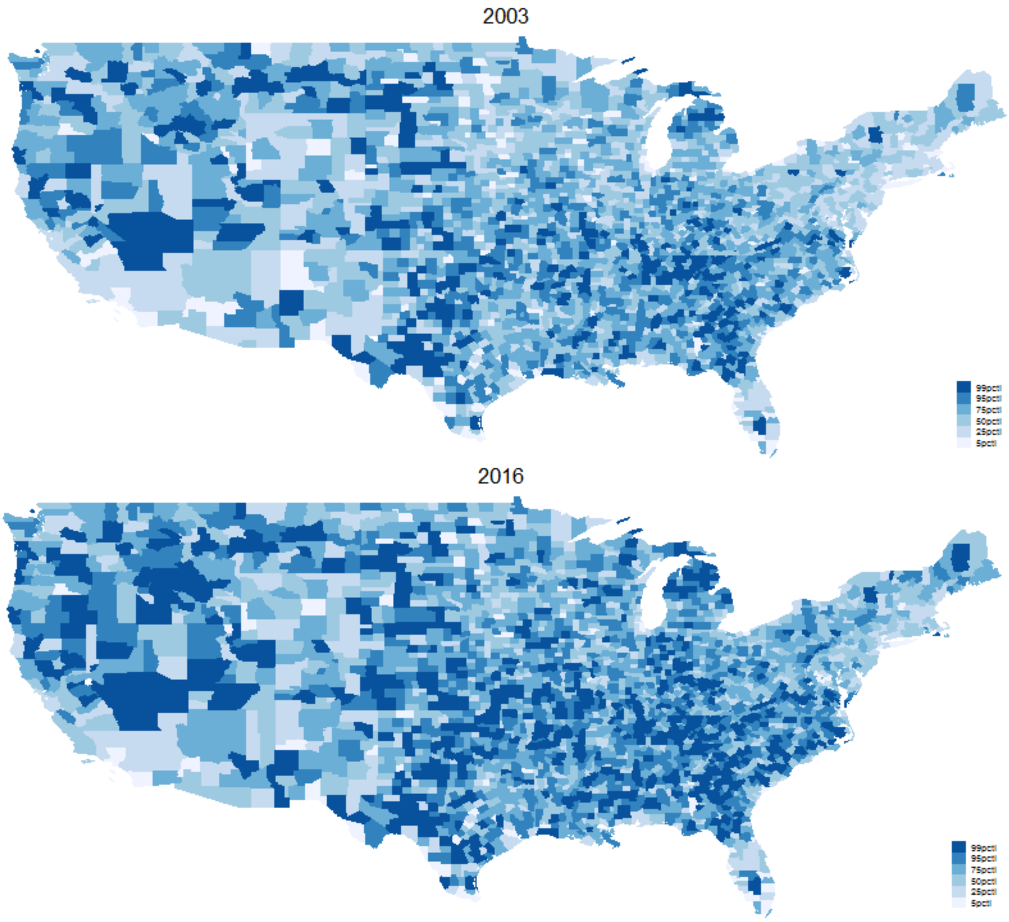
Note: * p<.10 ** p<.05 *** p<.01. Full sample (3,109 counties, 2003q1-2016q4). All dependent variables are expressed in delta log and per capita. OpiumP is the average traders price of opium. Mines1983pc is the number of mining sites per capita in 1983. All columns include quarter and county fixed effects and county-specific linear trends. Clustered-robust standard errors at county level in parenthesis.

