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Opium Price Shocks and Prescription Opioids in the USA*

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Abstract

We investigate the effect of international opium price shocks on the per capita dispensation of prescription opioids in the USA. Using quarterly county-level data for 2002q4–2016q4, three main results emerge. First, reductions in opium prices significantly increase the quantity of opioids prescribed, and more so in counties with a larger pre-existing market for pain relief, as captured by the incidence of mining sites. Second, the increase involves only natural and semi-synthetic, but not fully-synthetic, opioids, suggesting that the effect is moderated by the amount of raw material contained in the products. The impact is larger prior to 2010, when overdose deaths were more related to the use of legally prescribed opioids. Third, advertising expenses, stock prices and the profits of opioid producers increase following negative opium price shocks, suggesting an important role of supply-side economic incentives.

I. Introduction

More than 750,000 people died from a drug overdose in the USA between 1999 and 2018, and nearly two thirds of these fatalities involved prescribed or illicit opioids.

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One of the most striking aspects of the US opioid epidemic is that even if users later go over to illicit or illegal opioids, most of the abuse starts with commonly prescribed opioids legally provided by physicians and health professionals (Okie, 2010).

Multiple hypotheses have been analysed regarding the causes of the opioid crisis (Maclean *et al.*, 2022). Demand-side explanations concentrate on deteriorating cultural and economic conditions as main drivers of the 'deaths of despair' (Case and Deaton, 2015). Alternative hypotheses consider the role of supply-side factors, such as changes in healthcare, physician prescribing attitudes, and the aggressive marketing of prescription opioids at the origin of health crisis (Alpert *et al.*, 2022; Arteaga and Barone, 2022).[1]

In this paper, we study the extent to which opioid manufacturers' economic incentives have contributed to the rapid growth in the dispensation of prescription opioids (PO) in the USA over the last few decades. Differently from previous works, we seek to determine whether shocks to the international price of opium (i.e. the raw material used for producing opioid-based drugs), by altering incentives to opioid producers, affect the per capita dispensation of PO in the USA.

Our main hypothesis is that a fall in the price of opium, that is, the cost of the raw material, might prompt an increase in the quantity of opioid-based drugs dispensed, with this effect varying across US counties depending on their initial exposure to analgesics use. Specifically, we postulate larger effects in counties where the initial exposure to PO is greater, as the incentives for pharmaceutical companies to promote opioid painkillers should be stronger where the potential market for analgesics is larger (Nguyen, Bradford, and Simon, 2019a; Alpert *et al.*, 2022). In fact, the marginal rate of success in marketing PO is higher where the pool of people suffering from chronic pain is larger.[2]

To test this hypothesis, we use US quarterly data at the county level for the period 2002q4–2016q4 and measure local price shocks by interacting the log change in the quarterly price of opium in Afghanistan – the world's largest opium producer – with US counties' *ex-ante* exposure to opioid-based analgesics.[3] In 2007, Afghanistan produced 92% of global illicit opium production (Office on Drugs and CrimeUNODC, 2007). While Afghan opium is illicitly produced, variations in its price can arguably be used as a proxy for shortages of licit raw opium in the international market, if connections between the

[1] Case and Deaton (2015, 2018) document that worsening labour market conditions and a lack of access to healthcare have fueled a rise in drug, alcohol and suicide deaths, or 'deaths of despair'. Over the years, opioid-analgesic poisoning death rates have increased for all age groups, but especially for non-Hispanic white men and women (Chen, Hedegaard, and Warner, 2014; Case and Deaton, 2015). 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 employment (Carpenter, McClellan, and Rees, 2017; Krueger, 2017; Currie, Jin, and Schnell, 2019; Harris *et al.*, 2020), crime (Mallatt, 2017; Meinhofer, 2017; Doleac and Mukherjee, 2022), duration of disability benefits (Savych, Neumark, and Lea, 2019) and child removals (Gihleb, Giuntella, and Zhang, 2022). Evans, Lieber, and Power (2019) and Alpert, Powell, and Pacula (2018) analyse the effect of the OxyContin reformulation in 2010 on heroin and opioid deaths, offering evidence of a consumer substitution response. Maclean *et al.* (2021, 2022) review the novel literature on the opioid crisis and its consequences for health, healthcare management, and crime.

[2] Arteaga and Barone (2022) find that pharmaceutical promotion strategies initially targeted the cancer pain market and then expanded to the non-cancer pain market, producing long-term effects on opioid mortality. Communities with higher cancer incidence in the past have been more exposed to the use of potent PO to treat both moderate and chronic pain.

[3] This strategy recalls the approach of Brückner, Ciccone, and Tesei (2012) in studying the effect of oil price shocks on democratization.

two markets exist. We examine how the relatively large size of Afghan opium production might have generated incentives for the diversion of licit opium to the illegal market, thus likely making the supply of licit opium destined to the pharmaceutical industry vary accordingly (Ventola, 2011).[4]

To assess the *ex ante* county-level exposure to PO prior to the opioid epidemic, we employ the number of mining sites per capita in 1983 as a proxy. This is because in counties with a greater concentration of mining sites the workforce and the residents are more likely to suffer from chronic pain (Metcalf and Wang, 2019). Indeed, most manual occupations in mining and construction are by nature exposed to the risk of chronic pain, often associated with greater use of painkillers to allow a speedier return to the job (Leukefeld *et al.*, 2007), as well as higher incidence of cancer diseases and neoplasms (Beach and Hanlon, 2018).[5] Thus, mining places represent the ideal targets for more aggressive marketing campaigns for opioids (Alpert *et al.*, 2022; Arteaga and Barone, 2022).

We find that a reduction in the price of opium in Afghanistan significantly increases per capita PO dispensation in the USA, and the estimated effect increases depending on the initial demand for opioids in the county. In our data, a 1-SD decrease in opium price growth (i.e. a fall of 20 percentage points) increases per capita dispensation of PO by 5 to 6 doses per quarter (moving from a county at the 12th percentile of the mining site distribution to a county at the 76th percentile). This corresponds to a 2% increase in the mean.

The result is robust to a battery of tests, including the addition of county-year and state-quarter fixed effects, and the use of alternative measures of pre-existing exposure to PO at the county level, namely the share of miners, the share of veterans, and the cancer incidence. Placebo and randomization tests confirm the main result. Moreover, since the evolution in the price of opium is determined by the instability in Afghanistan (Lind, Moene, and Willumsen, 2014), we provide further evidence that our main result holds when using variation in conflict intensity, as measured by the number of Western casualties per quarter in Afghanistan.

We expect our results to be stronger for drugs whose production requires opium. Indeed, we find that opium price shocks have an asymmetric effect on the quantity of opioids dispensed depending on the presence of opium in the manufacturing process. We show that the effect relates only to natural and semi-synthetic drugs, which are produced either by natural processes or by chemical modifications to opium.[6] Instead, we find no effect on fully synthetic opioids, in which raw opium is not an input.[7]

[4]The licit market for opium in the US relies on imports, which are subject to the so-called 80/20 rule. This requires that at least 80% of the morphine-rich opium imported to the USA is sourced in India and Turkey. Using data on the production of licit opium in India, we show the existence of a connection between licit and illicit markets for opium.

[5]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).

[6]According to the United Nations (2003), 10 kg of opium are needed to produce around 1 kg of morphine base, which implies a yield of about 10%. However, higher morphine content in raw opium and/or more advanced extraction technologies may determine a lower ratio. See also DEA (1992).

[7]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).

Relatedly, the effect is more pronounced during the first wave of the epidemic, that is, prior to 2010, when the effect amounts to a 5% increase in the mean. This evolved with a steady rise in the dispensation of natural and semi-synthetic opioids, such as oxycodone-based drugs, which reflected changes in the promotional practices of drug manufacturing and retailing companies and in the prescribing routines of physicians (Van Zee, 2009; Alpert *et al.*, 2022). Conversely, the price elasticity on the changes in PO distributed is less evident in the post-2010 years, when the reformulation of OxyContin ignited the heroin epidemic and fully synthetic opioids increased in popularity (Alpert *et al.*, 2018; Evans *et al.*, 2019; Cutler and Glaeser, 2021). Moreover, in the period of greatest expansion of natural and semi-synthetic opioids, reductions in the price of opium are significantly associated with higher per capita drug overdose death rates and drug-related crimes. Counties with higher initial exposure to PO and, hence, more exposed to opium price shocks, exhibit higher rates of drug-related deaths and crimes.

Finally, using firm-level data we show that opioid producers internalize the economic incentives from changes in the price of opium, that is, the raw material. The analysis reveals that negative opium price shocks significantly increase the advertising expenses of US pharmaceutical companies that have ever obtained FDA approval for opioid painkillers. This suggests that opioid producers might react to the drop in raw material costs by using promotion as a strategy to expand demand at a time when their markup has increased (Zejcirovic and Fernandez, 2018). This result is consistent with the theoretical prediction of the monopoly and oligopoly models introduced by Dorfman and Steiner (1954) and Waldman and Jensen (2001), respectively. Our estimates indicate that a negative shock to the price of opium is also associated with higher stock prices and profits for PO manufacturers in the USA. This implies that investors perceive opioid-producing companies as factoring fluctuations in the price of opium into their business strategies, thus expecting higher future profits.

Although this evidence suggests a supplier-induced demand mechanism, an alternative explanation is that changes in patient demand might have contributed to the increase in opioid dispensation. This could occur if shocks to the price of opium led to a decrease in the market price of PO and, consequently, an increase in patient demand. To test this alternative hypothesis, we replace the price of opium with the average retail price of generic opioid-based painkillers. Our results indicate that a decrease in the market price of opioids leads to an increase in per capita PO dispensation, although the effect is not statistically significant at conventional levels, suggesting a limited role of demand. To further explore the role of demand-side factors, we examine whether the response of PO dispensation is symmetric to positive vs. negative changes in the drugs retail price growth rate. If demand-side forces are driving our main findings, price growth rate increases may have smaller effects relative to decreases in the price growth rate. We document a symmetric response, thereby weakening the evidence on demand-side forces as main driver of the results.

