



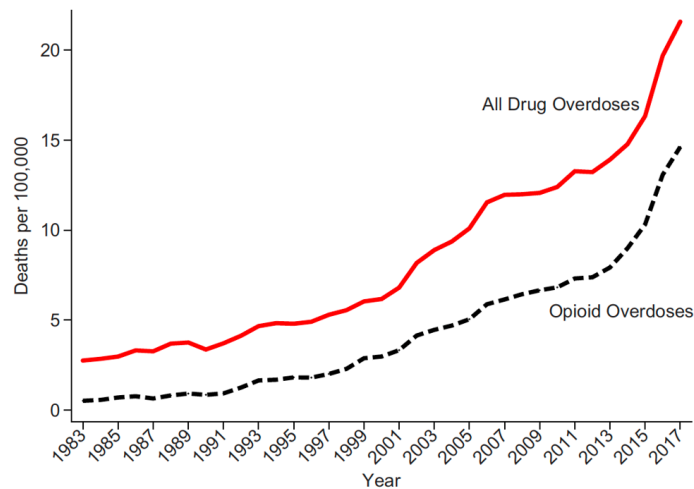
Origins of the Opioid Crisis Reexamined

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In an article in the *Quarterly Journal of Economics* titled “Origins of the Opioid Crisis and Its Enduring Impacts,” Abby Alpert, William Evans, Ethan Lieber, and David Powell—henceforth AELP (2022)—investigate the cause of the origins and persistence of the opioid crisis. The opioid crisis (also called the opioid epidemic) in the United States is commonly illustrated as in their Figure I, which I reproduce directly here:

Figure 1. National drug overdose death rates (this figure directly reproduces AELP’s Figure I)



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As AELP (2022, 1141) explain: “Opioid overdoses are defined as overdoses that report opioid involvement (including natural/semisynthetic opioids, methadone, heroin, and synthetic opioids). These overdoses may or may not also include nonopioid substances.” Thus, when we speak of opioid deaths, we mean all opioid deaths, not just from prescription opioids.

The crisis calls out for explanation. As AELP note, some scholars have pointed to explanatory factors on the demand side, such as “deaths of despair” (Case and Deaton 2015; 2017), while other scholars point to factors on the supply side. AELP (2022, 1140) note a major supply-side explanatory factor: “Beginning in the 1990s, changing attitudes and new treatment guidelines encouraged doctors to treat pain more aggressively with opioids (Quinones 2015; Jones et al. 2018).”

AELP (2022, 1140) explore a specific aspect of supply-side explanation: “in 1996, Purdue Pharma launched its drug OxyContin, a prescription opioid pain reliever that quickly became one of the leading drugs of abuse in the United States.”² AELP (ibid., 1142) say: “The aggressive and deceptive marketing of OxyContin has been the subject of enormous public and scholarly discussion (e.g., Van Zee 2009; Kolodny et al. 2015; Quinones 2015) and thousands of lawsuits from state and local governments, which have implicated OxyContin as ‘the taproot of the opioid epidemic.’”

The linchpin of AELP’s investigation related to the investigation of the role of OxyContin is triplicate prescription programs. States varied in their adoption of triplicate programs,³ and AELP assume with only limited evidence to support the assumption that triplicate prescription programs affected the amount of prescription opioids and in turn deaths from opioids and other drugs (Department of Health and Human Services 1992). They claim that “if nontriplicate states had the same initial exposure to OxyContin’s introduction as triplicate states, they would have had 34% fewer drug overdose deaths and 45% fewer opioid death overdose deaths on average from 1996 to 2017” (AELP 2022, 1173). They also suggest that “the introduction of OxyContin explains 79% of the rise in the overdose death rate since 1996” (ibid.).

In this article, I discuss several conceptual and empirical problems with AELP’s article that render the evidence in it largely uninformative about the role of OxyContin in the opioid epidemic. I believe that it is reasonable to think that

2. To bring readers up to speed, let me note that an OxyContin pill is time-released oxycodone designed to digest gradually over a 24-hour period, to give the same sort of effect as taking another opioid such as hydrocodone throughout the day. However, a user can access all of the oxycodone by chewing or crushing it to obtain a stronger effect.

3. In a triplicate program, the doctor writes a prescription on a state-issued prescription form and provides one copy to the patient, one to the pharmacist, and one to a state agency. These programs are thought to reduce abuse and fraud (see Department of Health and Human Services 1992).

the introduction and marketing of OxyContin accounts for some percentage of the increase in deaths from opioids, but only as part of the broad increase in use of all prescription opioids that occurred from 1991 to 2012.