Figure A.1: Drugs Retail Prices



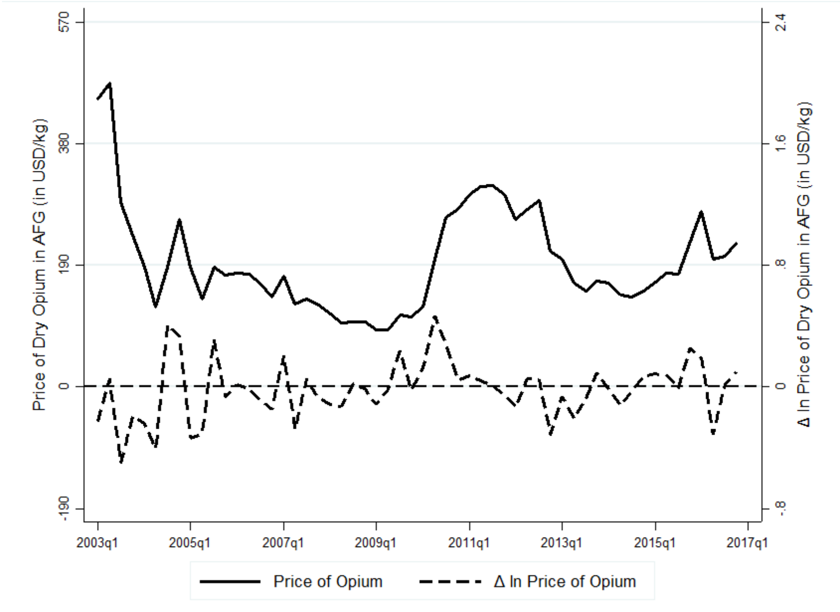
Note: Prices refer to the average total price for one tablet or patch of hydrocodone/APAP (325/10), hydromorphone (2), oxycodone/APAP (325/5), morphine (30) and ibuprofen (400). The price of fentanyl is rescaled by a tenth. Raw averages. Dashed lines represent the confidence intervals. Source: Medical Expenditure Panel Survey, 2000-2015.

Figure A.2: Quantity of MGE per Capita Dispensed in 2003 and 2016 by County



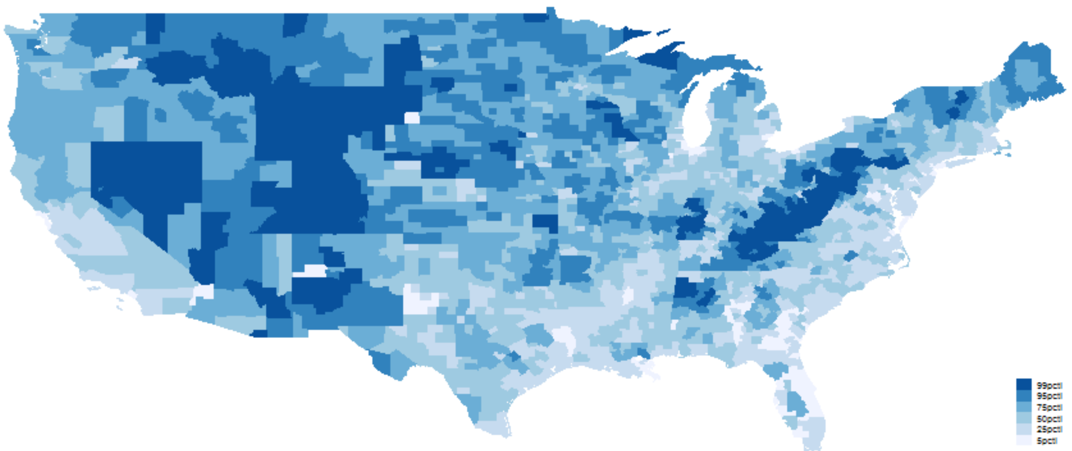
Note: Darker areas are associated with higher values of MGE per capita. Thresholds are set at the 5th, 25th, 50th, 75th and 95th percentiles of the pooled 2003-2016 distribution.