Our findings are in line with Cutler *et al.* (2019) and Cutler and Glaeser (2021). The former show that patient demand is relatively less important than supply-side factors in explaining variation in healthcare spending. The latter explain how technological innovation produces negative health outcomes if professionals and regulators underestimate the downsides of new drug innovations. Our results suggest that the rapid increase in the dispensation of PO in the USA has, to some extent, been a supply-driven process based on changes in the international price of the raw materials, particularly prior to 2010, when natural and semi-synthetic opioids were frequently distributed.

This work adds to the literature that documents the importance of supply-side factors as initial causes of the opioid crisis (Van Zee, 2009; Alpert *et al.*, 2018, 2022; Zejcirovic and Fernandez, 2018; Cutler *et al.*, 2019; Evans *et al.*, 2019; Cutler and Glaeser, 2021; Arteaga and Barone, 2022) relative to demand-side factors (Case and Deaton, 2015, 2018). For instance, Alpert *et al.* (2022) and Arteaga and Barone (2022) show robust evidence that a substantial share of US overdose deaths during the past two decades are attributable to the introduction and marketing of OxyContin by Purdue Pharma. Here, we use an indirect approach that combines unique data on the price of the raw material with measures of *ex ante* exposure to painkillers at the county level to provide additional evidence on the role of supply-side factors.

This paper also contributes to two other strands of research. First, we add to the supplier-induced demand literature by examining local consequences of the dramatic increase in PO use.[8] 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 Couttenier, 2015; Berman *et al.*, 2017), democracy (Brückner *et al.*, 2012), mental health (Adhvaryu, Fenske, and Nyshadham, 2014) and schooling (Brückner and Gradstein, 2013). We show that price shocks in raw materials impact the dispensation of prescription drugs in the USA.

The paper is organized as follows. Section II describes the development of the opioid crisis in the USA. Section III describes the trade of narcotics to the USA and the link between licit and illicit markets for opium. Sections IV and V present the data and our empirical strategy. Section VI discusses the main results on PO dispensation, while section VII interprets our findings in the light of demand- and supply-side mechanisms. Section VIII offers some concluding remarks. In the Appendix S1 we provide several robustness checks (OA.A), evidence on drug-related deaths and crimes (OA.B) and additional heterogeneity analyses (OA.C).

II. The US opioid epidemic

Over the last three decades, the USA has seen an unprecedented escalation in the abuse and diversion of PO, which has been labelled the 'opioid crisis'. According to the Centers for Disease Control and Prevention (CDC, Centers for Disease Control and Prevention, 2017), in the 1999–2016 period 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). Pain began

[8]See Rice (1983); Rice and Labelle (1989); Iizuka (2007); Liu, Yang, and Hsieh (2009); Currie, Lin, and Zhang (2011); Iizuka (2012); Currie, Lin, and Meng (2014); Lu (2014); Shigeoka and Fushimi (2014); Sekimoto and Ii (2015); Helland *et al.* (2020).

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, along with temperature, blood pressure, respiratory rate and heart rate (Walid *et al.*, 2008). As prescription rates for opioid pain relievers rose, so did their misuse (Okie, 2010). Misuse and diversion of PO spread rapidly across the country. Opioid users 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 drugs (Alpert *et al.*, 2018; Evans *et al.*, 2019).

The sharp increase in the use of analgesics has been largely attributed to the strategy adopted by some pharmaceutical companies and related stakeholders to promote their opioid-based products – the supply side of the market (Alpert *et al.*, 2022). Pharmaceutical firms in the US invest billions of dollars annually in the advertising of drugs and medical equipment. The bulk of promotional spending is targeted at physicians and other healthcare professionals through office visits by company representatives (i.e. detailing), product sampling and advertising in professional journals. Over the years, the growth in the share of prescription drug expenditure coincided with the growth in pharmaceutical promotion, which rose from US $11.4 billion in 1996 to US $29.9 billion in 2005 (Datta and Dave, 2017) and US $32.3 billion in 2008 (Cegedim, 2013).[9] Recently, Hadland *et al.* (2019) and Nguyen, Bradford, and Simon (2019b) find that marketing payments on opioid products received by physicians are positively correlated with opioid mortality rates and opioid prescription rates, respectively.[10]

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 US $200 million in promoting OxyContin in 2001 alone.[11] In that year, OxyContin accounted for more than two-thirds of all oxycodone sales in the USA. As Van Zee (2009) documents, the producer's marketing practices were unusually aggressive.[12] These 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 (Arteaga and Barone, 2022), while those for non-cancer-related pain, which accounted for 86% of the total opioid market in 1999, increased tenfold (General Accounting Office, 2003).

[9] According to Cegedim (2013), detailing and free sampling accounted for about 83% of the US pharmaceutical promotional budget in 2011. Campbell *et al.* (2007) show that in 2004 a good fraction of US physicians received gifts from pharmaceutical sales representatives. 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.

[10] David, Markowitz, and Richards-Shubik (2010) show a positive correlation between different types of promotion of pharmaceuticals in the USA and adverse drug events, such as overdoses and allergic reactions. See Morton and Kyle (2011)[ch.12] for a description of the market for pharmaceutical products.

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

[12] They comprised profiling of physicians, distribution of complimentary merchandise 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 USA and had distributed patient starter coupons for free prescriptions of the drug for 7 or 30 days. By 2001, 34,000 coupons had been redeemed nationwide.

Because of its misleading promotional campaigns, and in particular the misrepresentation of addiction risk, Purdue Pharma and some of its executives were fined over US $600 million in 2007. Since then, many other opioid manufacturers and distributors have been facing lawsuits on similar grounds.

III. The trade of narcotics to the USA

The International Trade of Narcotics to the USA

The USA is one of the largest importers of narcotic raw materials (NRM) worldwide. US manufacturers account for one third of the world's morphine manufacturing capacity, most of which is prescribed within the USA in the form of codeine.[13]

Based on a long-standing policy, the USA does not cultivate or produce NRM, and relies solely on opium, poppy straw and concentrate of poppy straw (CPS) produced in other countries. These are the materials from which morphine, codeine, thebaine and oripavine are extracted. The Drug Enforcement Administration (DEA) is in charge of overseeing the imports of NRM under the Comprehensive Drug Abuse Prevention and Control Act of 1970, often referred to as the Controlled Substances Act, and the Controlled Substances Import and Export Act (21 U.S.C. 801), which specifically address the purchase of NRM that are used in the production of controlled substances for medical purposes in the USA.

NRM can be imported to the USA from only seven countries. India and Turkey benefit from the so-called 80/20 rule, which foresees that at least 80% of NRM imported to the USA are sourced from these two countries. The remaining amounts may be sourced from Spain, France, Poland, Hungary and Australia. While limiting the number of supplying countries, this approach ensures an adequate and uninterrupted supply of NRM to the USA (DOJ, 2008).[14] Of the countries included in the 80/20 rule, India is the only one that is authorized by the 1961 UN Single Convention on Narcotic Drugs to produce and export opium gum. All other countries also cultivate opium poppy but do not extract gum. They process the entire plant, including the stalk, to produce poppy straw. When portions of the plant are then processed into a concentrate, CPS is made.

The alkaloids extracted from NRM are morphine, codeine, thebaine and oripavine. Morphine is prevalent in Indian opium and Turkish CPS, and historically, it has been the most popular alkaloid extracted from NRM in the USA. It is used to manufacture morphine-based pharmaceutical products, codeine (which is utilized to produce codeine-based pharmaceutical preparations and hydrocodone), and hydromorphone. Thebaine

[13] See details on the authorized sources of NRM at https://www.federalregister.gov/documents/2008/02/06/E8-2142/authorized-sources-of-narcotic-raw-materials, last accessed on 19 October 2023.

[14] The figures to which this rule refers are computed on the basis of the morphine alkaloid contained in each NRM. Article *1312.13 (f)* on the issuance of import permits specifically states: *The importation of approved narcotic raw material (opium, poppy straw and CPS) having as its source: Turkey, India, Spain, France, Poland, Hungary, and Australia. At least eighty percent of the narcotic raw material imported into the United States shall have as its original source Turkey and India. Except under conditions of insufficient supplies of NRM, not more than twenty percent of the narcotic raw material imported into the United States annually shall have as its source Spain, France, Poland, Hungary and Australia*. See details at https://www.ecfr.gov/current/title-21/chapter-II/part-1312/subject-group-ECFRc11ae182f37bc43/section-1312.13, last accessed on 19 October 2023. Recently, the UK also gained a role in the trade of narcotics.

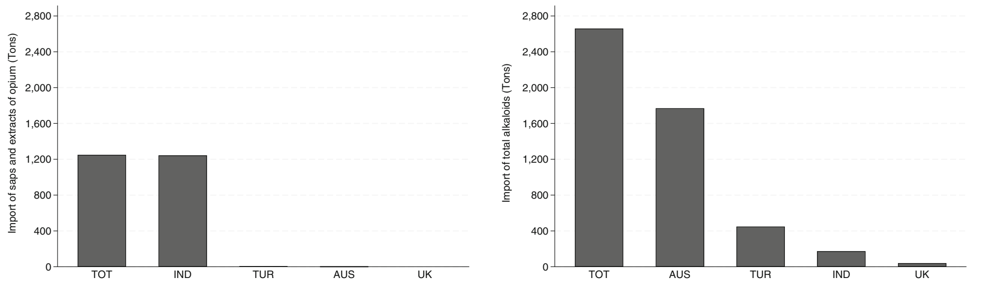

Figure 1. Opium Imports to the USA by Source Country.
Notes: US imports of opium saps and extracts (commodity code *130211*) and of concentrate of poppy straw (CPS) and alkaloids of opium and their derivatives (commodity codes *293911* and *293919*), by source country.

is used to manufacture several opioids, including oxycodone. Its production has seen a significant rise since the late 1990s, in response to the increasing demand for oxycodone and other thebaine-derived substances. Primarily extracted from poppy straw, the main exporting countries are Australia and Spain, which in 2009 accounted for almost 97% of the world total thebaine exports. Thebaine is also present in Indian opium at approximately one sixth the level of morphine. Oripavine is found primarily in Australian CPS and is used in the manufacture of buprenorphine and oxymorphone.[15]

Using official data on international trade from the Comtrade database, we describe the US imports of opium by country. The left plot in Figure 1 shows US imports of opium saps and extracts. Of around 1,200 tons imported in the form of opium saps and extracts over the period 2003–16, almost all was sourced from India. The right plot of Figure 1 refers to CPS and alkaloids of opium and their derivatives. Of about 2,700 tons imported in the years 2003–16, around two thirds come from Australia, while the remaining quantities are sourced from the two traditional suppliers (India and Turkey).