The aggressive marketing of OxyContin cannot explain the trend in deaths from opioids

There is little dispute that OxyContin was aggressively marketed after its introduction in 1996 and that sales rose rapidly until 2001 (General Accounting Office 2003). What is less known is that over the same period there was a large increase in other types of prescription opioids. From 1996 to 2001, hydrocodone sales in morphine milligram equivalents (MMEs) doubled, and—normalizing here and henceforth to MMEs so that we compare apples to apples—hydrocodone sales were greater than OxyContin sales in every year from 1991 to 2017 (Food and Drug Administration 2018; Volkow 2014). It is also apparent that a substantial portion of the increase in OxyContin sales came at the expense of propoxyphene (Darvon, Darvocet), which was the most widely prescribed opioid prior to 2002. After 2001, OxyContin sales growth slowed considerably and was less than the growth in sales of hydrocodone. From 2001 to 2011, hydrocodone sales increased by about 250 percent whereas OxyContin sales increased by less than 50 percent. By 2011, OxyContin sales were less than 50 percent of what hydrocodone sales were, and OxyContin sales constituted about 25 percent of all oxycodone sales—OxyContin is a form of oxycodone (Food and Drug Administration 2018).

The upshot of these figures is that while OxyContin was marketed aggressively after its introduction, its growth was not particularly unusual relative to other opioids except for the five-year period after its introduction, and over a much longer period its growth was significantly slower than that of hydrocodone, which had much larger sales. While OxyContin has received much media attention, that attention is not commensurate with its numerical importance in the overall growth of prescription opioid sales. Nor was the marketing of OxyContin very different than the marketing of any branded drug by pharmaceutical companies. In 1998, narcotic analgesics (e.g., OxyContin) accounted for less than 1 percent of expenditures by pharmaceutical companies promoting prescription drugs to providers (Ma et al. 2003). Promotional expenditures on antihypertensives and antidepressants were 10 times that of analgesic narcotics (ibid.).

From 1996 onward, hydrocodone and non-OxyContin forms of oxycodone were numerically much more important than OxyContin, which reached its peak in

terms of share of prescription opioids in 2001. According to a Drug Enforcement Agency fact sheet dating to 2012, “Hydrocodone is the most frequently prescribed opioid in the United States and is associated with more drug abuse and diversion than any other licit or illicit opioid” ([link](#)). Similarly, other forms of oxycodone are abused, as is propoxyphene, which was taken off the market in 2011, and other prescription opioids. Given this general and widespread increase in prescription opioids, it is unlikely that the short period of rapid OxyContin sales explains the time pattern of deaths due to opioids. Figure I in AELP (2022, 1141) shows that deaths due to opioids increase smoothly, seemingly at an exponential rate from 1983 to 2017. The time pattern of deaths due to opioids seems much more consistent with the time pattern of opioid sales more broadly than with the pattern of OxyContin sales.

AELP (2022) never provide an ex-ante conceptual model linking the time pattern of OxyContin sales to the time pattern of deaths due to drugs or opioids. Instead of a developed theory with hypotheses, a statistical identification strategy is used as a replacement under the assumption that any significant correlations found represent meaningful causal relationships. The authors suggest there are many potential pathways linking the hypothesized cause (i.e., OxyContin marketing starting around 1996) to the outcome (deaths from opioids). According to the authors in an earlier draft of the article, which I shall cite as Alpert et al. (2019) to distinguish from the 2022 QJE version: “A motivation of this paper is to understand the initial conditions of the opioid crisis, which has potentially affected a wide range of outcomes” (Alpert et al. 2019, 18). And then after seeing the results, AELP (2022, 1173–1174) claim the following in conclusion: “Our estimates capture both the direct and indirect consequences of initial exposure to OxyContin’s introduction, including spillovers of OxyContin promotion to other opioid drugs and transitions to heroin and fentanyl in the later waves of the epidemic. They also internalize downstream indirect effects of OxyContin’s introduction on the behaviors of other entities in the supply chain—distributors, pharmacies, and doctors—which may have further amplified OxyContin’s effects.” This ex-post claim is speculative and the result of an exploratory, observational study with serious flaws that I describe below.