Figure A.3: Price of Opium in Afghanistan



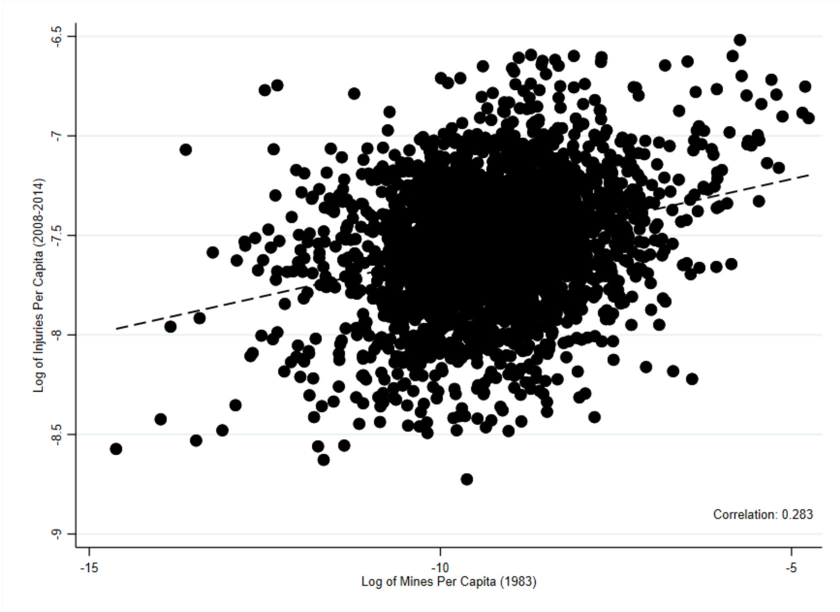
Note: Average quarterly price of dry opium in Afghanistan. Source: UNODCCP, United Nations and Ministry of Counter Narcotics, Islamic Republic of Afghanistan.

Figure A.4: Per Capita Number of Mining Sites in 1983 by County



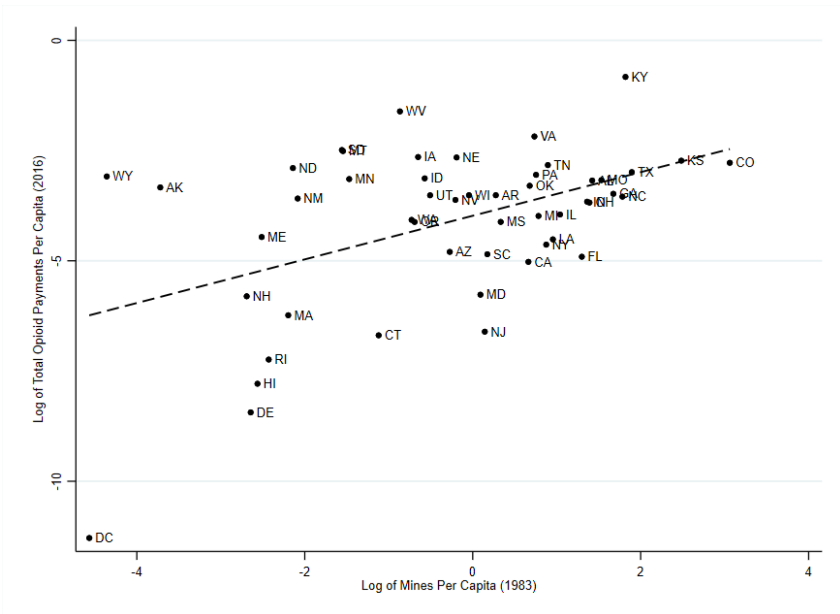
Note: Darker areas are associated with a higher concentration of mining sites per capita. Thresholds are set at the 5th, 25th, 50th, 75th and 95th percentiles of the 1983 distribution of mining sites per capita.

Figure A.5: Log of Injuries per Capita and of Mines Per Capita



Note: Data on injuries per capita come from the Centers for Disease Control and Prevention (CDC) and refer to all unintentional accidents occurred at the workplace (2008-2014). We exclude six outlier counties.

Figure A.6: Log of Total Opioid Payments and Log of Mines Per Capita



Note: Data on payments come from the Centers for Medicare & Medicaid Services (CMS), which is part of the Department of Health and Human Services (HHS). They only refer to opioid-related payments received by health care professionals in 2016.