India is relevant as an opium source country both in terms of legislation (i.e. the 80/20 rule) and in terms of actual trade flows towards the USA. Indian opium accounts for almost all imports of opium saps and extracts throughout the whole period. As for CPS and other alkaloids, India's importance is smaller, although it still produced nearly a fifth of the total imports in the years 2003–10.[16]

[15]See the final rule adopted by the DEA, Department of Justice, 73 FR 6843, available at https://www.federalregister.gov/documents/2008/02/06/E8-2142/authorized-sources-of-narcotic-raw-materials, last accessed on 19 October 2023. Additional statistics on the international trade of NRM are available at https://www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2010/NAR_2010_EFS_Part4.pdf, last accessed on 19 October 2023.

[16]Australia, and especially Tasmania, produces large amounts of thebaine-rich poppies. However, thebaine is not applicable to the 80/20 rule (see https://www.federalregister.gov/documents/2008/02/06/E8-2142/authorized-sources-of-narcotic-raw-materials, last accessed on 19 October 2023). This would explain why Australia accounts for such large share of CPS while only opium gum has been produced in India. It should also be noted that regions that produce CPS may be less exposed to the risk of diversion to the illicit market because CPS can be easily transformed into morphine but its conversion into heroin is relatively more difficult, as it requires a series of complex chemical modifications (U.S. Committee on the Judiciary, 1990).

The connection between licit and illicit markets for opium

So far, we have been describing the *licit* market of narcotics. Since information on international prices of legal opium is sealed, we use an indirect approach based on the price of raw *illicit* Afghan opium and discuss potential leakages between the two markets.

Afghanistan has been the world's leading producer of illicit opium for decades, ahead of the Golden Triangle (Myanmar, Laos and Thailand) and Latin America. In the 1990s, poppy cultivation under the Taliban regime increased spectacularly, from under 22,000 hectares in 1995 to over 38,000 in 1999, when Afghanistan supplied around 70% of illicit opium worldwide.[17] 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 obtaining concessions from 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 for opium went back up to over 34,000 hectares in 2002 and 190,000 in 2007.[18]

After peaking in the early 2000s, owing to the ban on opium production, the average price fell steadily as output soared. The left panel of Figure A1 plots opium prices and the land area of opium poppy cultivation in Afghanistan over time. Predictably, the trader price (solid line) is always a bit higher than the farm-gate price (dashed line), but the two series are closely correlated and inversely related to the number of hectares of opium poppies in Afghanistan (grey bars). 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).[19] The right panel of Figure A1 shows the negative relationship between opium price shocks and changes in cultivated hectares in Afghanistan. As expected, the changes in the price and in the production of opium are negatively correlated.

As for the *legal* market, India is one of the largest producers of licit opium. Geographically, India is also close to the major illicit opium-cultivating regions of the world, being located between Afghanistan and the Golden Triangle. Indian production is regulated under a system of licenses issued by the Indian Central Bureau of Narcotics (CBN). Opium cultivators need to produce a minimum yield per hectare each year in order to maintain their license, but they cannot exceed 5% of the licensed area. Once harvested, opium is paid a set price by CBN officials, who collect it and deliver it to the government's opium and alkaloid factories, where it is processed for supply to global pharmaceutical manufacturers, primarily US-based. The CBN oversees the whole opium production process and its licit trade. Diversion to the illicit market is prohibited, but

[17]The UN Office on Drugs and Crime (UNODC) has been monitoring Afghan opium poppy production since 1994.
[18]See news reports such as: https://www.theguardian.com/world/2001/apr/01/internationalcrime.drugstrade and https://www.theglobeandmail.com/news/world/kabul-may-be-lifting-opium-ban/article4153970/, last accessed on 24 March 2023.
[19]The peak in 2009–11 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. To provide further evidence that the variation in opium price affecting the changes in prescription rates is exogenously determined by conflicts in Afghanistan, in the Appendix S1 we implement a robustness test where we replace 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.

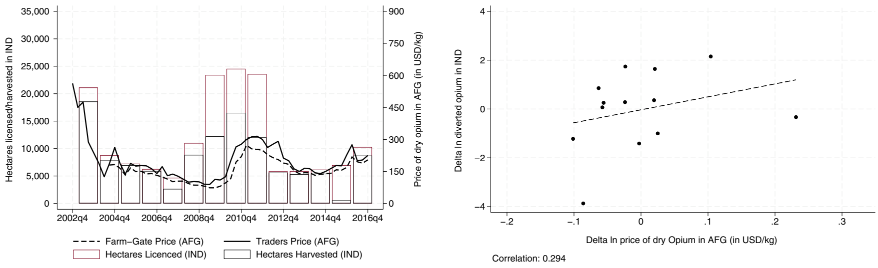

Figure 2. Price of opium in Afghanistan vs. production in India.
Notes: The left panel shows the number of hectares licensed for opium cultivation (red bars) and those actually harvested (black bars) in India annually, and the average quarterly trader and farm-gate prices of dry opium in Afghanistan (solid and dashed line, respectively). The right panel shows the correlation between yearly opium price shocks in Afghanistan and changes in the number of hectares not harvested (proxy of diverted opium) in India. [Colour figure can be viewed at *wileyonlinelibrary.com*]

the price paid to farmers by the government is very low compared to the price paid by smugglers, hence there persist high levels of diversion to the illicit opium market.[20]

The UN has repeatedly reported the existence of leakages into the illicit market (United Nations, 2005). Paoli *et al.* (2009) propose a method to estimate the amount of diversion occurring each year in India, using the gap between licensed opium cultivation and actual harvest as a proxy for the diversion of licit opium. The left panel of Figure 2 reports information on the production and estimated diversion of opium in India. The graph shows the price of illicit opium in Afghanistan, the number of hectares licensed for cultivation of licit opium in India and those actually harvested. The proxy for diversion of licit opium computed as in Paoli *et al.* (2009) 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 potential incentives for diversion from licit production when the price of opium in the illegal market is high. *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. The right panel of Figure 2 shows the existence of a positive correlation between shocks to the price of opium in Afghanistan and fluctuations in diversion measured in India. These, in turn, are negatively related to changes in PO distributed in the USA, as we demonstrate in section VI.

This evidence supports the hypothesis that, to some extent, the propensity to divert raw materials from licit to illicit markets varies according to the incentives in the international illegal market, as captured by the Afghan opium price. Specifically, positive changes in the Afghan opium price increase the diversion incentives, leading to a lower supply of licit opium as a proportion of the total opium available for legal use. This, in turn, results in larger production costs for manufacturers of opioid prescription drugs.

The potential relevance of these mechanisms for the licit production of opioid-based drugs is confirmed by the fact that drug shortages are increasingly frequent in the USA (Fox *et al.*, 2009; Ventola, 2011), with medical reports indicating a scarcity of pain

[20]For details, see https://cbn.nic.in/en/opium/overview/ and https://www.unodc.org/pdf/india/publications/south_Asia_Regional_Profile_Sept_2005/10_india.pdf, last accessed 19 October 2023.

medications as well (Jenks, 2011). While drug shortages can be caused by a variety of factors, including manufacturing or regulatory issues, disruptions in the supply of raw materials are a common cause of drug shortages in the USA, where the pharmaceutical industry depends on imports for around 80% of its raw material needs (Ventola, 2011).

Although we do not claim that pharmaceutical companies utilize raw opium obtained illicitly, our findings provide suggestive evidence that fluctuations in the price of illicit opium, as measured in Afghanistan, are linked to incentives for the diversion of raw opium from the legal to the illegal market.[21] Thus, we take the price of raw opium in Afghanistan as a proxy for world opium prices, assuming that it positively correlates with wholesale legal prices, and we evaluate whether shocks to the market of raw opium might have hampered the legal market for PO in the USA. Figure A2 displays the correlation between the shocks in the opium market in Afghanistan, measured as the delta log in price (left panel) and hectares (right panel), and the changes in the per capita dispensation of PO in the USA. Changes in the quantity of drugs prescribed in the USA are negatively associated with shocks to the price of the raw material and positively related to changes in the production of opium in Afghanistan, proxied by the hectares cultivated.

IV. Data

To provide empirical support for our claims, we collect and merge an extensive number of datasets. We summarize all sources of data in Table A1.

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 on Drugs and Crime (UNODC).[22]

The data on PO come from the Automation of Reports and Consolidated Orders System (ARCOS), maintained by the US DEA's Office of Diversion Control. The annual ARCOS reports record the quantities (in grams) of every controlled active ingredient sold in the USA. The data are disaggregated at the three-digit zip code level across the USA and are available quarterly. We digitize the data for the 2003–16 period. We also draw zip-code level information on mining sites in 1983 from the Mine Safety and Health Administration (MSHA).[23] As the rest of the data is at county level, we transpose the prescription drugs and mining sites figures from zip-code 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 inter-census population estimates (total counts and counts by sex, age band, race and ethnicity). The 1980 and 1990 population counts come from the US Census Bureau. Our final sample comprises 3,109 (out of 3,142) US counties and quarterly data for 14 years (2002q4–2016q4).

[21] However, the link between opium prices, diversion of raw materials and US firms' incentives may differ depending on the type of NRM and source country. As we show later in the analysis, this mechanism seems to exist in the case of opioids such as morphine, which are likely sourced from India, while it is partially observed for opioids like hydrocodone or oxycodone, that are instead likely sourced from Australia.

[22] We use the average price (in USD per kg) drawn from traders in Nangarhar and Kandahar provinces. The average farm-gate price, which is available only from 2004q3, is used in a robustness check.

[23] 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.

We also exploit the CDC's Wide-ranging ONline Data for Epidemiologic Research (WONDER) database, which provides detailed yearly data on drug fatalities at the county level.[24] County-level cancer-related deaths in 2000 are also drawn from WONDER. Moreover, we employ the Uniform Crime Reporting (UCR) Program Data provided by the FBI, which gives the number of arrests by county and by type of drug-related crime.[25]

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: advertising expenses, stock prices and profits.

All other data sources referred to the variables employed in the descriptive statistics, the robustness checks and the heterogeneity analyses are listed in Table A1.