Evolution of the increase in opioid use

So, from 1991 to 2012, there was a steady, broad increase in prescription opioids beginning before the introduction of OxyContin in 1996 and continuing without a noticeable change in trend after the introduction of OxyContin until 2012 that matches well the steady increase in deaths due to drugs and opioids

during this period (Food and Drug Administration 2018; Volkow 2014). OxyContin contributed, but fractionally, to this growth in prescription opioids mostly during one short period from 1996 to 2001. Prior to 1996 and after 2001, the growth in hydrocodone and other forms of oxycodone were much more numerically important than OxyContin (Food and Drug Administration 2018). While abuse of OxyContin is well documented, so is abuse of hydrocodone, other forms of oxycodone, and other opioids, and because of the numerical importance of these other opioids, it is likely that growth in hydrocodone and oxycodone explain most of the increase in deaths from opioids from 1991 to 2012.

After 2012, prescription opioid sales decreased significantly because of another change in clinical practice and norms ([link](#)), but deaths from opioids continued its upward trajectory, with a marked increase in deaths from fentanyl beginning in 2013 and growing exponentially to the current period ([link](#)). The decreased access to prescription opioids caused a shift to illicit and more deadly opioids among a small group of prescription drug users—first heroin and then drugs contaminated with illegally produced fentanyl.⁴ The use of more deadly opioids has resulted in an exponential growth in deaths from opioids starting in 2013, which is the same time that prescription opioids were declining. There is little controversy over this explanation of the origin and continuation of the opioid epidemic (Humphreys et al. 2022; Congressional Budget Office 2022; DeWeert 2019). Nothing about this widely held view of the opioid epidemic is in dispute, nor does it point to OxyContin as the origin and chief cause of the increase in deaths from opioids between 1996 and 2017.

Triplicate prescriptions

An important component of AELP's OxyContin story is triplicate prescription programs, so it is worth scrutinizing more closely its scientific plausibility. AELP argue that triplicate prescription programs limited consumption of prescription opioids. AELP (2022) provide some evidence to support this hypothesis. In Figure IIIA, data from Automated Reports and Consolidated Ordering System (ARCOS) shows that OxyContin sales in 2000 were approximately 50 percent lower in states with triplicate prescription programs in place in 1996 than in other

4. It is important to note that the vast majority of prescription opioids were used for medical purposes and had little adverse effects. In 2012, there were 250 million opioid prescriptions in the U.S. ([link](#)). In 2012, there were approximately 20,000 opioid deaths ([link](#)). Given these numbers, there can be a general decrease in opioid use at the same time there is an increase in deaths from opioids. The increase in risk of death for the small group who switch to deadlier illegal opioids outweighs the lower risk from fewer prescriptions.

states. However, by 2006, the same figure, as well as Figure IIIB, shows that OxyContin sales are about the same in states with and without triplicate prescription programs.⁵ The convergence in OxyContin use between triplicate and non-triplicate states was, according to the authors, because of the temporary entry of generic forms of OxyContin. Between 2006 and 2009, there was a relative increase in OxyContin sales (inclusive of generics) in non-triplicate states (Figure IIIA) followed by similar, steady declines in OxyContin sales in both types of states. Finally, as shown in Figure IIB and by estimates in Table 2 of Alpert et al. (2019, 48), in 2000 OxyContin sales in non-triplicate states were higher than in triplicate states (the peak difference), but the difference declined steadily over time by approximately 35 percent.

The evidence just reviewed indicates that, if anything, the declining difference in OxyContin sales between triplicate and non-triplicate states shown in Figure IV would suggest a declining difference in mortality—not a continuously diverging trend as shown in Figure IV in AELP (2022, 1159). Second, the OxyContin sales in triplicate states are far from zero indicating that the presence of a triplicate program had modest effects on OxyContin prescribing. In addition, OxyContin was a fraction of all prescription opioids, with a share that peaked (at approximately 20 percent) in 2001 and declined markedly afterward, as use of hydrocodone and non-OxyContin forms of oxycodone grew significantly faster than use of OxyContin (Food and Drug Administration 2018). Thus, the difference in OxyContin use between triplicate and non-triplicate states could explain only a small part of any difference in total prescription opioid sales between the two types of states and therefore a small part of the difference in mortality between triplicate and non-triplicate states. Thus, it is much more likely that the divergent trend in drug deaths between triplicate and non-triplicate states is because of different levels and trends in hydrocodone, non-OxyContin oxycodone, and other opioids.