V. Empirical strategy

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

If changes in the quantity of opioids dispensed in the USA are determined by economic incentives to suppliers based on the price of the raw material, this mechanism can be expected to be stronger in areas with higher *ex-ante* exposure to opioids, as proxied by (the log of) the per capita number of mining sites in 1983. These counties would represent the most fertile local markets for analgesics, where PO promotion campaigns presumably have the greatest chance of success (Cutler and Glaeser, 2021; Alpert *et al.*, 2022). Accordingly, we estimate the following model:

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

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 quarters $t-1$ and t, and $\ln Mines1983pc_c$ is the log of the per capita number of mining sites in 1983.[26] We include county and quarter dummies and county-specific linear trends, which should

[24] We follow Ruhm (2018) and consider the following underlying or contributing causes of death: accidental or intentional poisoning by and exposure to drugs (X40–X44, X60–X64, Y10–Y14) and assault by drugs, medicaments and biological substances (X85). Data are available at the county-month level. However, counts below nine are suppressed for confidentiality, which results in a large number of suppressed entries. We therefore aggregate at the year level.

[25] According to the UCR, drug-abuse violations are defined as state or local offences relating to the unlawful possession, sale, use, growing, manufacturing or making of narcotic drugs including opium, cocaine and their derivatives and synthetic narcotics.

[26] $Mines1983pc$ is rescaled by 100,000 residents in 1980 to ease interpretation. We use the log rather than the simple number of mining sites per capita in 1983 because the distribution of sites across counties is strongly positively skewed. By adopting the log, we lose only 6 counties due to zero values.

capture any changes in institutional or demographic factors during the period. The errors are clustered at the county level.[27]

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.[28] We rescale the quantity of each substance to account for relative potency and construct a single MGE indicator.[29] Table A2 reports descriptive statistics for the main outcome and control variables.

Figure A3 describes the geographical distribution of MGE per capita distributed in 2003 and 2016, that is, at the beginning and the end of our sample period. The darker the area, the higher the dispensation of PO. We observe substantial variation across counties and years. The lighter areas, indicating lower levels of MGE per capita, are located predominantly in the central regions. The two maps also reveal the remarkable nationwide increase in opioid use that marks our period of analysis.

Our explanatory variable measures shocks to the price of opium in Afghanistan, by exploiting price changes between two consecutive quarters to capture time variation. Fluctuations during the 2002q4–2016q4 period 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 the left panel of Figure 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 essentially depend on the violent conflicts in Afghanistan, ruling out potential reverse causality problems (Lind *et al.*, 2014).

The distribution of the number of mining sites per capita across the USA is shown in the right panel of Figure 3. We use this as main measure of geographical variation in local exposure to PO, given the common use of analgesics among workers employed in jobs marked by physical strain and risk of injury (Leukefeld *et al.*, 2007).

A recent paper by Metcalf and Wang (2019) finds that the share of coal miners among the total local labour force and county-level opioid mortality rates are positively related. The authors argue that this is due to the fact that higher injury rates induce higher consumption of opioid painkillers and thus, in turn, higher opioid-related mortality. Indeed, Figure A4 (left panel) shows a positive link between our measure for the *ex ante*

[27]Clustering the errors at the 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.

[28]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 considered Schedule V. Schedule II and Schedule III substances are those that have high and moderate potential for abuse, respectively, and are known to lead to psychological or physical dependence.

[29]Our choice of multipliers for conversion into MGE units conforms to Gammaitoni *et al.* (2003), Paulozzi, Kilbourne, and Desai (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.

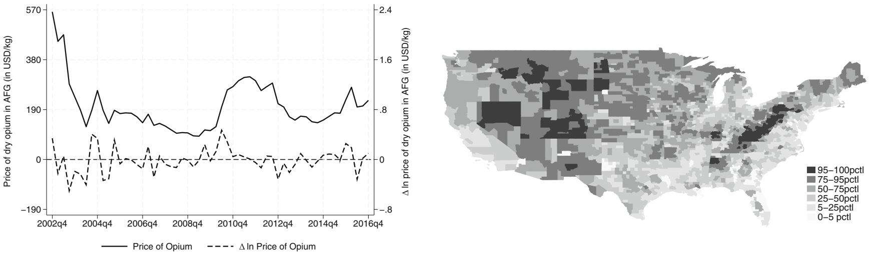

Figure 3. Price of opium in Afghanistan and per capita number of mining sites in 1983.
Notes: The left panel shows the average quarterly price of dry opium in Afghanistan in levels (solid line) and as a first-differenced log transformation (dashed line). The right panel shows the geographical distribution of mining sites per capita in 1983. Darker areas are associated with a higher concentration of mining sites. Thresholds are set at the 5th, 25th, 50th, 75th and 95th percentiles of the 1983 distribution of mining sites per capita.

exposure to painkillers, that is, mines, and the incidence of unintentional injury rates at work. Figure A4 (right panel) shows a positive relationship between the number of injuries and the average amount of MGE per capita distributed across counties. As additional suggestive evidence of mining sites predicting the future geographical distribution of PO, we show that their concentration positively correlates with changes in payments or transfers of value to physicians or hospital recipients over the 2013–16 period (Figure A5).

The top-left panel of Figure A6 displays a positive correlation between the distribution of mining sites and the average opioid dispensation rate over the 2002q4–2016q4 period. The remaining panels in Figure A6 shows that average MGE dispensation positively correlates to various alternative cross-sectional exposure measures that we use in the empirical analysis, namely the number of miners in 1983, the number of veterans in 1999, and the cancer incidence in 2000. All these proxies are meant to capture that locations where the pool of individuals suffering from chronic diseases is larger are also more likely to experience higher rates of PO dispensation, often as a result of opioid producers' aggressive marketing campaigns.

Our identification strategy relies on the random variation in opium price over time. This randomness is ensured by the time series being stationary, and this allows us to identify local shocks, i.e. exogenous variation in the cost of the raw material for opioid-based drugs. At the same time, the cross-sectional distribution of mining sites is plausibly 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) captures the impact of opium price shocks on per capita MGE units distributed 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 suggests that we should expect the coefficient β to be negative. In this case, the underlying mechanism would be purely economic and would imply that where dependence on painkillers is greater, a negative shock in the price of opium should trigger a larger increase in the per capita dispensation of PO.

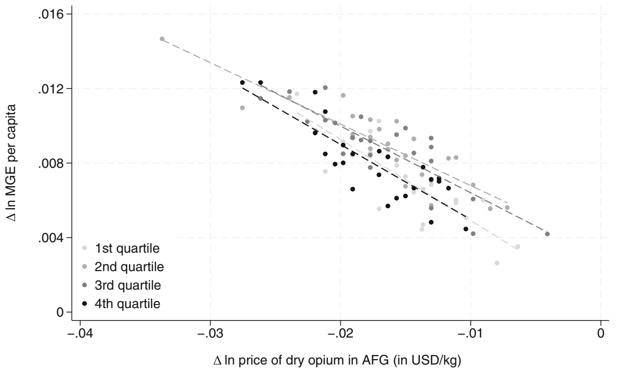

Figure 4. Opium price shocks and MGE dispensation by percentile of mining sites.
Notes: Correlation plot and linear prediction between the average value of ΔlnMGEpc and ΔlnOpiumP by percentile of lnMines1983pc. The darker the dot and the line, the higher the quartile of lnMines1983pc.

The Dlog-Dlog model assumes a linear relationship between the main explanatory variable and the dependent variable. In Figure 4, we plot $\Delta \ln MGEpc$ against $\Delta \ln OpiumP$ by different levels of our exposure variable $\ln Mines1983pc$. Here, each dot corresponds to a given percentile of $\ln Mines1983pc$, and the darker the dot the higher the quartile of $\ln Mines1983pc$. The figure shows the existence of a linear downward-sloping relationship between $\Delta \ln MGEpc$ and $\Delta \ln OpiumP$ for any given quartile of $\ln Mines1983pc$, and that this relationship is steeper for higher quartiles.

VI. Results

The effect of opium price shocks on prescription opioid dispensation

Table 1 shows the main results. Column 1 reports the unconditional estimate of the effect. This coefficient is negative and statistically 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 USA. Our interaction term implies that the impact of opium price changes should be larger in counties with a higher initial exposure to analgesics (i.e. heavier dependence on opioids), proxied by mining sites. Indeed, we expect pharmaceutical companies to have a higher marginal rate of success promoting opioids in areas where relatively more people suffer from chronic pain and are therefore in need of analgesics (Alpert *et al.*, 2022; Arteaga and Barone, 2022).

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. The coefficient doubles and remains statistically significant at the 1% level, which suggests considerable heterogeneity in opioid use across quarters and counties.[30]

[30]The magnitude of the coefficients increases with the inclusion of fixed effects. In particular, quarter dummies capture unobserved heterogeneity across time, with the coefficient moving from −0.0025 to −0.0054 (notably, R^2 rises from 0.003 to 0.3). This increase reflects a weaker elasticity in the post-2010 period. The residual heterogeneity is captured with geographical fixed effects.

TABLE 1
Effects on MGE

Dep. variable	*(1)* Δ *lnMGEpc*	*(2)* Δ *lnMGEpc*	*(3)* 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^2	0.0033	0.3281	0.3330
County dummies		✓	✓
Quarter dummies		✓	✓
County-specific linear trends			✓

Notes: Full sample (3,109 counties, 2002q4–2016q4). 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. Robust standard errors clustered at the county level are in parentheses.
*$P < 0.10$; ** $P < 0.05$; ***$P < 0.01$.

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 the county level. This should rule out the possibility that counties with different initial levels of exposure to PO were already on differential growth trajectories of opioid dispensation, so that the change in use would have 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.

Our estimate suggests that when $\ln Mines1983pc$ is equal to one, which is 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-SD decrease in opium price growth (i.e. a fall of around 20 percentage points) increases per capita MGE growth by 0.0013, that is, by 0.13 percentage points. On average, the growth of per capita MGE units is 0.0082. An increment of 0.0013 implies that the growth of MGE units becomes 0.0095. Given that at the average $\overline{\text{MGEpc}} = 8.5965$ and that $\Delta(\%\Delta\text{MGEpc}) = \frac{\widehat{\text{MGEpc}}-\widetilde{\text{MGEpc}}}{\widetilde{\text{MGEpc}}} - \frac{\widetilde{\text{MGEpc}}-\overline{\text{MGEpc}}}{\overline{\text{MGEpc}}} = 0.0095 - 0.0082 = 0.0013$, it follows that $\Delta\text{MGEpc} = \widehat{\text{MGEpc}} - \overline{\text{MGEpc}} = 0.1525$. Thus, our main estimate translates into an increase of 0.1525 MGE units per capita, which is equivalent – given the standard morphine dose of around 30 mg – to 5 doses per capita in a quarter (i.e. a 2% increase in the mean).