Indeed, Figure IIIC in AELP (2022, 1156) shows exactly that, although it is obscured because the figure does not show oxycodone other than OxyContin separately. Figure IIIC shows that oxycodone (inclusive of OxyContin) grew much faster from 1997 onward in non-triplicate states than in triplicate states. As already noted, after 2001 OxyContin grew more slowly than hydrocodone and non-OxyContin oxycodone. Therefore, most of the sustained growth in oxycodone in non-triplicate states relative to triplicate states is from an increase in non-OxyContin oxycodone. Estimates in Table 2 in Alpert et al. (2019, 48) also demonstrate this fact. Oxycodone (inclusive of OxyContin) grew four to six times faster than OxyContin in non-triplicate states relative to triplicate states. The reason

5. In Appendix Figure A3 the same convergence is reported using data from the Medical Expenditure Panel Survey (MEPS).

for this difference is unknown. AELP (2022, 1158) offer the following: “Such spillovers are likely generated by Purdue Pharma’s marketing strategies that aimed to expand the opioid market by normalizing the use of strong opioids for noncancer chronic pain and creating the message that opioids carry a low risk of addiction (Van Zee 2009). Moreover, individuals introduced to OxyContin will often transition to using other opioids, especially similar products containing oxycodone.”

No meaningful model of Purdue Pharma or physician behavior is offered to support this spillover explanation. If Purdue Pharma marketing efforts increased sales of opioids other than OxyContin, then that would erode OxyContin sales, at least to some extent, as physicians substitute other opioids for OxyContin. This would reduce the return on the marketing investment. Moreover, there is no noticeable increase in non-OxyContin oxycodone after 1996 in national data, which is dominated by the 46 non-triplicate states (including Washington DC), that would support the spillover argument (Food and Drug Administration 2018). Data in Alpert et al. (2019) show that hydrocodone use was the same in triplicate and non-triplicate states. This is surprising because hydrocodone and oxycodone are substitutes. Consider physicians in triplicate states. Hydrocodone products were not Schedule II drugs until 2014 and were not subject to triplicate prescribing program at the time of OxyContin introduction. Why would these physicians not substitute hydrocodone for oxycodone including OxyContin? All else equal, there should be more hydrocodone use in triplicate states than non-triplicate states, but this is not what Alpert et al. (2019) report. In addition, there are other prescription opioids that are not considered by AELP (2022) with an important one being propoxyphene, which was the most widely prescribed opioid until 2002. After the introduction of OxyContin, propoxyphene use decreased. It is likely that propoxyphene use was lower in non-triplicate states than in triplicate states offsetting some of the greater use of oxycodone in non-triplicate states.

In sum, AELP (2022) provide little evidence about the difference in all prescription opioids between triplicate and non-triplicate states. My review of what little evidence that is presented in AELP (2022) related to differences in opioid prescriptions in triplicate and non-triplicate states does not provide much support for the hypothesis that OxyContin was the chief origin and enduring cause of the increase from 1996–2017 in deaths from opioids.

There is a widely accepted explanation for the large, steady increase in deaths from drugs including opioids, and the authors largely agree with it (Humphreys et al. 2002; De Weerd 2019; Congressional Budget Office 2022). As the authors write in their introduction, there was a change in clinical practice related to pain management and a greater willingness to prescribe opioids to treat pain. This change in practice patterns resulted in an increase in prescription opioids broadly

and not just OxyContin. The introduction of OxyContin was part, albeit a numerically rather small part, of this broad increase in prescription opioids.

A statistical model unhinged from theory

Without theory, the AELP (2022) claim that the introduction of OxyContin is the origin of the opioid epidemic (i.e., pattern of deaths from opioids) rests on a statistical result. The statistical analysis of AELP (2022) is based on a difference-in-differences research design. In it, deaths from opioids (or, alternatively, all drugs) from 1991 to 2017 in states that had a triplicate prescription program are compared to deaths from opioids (or all drugs) during the same period in states that did not have a triplicate program. The authors use the introduction of OxyContin in 1996 to divide the 1991 to 2017 period into a before and after period.⁶

Note that there is no measure of OxyContin usage in this analysis. Nor is there any other measure of drug usage (e.g., total prescription opioids). It is only an analysis of mortality. The article does not include any analysis linking OxyContin or any measure of prescription opioid use to mortality. The only link to OxyContin in the statistical analysis is the use of 1996 to divide 1991–2017 period into two. The inadequacy of this statistical model to incorporate and utilize knowledge about the growth in prescription opioid use and OxyContin's limited role, summarized above, is obvious.

More importantly, without any theory, there is no clearly identified hypothesis that is being tested. As such, it is purely an exploratory analysis and results from it cannot be given a causal interpretation. Without theory, there is no basis for deciding what covariates to include in the statistical model. At best, and this is unstated, the statistical model is assumed to be an experiment with random assignment of treatment (triplicate program) that interacted with the introduction of OxyContin in 1996 to cause an unspecified difference in the pattern of opioid use in triplicate and non-triplicate states that in turn caused an unspecified difference in the pattern of deaths from opioids in these two types of states.