For counties in the 40th percentile (e.g. Maverick County, TX, with 7.39 mining sites per 100,000 inhabitants), that is, when $\ln Mines1983pc$ is equal to 2, the effect amounts to 5.5 doses per capita, and for counties in the 76th percentile (namely, when $\ln Mines1983pc$ is equal to 3, for example, Marinetti County, WI, with 20.10 mining sites per 100,000 inhabitants), to roughly 6 doses per capita.

In Table A3, we consider the dispensation of opioids with the exclusion of methadone and oxycodone (columns 1 and 2, respectively). Methadone is considered clinically different from other PO and is often used as replacement therapy in the treatment of opioid and heroin use disorders (Paulozzi, 2012). Yet, the use of prescription methadone for the treatment of pain, as opposed to the treatment of opioid use disorders, has been identified as a contributor to the US opioid overdose epidemic (Jones *et al.*, 2016). Similarly, oxycodone use led to a large number of fatal overdoses in the USA when OxyContin became the most popular brand-name narcotic medication for treating moderate to severe pain. Reassuringly, our main effect also holds when these two active ingredients are excluded from the main outcome.

We conduct a series of tests to ensure that our results are robust and well-identified, which we report in Section OA.A in the Appendix S1. In particular, we verify that: (i) leads and lags of our interaction term are not statistically different from zero; (ii) our measure of opium price shocks is not capturing fluctuations in the prices of other commodities; (iii) results are not driven by a spurious correlation by using randomization inference; (iv) results are not biased by the price of heroin; (v) the effect on the dispensation of other non-opioid schedule II drugs is null; (vi) the main estimate survives the inclusion of several controls and fixed effects in the model; (vii) results hold when we consider alternative measures that capture the effect of opium price shocks (i.e. conflict intensity) and the local exposure to drug dispensation, such as the predetermined county-specific number of veterans per capita and the cancer mortality index; (viii) results are robust to combining these different exposure indicators with principal component analysis and to the test proposed by Altonji, Elder, and Taber (2005).

The asymmetric effect of opium price shocks

The analysis presented so far highlights a robust, statistically significant and negative relationship between changes in opium price and changes in the quantity of PO dispensed. In this section, we discuss the asymmetric effects of opium price shocks on different types of PO. The hypothesis is that negative price shocks to the raw material induce an increase in the quantity of drugs dispensed. 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. 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 USA. Thus, we can divide the drugs studied here into three groups according to their active ingredient: natural (morphine), semi-synthetic (hydrocodone, hydromorphone and oxycodone) and fully synthetic opioids (fentanyl and meperidine).[31]

If agents and stakeholders in this market are interested in profit maximization, we expect to find different responses to opium price changes depending on the type of opioid manufactured, since natural and semi-synthetic opioids should logically be more responsive than fully synthetic opioids to a variation in the price of the raw material. If raw

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

TABLE 2

Effect by Period and Type of Drug

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc (Natural/semi-synthetic)	(4) Δ lnMGEpc (Natural/semi-synthetic)	(5) Δ lnMGEpc (Synthetic)	(6) Δ lnMGEpc (Synthetic)
lnMines1983pc * Δ lnOpiumP	−0.0095***	−0.0023**	−0.0096***	−0.0024*	−0.0027	0.0041
	(0.0035)	(0.0012)	(0.0037)	(0.0013)	(0.0038)	(0.0046)
Observations	87,052	87,052	87,052	87,052	87,052	87,052
R^2	0.2288	0.2409	0.2191	0.2644	0.1466	0.0712
Period	<2010	≥2010	<2010	≥2010	<2010	≥2010
Mean of dep. variable	0.0188	−0.0058	0.0272	−0.0036	−0.0200	−0.0331

Notes: Full sample (3,109 counties, 2002q4–2016q4). 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. Methadone is excluded. Robust SEs clustered at the county level are in parentheses. $^*P < 0.10$; $^{**} P < 0.05$; $^{***}P < 0.01$.

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.[32]

Since the surge in the use of opioid prescription drugs occurred especially in the first phase of the epidemic, in Table 2 we investigate whether opium price shocks affect the dispensation of PO across the USA before and after 2010. The coefficients reported in columns 1 and 2 show that the responsiveness of the quantity of opioids distributed was high in the years prior to 2010, when the opioid crisis was largely fueled by natural and semi-synthetic opioids.[33] The coefficient associated with the period starting in 2010 drops in magnitude, which is coherent with the rising use of fully synthetic opioids during the same years.

We test whether the quantities of natural and semi-synthetic and synthetic PO 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. Columns 3 and 4 consider only natural and semi-synthetic opioids. Here, the effect of price shocks persists, although it is more substantial in the pre-2010 years.[34] Columns 5 and 6 refer to the per capita dispensation of fully synthetic opioids as the dependent variable. In this case, the coefficients lose their statistical significance in both periods, as expected. Interestingly, the sign of the coefficient for fully synthetic opioids in the post-2010 years (column 6) becomes positive.

[32]Figure A7 shows that the increase in the total quantity of PO over time (solid line) is determined mainly by 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 decreases (see Figure A1).

[33]This specification suggests that the main effect discussed in the previous subsection is neither driven by the reformulation of OxyContin in 2010 nor by the wave of opioid-related policies enacted at the state level in the 2010s. Moreover, the pre-2010 sub-sample only refers to a period in which the price of opium was declining. This rules out that the effect is due to the spike in the price of opium observed in the years 2010–11.

[34]Table A4 shows results by single active ingredient. To some extent, the effect is heterogeneous across types of active ingredient and periods. It is worth emphasizing that while oxycodone and hydrocodone are two popular semi-synthetic opioids, our main result holds when looking at the dispensation of natural opioids only (i.e. morphine). This suggests that the connection between Afghan opium prices and market diversion in India as a mechanism linking opium prices and US firms' incentives is observed for opioids like morphine that are likely sourced from India, while it is partially observed for the case of opioids like hydrocodone or oxycodone that are instead likely sourced from Australia, as discussed in section III.

TABLE 3

Effects by period and type of drug using diversion in India

Dep. variable	(1) Δ lnMGEpc	(2) Δ lnMGEpc	(3) Δ lnMGEpc (Natural/semi-synthetic)	(4) Δ lnMGEpc (Natural/semi-synthetic)	(5) Δ lnMGEpc (Synthetic)	(6) Δ lnMGEpc (Synthetic)
lnMines1983pc * Δ lnDiversion	−0.0067*** (0.0015)	−0.0005 (0.0005)	−0.0077*** (0.0016)	−0.0006 (0.0005)	−0.0030 (0.0019)	−0.0004 (0.0010)
Observations	21,763	21,763	21,763	21,763	21,763	21,763
R^2	0.4856	0.4806	0.4783	0.4834	0.4525	0.1894
Period	<2010	≥2010	<2010	≥2010	<2010	≥2010

Notes: Full sample (3,109 counties, yearly data, 2002–16). MGEpc is the quantity of MGE dispensed per capita. Methadone is excluded. Diversion is the difference between licensed and harvested hectares of opium in India. Mines1983pc is the number of mining sites per capita in 1983. All columns include year and county fixed effects, county-specific linear trends and the log-change in harvested hectares. Robust SEs clustered at the county level are in parentheses.
$^*P < 0.10$; $^{**} P < 0.05$; $^{***}P < 0.01$.

This is a period characterized by a remarkable increase in overdose deaths involving synthetic opioids, particularly fentanyl.

Overall, estimates presented in Table 2 support the hypothesis that the quantity of opioid-based drugs dispensed in the USA increases as the price of opium in Afghanistan falls, and that this increase mainly involves drugs that require at least some input of raw opium. In contrast, fully synthetic opioids do not react to changes in the price of opium. These results also 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.

In Section OA.B of the Appendix S1, we examine how declines in opium prices, by fuelling an increase in PO usage, impact local-level socio-economic outcomes. We focus on two critical metrics: drug-related fatalities and opioid-related criminal activities. We show evidence on the link between changes in opium prices and the rapid increase in drug-related overdose deaths and opioid-related crimes and that this relation is largely driven by the years of greatest expansion of opioid drugs (pre-2010).[35]

To further corroborate our evidence on the asymmetric effect of opium price shocks on PO dispensation while providing additional support to our identification strategy, we test the effect of changes in the diversion from *licit* crops in India on changes in PO dispensation in the USA. Using Indian data on the number of hectares of opium licensed and harvested, in Table 3 we substitute the shocks to the price of opium in Afghanistan with changes in the indicator for diversion from licit crops in India as computed by Paoli *et al.* (2009).

First, we show evidence of a statistically significant negative correlation between changes in the diversion from licit crops in India and changes in PO dispensation in the USA, as discussed in section III. The negative correlation implies that an

[35]In section OA.C of the Appendix S1 we also show that the impact on PO dispensed is smaller in counties with higher initial levels of income, education, urbanization or health insurance coverage. Conversely, it is stronger in areas with a higher initial share of healthcare workers in the population. We also show that the effect is homogeneous across states with different pre-existing prescription regulations.

increase in diversion, resulting in a reduction of opium available in the market, leads to a decrease in PO dispensation. This suggests that the shortage of raw materials may be an important mechanism driving changes in PO dispensation in the USA.

Second, the effect on the changes in the total amount of MGE units dispensed in the USA is primarily observed in the early phase of the opioid epidemic (column 1), while it weakens in the post-2010 period (column 2).[36] Third, in columns 3 and 4 we analyse the impact on the dispensation of natural and semi-synthetic drugs in the USA, while in columns 5 and 6 we focus on fully synthetic opioids. Again, the only statistically significant coefficient is associated with the pre-2010 period and with the drugs that require opium in their manufacturing process. As expected, we do not find any statistical relationship in the case of synthetic substances.

VII. The role of demand- and supply-side factors

The role of changes in patient demand

The previous findings support the hypothesis that supply-side economic incentives have played a role in the soaring use of PO in recent decades. A possible alternative hypothesis is that it was a consequence of a change in 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 patient demand for opioids. To test this alternative hypothesis directly, we use the yearly time series of retail prices of opioid-based drugs. 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. Figure A8 shows the variability exploited, that is, the growth in retail prices of generic PO and the substitute analgesic, ibuprofen, over the period 2000–15.[37]

In column 1 of Table 4, we show that using yearly data we obtain a negative and statistically significant coefficient in line with our main estimate. While the coefficient associated with the log change in retail price of opioids is also negative, we fail to detect a statistically significant effect on the quantity of drug substances prescribed (column 2). This suggests that it is unlikely that our main results are entirely driven by a change in patient demand. The comparison between the two standardized coefficients in column 3

[36] While the quantity of opium diverted from the licit market would not be sufficient to influence the price of illicitly cultivated opium, the price of opium in Afghanistan may still play a role in the illegal drug market. If so, the price of illegal drugs would follow the price of opium. Then, one would expect falling prices to be associated with an increased availability of illicit drugs and thus larger chances of substituting PO with illegal drugs (hence, no effect of prices on the dispensation rates of legally prescribed opioids).

[37] Prices are computed from the full sample of the Medical Expenditure Panel Survey (MEPS) as the average total expenditure for each dose (tablet or patch) of the generic drug in a given year, then standardized to account for potency relative to morphine. We acknowledge that retail prices could be a poor proxy for market behaviour due to the fact that prices are fixed for the share of the market operating via Medicare and Medicaid reimbursements. We address this concern by considering total rather than out-of-pocket retail prices. Here we only focus on natural and semi-synthetic PO, given the evidence shown in section VI.

TABLE 4

Effects of fluctuations in opioid retail prices on MGE dispensation

Dep. variable	*(1)* Δ *lnMGEpc*	*(2)* Δ *lnMGEpc*	*(3)* Δ *lnMGEpc*	*(4)* Δ *lnMGEpc*
lnMines1983pc * Δ lnOpiumP	−0.0074***		−0.0100***	−0.0160**
	(0.0027)		(0.0037)	(0.0069)
			[−0.0065]	[−0.0118]
lnMines1983pc * ΔlnOpiumP *				0.0120
$\mathbb{1}(\Delta\text{lnOpiumP}_t > \Delta\text{lnOpiumP}_{t-1})$				(0.0077)
				[0.0140]
lnMines1983pc * Δ lnOpioidsP		−0.0032	−0.0096	−0.0161
		(0.0049)	(0.0065)	(0.0124)
			[−0.0020]	[−0.0029]
lnMines1983pc * ΔlnOpioidsP *				0.0174
$\mathbb{1}(\Delta\text{lnOpioidsP}_t > \Delta\text{lnOpioidsP}_{t-1})$				(0.0139)
				[0.0042]
Observations	40,417	40,417	40,417	40,417
R^2	0.5769	0.5760	0.5775	0.5783
F-test equality standardized coeff. (*P*-value)			0.0068	0.0048

Notes: Sample: 3,109 counties, yearly data, 2002–15. 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. Robust SEs clustered at the county level are in parentheses. Standardized coefficients are in square brackets. *P*-values refer to the test of equality of standardized coefficients on lnMines1983pc*ΔlnOpiumP and lnMines1983pc*ΔlnOpioidsP.
$^*P < 0.10$; $^{**}P < 0.05$; $^{***}P < 0.01$.

suggests that demand factors account for roughly 30% of the supply incentives (–0.0020 and –0.0065, respectively). Thus, although we cannot exclude the existence of a demand channel, the evidence is consistent with the presence of a supply-side economic incentive mechanism.

Next, we consider whether the response to price growth increases (positive shocks) and decreases (negative shocks) is asymmetric. If price growth increases had smaller effects relative to price growth decreases, this would indicate that demand-side forces are driving our results. Thus, we define a dummy equal to one if the log change of prices is greater than in the previous period. We include in our model two new triple interactions, where the dummy for positive shocks is interacted with either opium price shocks or opioids retail price shocks.

Column 4 implies that: (i) the response of PO dispensation to positive vs. negative opium price shocks is asymmetric, consistent with pharmaceutical companies increasing their advertising expenses when they have a higher mark-up; (ii) the response to positive and negative changes in the retail price of the drugs is symmetric, suggesting that demand-driven forces are unlikely to be driving our main findings. This evidence is consistent with recent contributions by Cutler *et al.* (2019) and Cutler and Glaeser (2021), who show that patient demand is relatively less important than supply-side factors in explaining the US opioid crisis. Furthermore, this result is in line with the literature that investigates the initial causes of the opioid crisis, showing the crucial importance of supply-side factors (Van Zee, 2009; Alpert *et al.*, 2022; Arteaga and Barone, 2022).

Opium shocks, advertising expenses, stock market prices, and profits

In this final part of the study, we explore how fluctuations in the price of opium affect firms' advertising expenses, and whether pharmaceutical companies are seen by investors as exploiting opium price variations in their business strategies.

If changes in the price of opium are perceived as persistent – and they are, as the existence of a unit root confirms (see section V) – then investors can expect opioid producers to factor such changes into their production and distribution decisions. Opioid producers might then react to a drop in raw material costs by using promotions as a strategy to expand demand when their markup has increased, consistent with Dorfman and Steiner (1954) and Waldman and Jensen (2001). The former consider a monopolist whose demand is a function of price and advertising expenditure and demonstrate that in equilibrium, via profit maximization over price and advertising, the intensity of the advertising positively depends on the markup (i.e. it increases when marginal costs decline). The latter extend the model to the case of oligopoly, where firms have an additional incentive to advertise because this leads to an increase in not only the total demand for the product but also in the firm's market share.

It is difficult to precisely estimate the extent to which the price of opium would affect marginal costs for opioid manufacturers. In general, manufacturing costs are either the largest or second-largest expense for pharmaceutical firms, with drug manufacturing being surprisingly inefficient and lagging significantly behind the modernized manufacturing techniques of other industries (Price, 2014). Most drug manufacturers do not disclose the marginal manufacturing costs of patented drugs, thus precise production costs are generally unavailable (Berndt *et al.*, 1995). Yet, previous studies estimate that marginal production costs range from 3% to 4% for anti-retroviral drugs (Outterson, 2005) to 10%–25% for anti-ulcer drugs (Berndt *et al.*, 1995). Hence, we would expect opium prices to influence opioid manufacturing costs in a non-trivial way.

To investigate how opium price shocks affect the performance of US firms, we rely on quarterly firm-level data from Compustat, which provides balance-sheet data and other financial indicators for a sizable sample of firms operating in the USA. We focus on three main outcomes, namely advertising expenses, stock prices and profits. The idea is to determine the extent to which variation in the price of opium affects the advertising expenses and the stock prices and profits of firms in this sector. The sample includes all manufacturing firms operating in the USA during the 2003–16 period.

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.[38] 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.

[38] We retrieve information on approvals from the FDA's so-called Orange Book, that is, 'Approved Drug Products with Therapeutic Equivalence Evaluations'. This is a proxy 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 opioid market even without specific drug approval. The number of treated firms is 18, 10 and 30 out of 478 (columns 1, 2, and 3 in Panel A, Table 5, respectively). In each panel we restrict the sample to observations for which we have full information for the dependent variable.

Column 1 in Panel A of Table 5 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 an additional covariate a dummy that takes a value of 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 of interest slightly increases with respect to column 1. In addition, the positive and statistically 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. Given substantial heterogeneity in trends between

TABLE 5

Firm-level estimates

Dep. variable	*(1)* Δ *lnAdExpense*	*(2)* Δ *lnAdExpense*	*(3)* Δ *lnAdExpense*
Panel A			
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^2	0.148	0.148	
Panel B			
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^2	0.165	0.165	
Panel C			
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^2	0.205	0.205	

Notes: Full sample of firms operating in North American Industry Classification System (NAICS) sector 32. OpiumP is the average trader price of opium. The dummy variables for opioid approval and ibuprofen approval take a value of 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. Robust standard errors clustered at the NAICS level are in parentheses. The placebo exercise in column 3 is based on 200 replications.
*$P < 0.10$; ** $P < 0.05$; ***$P < 0.01$.

opioid manufacturers and other companies, the placebo test should show an effect comparable to our baseline coefficients (Abadie and Gardeazabal, 2003). Here, the lack of statistical significance supports our conclusions.

Taken together, Panel A shows that declines in the cost of the raw material are associated with increases in advertising expenses by firms who have 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. This evidence is consistent with the optimal advertising model by Dorfman and Steiner (1954), who show that the advertising budget increases with the monopolist's markup, that is, it increases when marginal costs decline. This result would hold even under the assumption of an oligopolistic regime (a more realistic assumption in the case of the pharmaceutical sector), where advertising incentives are larger than in a monopoly due to the fact that promotion increases not only the overall demand for the product but also the firm's market share (Waldman and Jensen, 2001).

Note also that the advertising expenses of pharmaceutical companies are mostly directed to physicians through detailing, product sampling and advertising in professional journals (Rosenthal *et al.*, 2002; Cegedim, 2013; Kornfield *et al.*, 2013; Zejcirovic and Fernandez, 2018). While direct-to-consumer (DTC) marketing has grown remarkably in the USA since the early 2000s and has been shown to increase demand for prescription drugs (Berndt *et al.*, 1995; Ling, Berndt, and Kyle, 2002; Hollon, 2005; Dave and Saffer, 2012), this is concentrated on a small fraction of prescription drugs (Rosenthal *et al.*, 2003).[39] Moreover, prior studies have shown that DTC advertising is mainly associated with an increase in the total demand for a therapeutic class of products, while direct-to-physician promotion is associated with increased market share among the within-class products, thus with an increase in companies' own sales (Berndt, 2002; Iizuka and Jin, 2005, 2007; Meyerhoefer and Zuvekas, 2008).

Next, we address the extent to which firms' stock prices react to opium price shocks. Reading across 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 paints a clear picture of investors also expecting 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. Coefficients in Panel C point to conclusions analogous to those obtained from Panel B. The positive and statistically 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.

All in all, tracking changes in the price of opium, we observe a clear inverse correlation with three important measures of firm performance, namely advertising expenses, stock prices and profits. The performance of opioid manufacturers, that is, firms with FDA approval to produce them, improves in response to reductions in the price of opium. That

[39] Suppliet (2020) shows that even consumer-directed advertising of non-prescription drugs has positive spillovers into the market for prescription drugs by affecting the decision to buy from the same firm ('umbrella branding effects').

is, opium price changes in Afghanistan are associated with changes in the expected future profits of pharmaceutical companies that produce opioid-based drugs, and hence with the economic incentive to promote and sell them.

VIII. Conclusions

The USA is in the throes of an opioid epidemic, with more than 2 million Americans 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 PO dispensed per capita responds to variation in the international price of opium.

The empirical analysis reveals a statistically significant positive effect of declines in the price of opium on the changes in the quantity of PO dispensed: a 20 percentage-point decrease in opium price growth generates an increase in the quantity of PO dispensed of about 5.5 medical doses of morphine per capita in counties in the 40th percentile of the distribution of mining sites. This corresponds to a 2% increase in the mean. Counties more exposed to opium price shocks have higher PO prescription rates. In addition, the effect is larger in the period of highest expansion of natural and semi-synthetic opioids, that is, before 2010.

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 appear to be correlated with increases in drug-related deaths per capita and in the arrest rates for possession and sale of opium or opioid-based illicit substances in the period of expansion of the opioid crisis. These effects are more pronounced in counties with higher *ex ante* levels of exposure to analgesics.

Finally, a firm-level analysis suggests that the advertising expenses of opioid manufacturers respond significantly to opium price shocks, and so do their stock prices and profits. This supports the hypothesis that supply-side economic incentives might have to a significant extent driven the distribution of opioids in the USA.

Our findings are relevant since prescription rates are still excessively high and have been widely recognized to not only be at the root of the surge in overdose mortality (Kolodny *et al.*, 2014; Case and Deaton, 2015; Schnell, 2017) but also to having produced a number of other adverse public health outcomes, such as increases in emergency room visits and neonatal abstinence syndrome (Patrick *et al.*, 2012; Chen *et al.*, 2014; Dart *et al.*, 2015). The total economic burden of opioid-related overdoses, abuse and clinical practice was calculated at about US $80 billion in 2013 alone (Pollack, 2016).

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 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 USA. This implies that policymakers should seriously reconsider the impact of 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 products.

Appendix

TABLE A1
List of datasets

Variables	*Data source*	*Aggregation*	*Time dimension*
US Data			
Grams of Schedule II and Schedule III drugs dispensed	ARCOS, Drug Enforcement Administration (DEA)	ZIP code	Quarterly (2003–16)
Mining sites and workers	Mine Safety and Health Administration (MSHA)	ZIP code	1983
Population (total counts and counts by sex, age band, race and ethnicity)	US Census Bureau	County	Yearly (1980, 1990, 2000, 2003–16)
Opium-related deaths	Wide-ranging ONline Data for Epidemiologic Research (WONDER), CDC	County	Yearly (2003–16)
Cancer-related deaths	Wide-ranging ONline Data for Epidemiologic Research (WONDER), CDC	County	2000
Imports of opium, CPS and alkaloids of opium	COMTRADE (Commodities Trade Statistics)	National, by source country	Yearly (2003–16)
Drug-related crime	Uniform Crime Reporting (UCR) Program Data: Arrests by Age, Sex, and Race, Summarized Yearly, FBI	County	Yearly (2003–14)
Firms' advertising expenses, stock prices and profits	Compustat, Wharton Research Data Services (WRDS)	Firm	Yearly (2003–16)
Companies having an FDA opioid-based drug approval	Approved Drug Products with Therapeutic Equivalence Evaluations (''Orange Book''), FDA	Firm	Yearly (-2016)
Fatal injuries at work	US Census Bureau	County	Yearly (2008–14)
Total opioid payments	Centers for Medicare & Medicaid Services (CMS)	State	Yearly (2003–16)
Number of veterans	US Census Bureau	County	1999
Drug retail prices	Medical Expenditure Panel Survey (MEPS)	National	Yearly (2000–15)
Income	Bureau of Economic Analysis (BEA)	County	1990
Number of graduates	US Census Bureau	County	1990
Urbanization	US Census Bureau	County	2000
Number of residents with health insurance	US Census Bureau	County	2000
People employed in the health sector	County Business Patterns (CBP)	County	1998
Triplicate states	Alpert et al. (2022)	State	—
Average consumer price index	FRED, Federal Reserve Bank of St. Louis	National	Quarterly (2003–16)

(Continues)

TABLE A1
Continued

Variables	*Data source*	*Aggregation*	*Time dimension*
Average street price of heroin in the US	UNODC	National	Yearly (2003–16)
Prescription Drug Monitoring Programs (PDMP)	Horwitz et al. (2021)	State	Quarterly (2003–16)
Employment rate	Quarterly Census of Employment and Wages	County	Quarterly (2003–16)
Veterans separating from service	Veteran Employment Outcomes (VEO)	State	Yearly (2000–14)
Non-US Data			
Price of opium in Afghanistan	Ministry of Counter Narcotics of the Islamic Republic of Afghanistan and the United Nations Office on Drugs and Crime (UNODC)	National	Quarterly (2003–16)
Hectares of opium cultivated in Afghanistan	Ministry of Counter Narcotics of the Islamic Republic of Afghanistan and the United Nations Office on Drugs and Crime (UNODC)	National	Yearly (2003–16)
Hectares licenced and harvested for the cultivation of opium in India	Indian Central Bureau of Narcotics (CBN)	National	Yearly (2003–16)
Number of conflict fatalities in Afghanistan	iCasualties.org	National	Daily (2003–16)
International prices of oil, copper, sugar, coffee, cocoa, wheat, and palm oil	Federal Reserve Bank of St. Louis	-	Quarterly (2003–16)

TABLE A2
Descriptive statistics

	Obs	*Mean*	*SD*	*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	3,443.2370
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	97,883.5700	314,821.4000	55	10,100,000
lnMiners1983p	173,880	−6.9885	1.5597	−23.0431	−2.1860
lnVeterans1999pc	173,936	−2.4162	0.2481	−5.5188	−0.9163
lnCancer2000pc	161,448	−6.0815	0.2954	−8.3419	−4.8063
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

(Continues)

TABLE A2

Continued

	Obs	*Mean*	*SD*	*Min*	*Max*
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 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	43,526	0.0413	0.1067	−1.0218	2.0128
Δ lnOpiumP	43,526	−0.0526	0.3386	−0.6427	0.7710
Δ lnOpioidsP	40,417	−0.0084	0.2100	−0.3745	0.3922
Deathspc	10,246	0.0002	0.0001	0.0000	0.0014
DrugTotpc	43,526	0.0010	0.0015	0.0000	0.0769
Δ lnDeathspc	8,455	0.0569	0.2942	−1.3654	2.0320
Δ lnDrugTotpc	28,838	−0.0097	0.6806	−6.5966	5.6930
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

TABLE A3

Effects on MGE dispensation: net of methadone and oxycodone

Dep. variable	*(1)* *Δ lnMGEpc* *(no methadone)*	*(2)* *Δ lnMGEpc* *(no oxycodone)*
lnMines1983pc * Δ lnOpiumP	−0.0063***	−0.0055**
	(0.0021)	(0.0023)
Observations	174,104	174,104
R^2	0.2447	0.3186
Mean of dep. variable	0.0065	0.0072

Notes: Full sample (3,109 counties, 2002q4–2016q4). 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. Robust standard errors clustered at the county level are in parentheses.
*$P < 0.10$; ** $P < 0.05$; ***$P < 0.01$.

TABLE A4

Effects on MGE dispensation: natural and semi-synthetic drugs by period

	(1)	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*
Dep. variable	*Hydrocodone*		*Hydromorphone*		*Oxycodone*		*Morphine*	
lnMines1983pc * Δ lnOpiumP	−0.0050	−0.0109***	−0.0187***	0.0069	−0.0160***	−0.0067**	−0.0063**	−0.0038**
	(0.0067)	(0.0030)	(0.0060)	(0.0075)	(0.0056)	(0.0027)	(0.0029)	(0.0019)
Observations	87,052	87,052	87,052	87,052	87,052	87,052	87,052	87,052
R^2	0.1915	0.3963	0.0530	0.1130	0.2457	0.3281	0.1804	0.0248
Period	<2010	≥2010	<2010	≥2010	<2010	≥2010	<2010	≥2010
Mean of dep. variable	−1.0587	−0.7506	−3.1049	−2.3123	−1.1092	−0.6570	0.2090	0.5434

Notes: Full sample (3,109 counties, 2002q4–2016q4). All dependent variables are expressed in delta log and 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. Robust SEs clustered at the county level are in parentheses.
*$P < 0.10$; ** $P < 0.05$; ***$P < 0.01$.

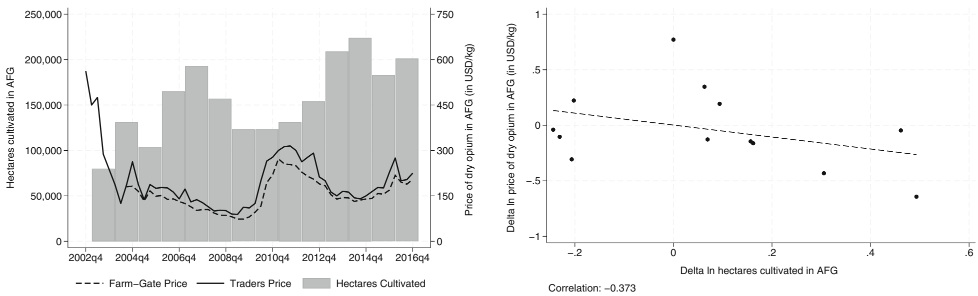

Figure A1. Hectares of poppies cultivated and price of opium in Afghanistan.
Notes: The left panel shows the number of hectares of poppies cultivated in Afghanistan annually (grey bars), the average quarterly trader price of dry opium in Afghanistan (solid line) and the farm-gate price (dashed line). The right panel shows the correlation between changes in the hectares cultivated and opium price shocks in Afghanistan, yearly

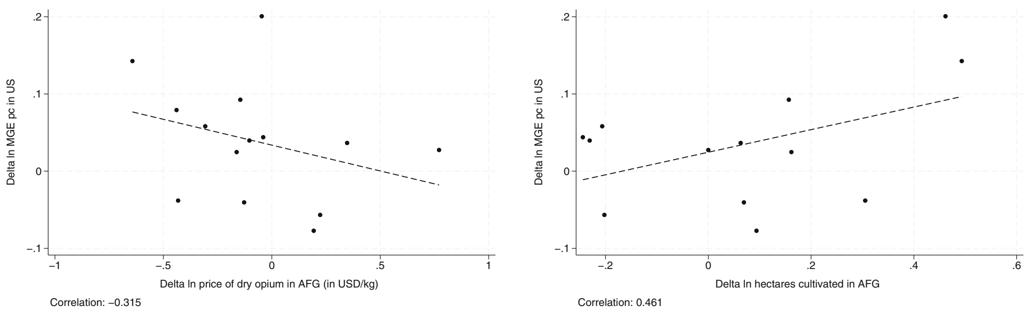

Figure A2. Opium in Afghanistan and prescription opioids in the USA.
Notes: The left panel shows the correlation between opium price shocks in Afghanistan and the delta log of the per capita dispensation of PO in the USA, yearly. The right panel shows the relationship between changes in hectares cultivated in Afghanistan and the delta log of the per capita dispensation of PO in the USA, yearly

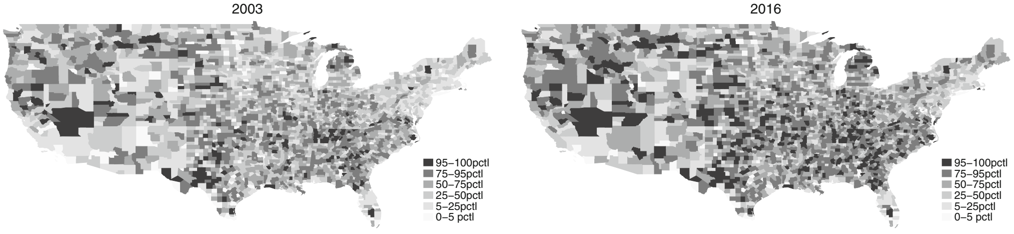

Figure A3. Quantity of MGE dispensed per capita in 2003 and 2016 by County.
Notes: Darker areas are associated with higher values of MGE dispensed per capita. Thresholds are set at the 5th, 25th, 50th, 75th and 95th percentiles of the pooled 2003–16 distribution.

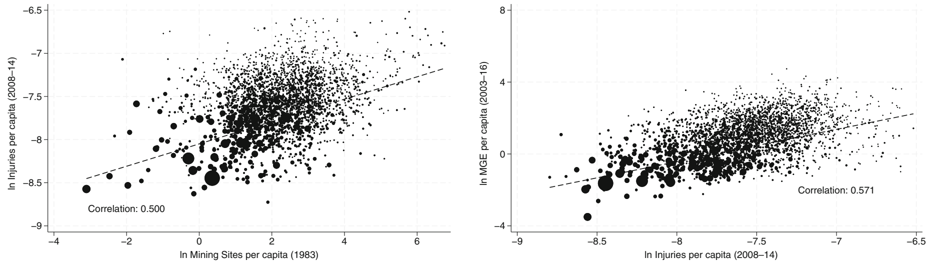

Figure A4. Correlation between mining sites, MGE dispensation and fatal injuries.
Notes: Population-weighted correlation plots between the average number of unintentional fatal accidents occurring in the workplace over the 2008–14 period and (i) the number of mining sites in 1983; (ii) the average value of MGE dispensation over the 2003-16 period. All variables are expressed in log and per capita

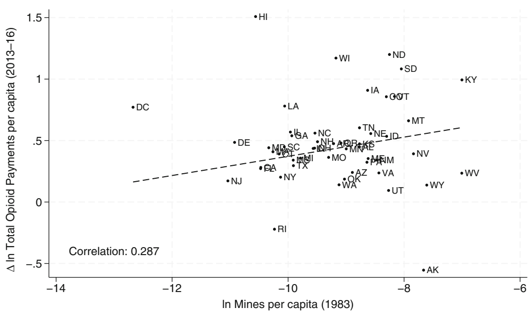

Figure A5. Correlation between mining sites and total opioid payments.
Notes: The y-axis refers to the average of the yearly changes in opioid-related payments received by healthcare professionals in the period 2013–16. We construct log-changes of the total opioid payments for the three periods 2013–14, 2014-15 and 2015–16. Then we average the values to obtain a cross-sectional state variation which we correlate with the exposure variable (mines per capita) aggregated at the state level (x-axis).

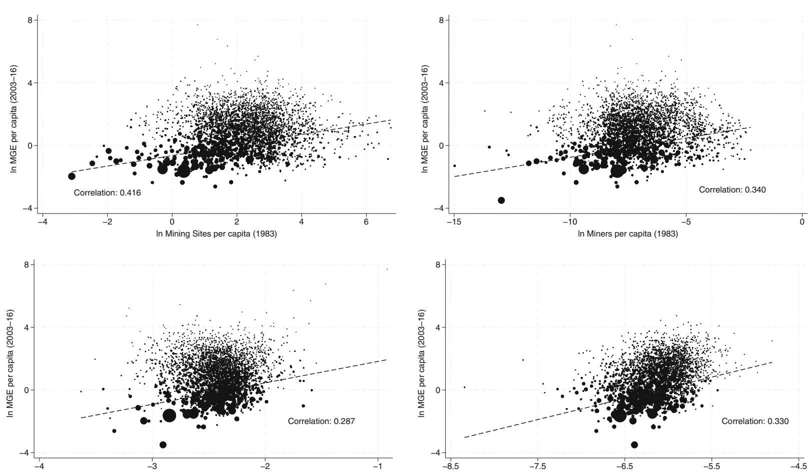

Figure A6. Correlation between exposure variables and MGE dispensation.
Notes: Population-weighted correlation plots between the average value of MGE dispensation and (i) the number of mining sites in 1983; (ii) the number of miners in 1983; (iii) the number of veterans in 1999; and (iv) cancer mortality in 2000. All variables are expressed in log form and per capita

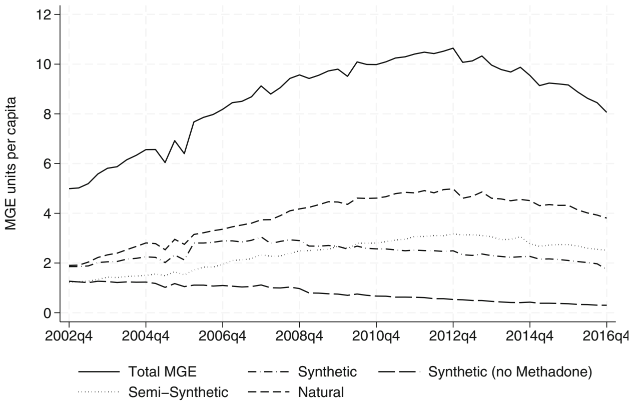

Figure A7. Trends in the prescription of MGE opioids per capita.
Note: Total MGE units dispensed by quarter and type

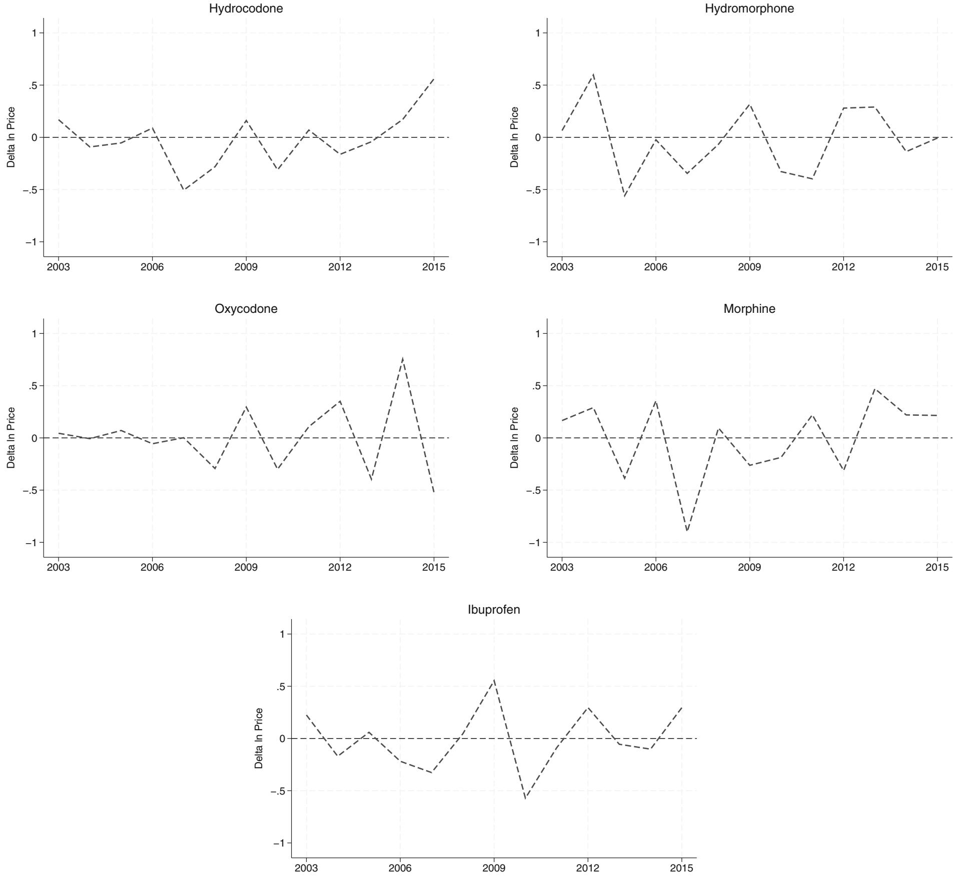

Figure A8. Drug retail prices.
Notes: Yearly changes in average total prices of one tablet or patch of hydrocodone/APAP (325/10), hydromorphone (2), oxycodone/APAP (325/5), morphine (30) and ibuprofen (400)

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Supporting Information

Additional Supporting Information may be found in the online Appendix:

Appendix S1. Supporting information

Data replication package: the data replication package is available at https://doi.org/10.3886/E188961