Consider the finding in the article that the divergence in deaths from opioids (all drugs) between triplicate and non-triplicate states is not observed until 2002—seven years after the introduction of OxyContin. How should this result be interpreted? There was no theory that predicted this finding. It is simply a result of an exploratory analysis with no causal basis. Some questions about the result naturally arise. Why did it take seven years for the introduction of OxyContin to affect drug deaths? Here are the authors' comments on this question: "It is

6. In some analyses the starting year is 1983.

not surprising that these mortality effects are delayed, given the expansions in OxyContin promotion and sales over time and the FDA’s relabeling in 2001 that expanded its market for chronic use. In addition, it would take time for a person to transition from an initial prescription for OxyContin to dependence and an overdose” (AELP 2022, 1160).⁷ This is an ex-post speculation. The explanation was the result of an exploratory analysis devoid of theory and hypotheses. If a different result was found, the authors would undoubtedly offer a different explanation. Another question is why do deaths from drugs other than opioids follow the exact same pattern, also showing a divergence beginning in 2002? While this result is not shown directly, it can be derived from Figure IV and Table I in AELP (2022).⁸ What theory about the introduction of OxyContin and the presence of triplicate states explains this result? Are other drugs complements or substitutes for oxycodone?

An alternative analysis that explicitly correlated prescription opioid use and mortality was possible. Specifically, data on mortality could be merged with data on prescription opioid use (ARCOS) to conduct an analysis of the effect of prescription opioid use on mortality. The authors might claim that this cannot be done because there is no readily available data on prescription opioid use prior to 1997, which is after the introduction of OxyContin. However, this is not a convincing argument. Central to the authors’ entire approach is a link between introduction of OxyContin and the *time pattern* of prescription opioid use and mortality. While the time pattern is unspecified and not formulated from theory, the authors explicitly claim that the introduction of OxyContin had enduring effects on mortality presumably because of enduring effects of prescription opioid use.

Given the authors’ claim—that the introduction of OxyContin had a persistent effect on opioid use and deaths—the following instrumental variables model could be estimated using data from 1997 onward:

$$MORTALITY_{st} = \alpha_s + \gamma_t + \beta \widehat{OPIOID}_{st} + u_{st} \tag{1}$$

$$OPIOID_{st} = \rho_s + \delta_t + \sum_{k=1997}^{2017} \lambda_k \times 1(NON_TRIPLICATE)_i \times 1(k = t) + e_{st} \tag{2}$$

$$t = 1997, \dots, 2017$$

$$s = 1, \dots, 51$$

7. Note that growth in OxyContin sales slowed after 2001 FDA relabeling.

8. For example, subtract coefficients in the bottom panel (related to opioids) of Table 2 from those in the top panel (related to all drugs). This yields the effect on drugs other than opioids.

Equation (2) is the first stage of the model. It measures the differential effect of the introduction of OxyContin in 1996 on prescription opioid sales (*OPIOID*) between states with and without a triplicate prescription program (*NON_TRIPPLICATE*). This model is consistent with the interpretation of AELP (2022), which assumes that the introduction of OxyContin had a different effect on prescription opioid use in triplicate versus non-triplicate states, and that that effect persisted over time (indicated by the interaction between non-triplicate indicator and year). The specification of the model is identical to the model that AELP (2022, 1154 eq. 1) used to estimate the effect of the introduction of OxyContin on mortality except that in this case prescription opioid use (in state s and year t) is the dependent variable instead of mortality. Equation (1) is the model that relates deaths from opioids (all drugs) to predicted prescription opioid use. Predicted opioid use is obtained from equation (2).

Equations (1) and (2) are a standard type of analysis. The value of it is that it yields a direct estimate of the relationship between prescription opioid use and deaths from opioids. Moreover, it uses variation in prescription of opioids caused by the introduction of OxyContin and the presence of triplicate prescription programs, which is exactly the argument underlying the AELP (2022) heuristic model. Therefore, this approach seems superior to that used by AELP (2022) that assumes such a relationship without ever assessing whether it exists. In addition, the instrumental variables approach exploits the same geographic variation in exposure to OxyContin's introduction that is the basis of the implicit quasi-experimental research design.

Why didn't the authors estimate this model? It is clear that AELP (2022) view the link between the introduction of OxyContin and deaths from all drugs (opioids) as to be the change in prescription opioid use. That is why they discuss the differences in prescribing patterns between triplicate and non-triplicate states, and in Alpert et al. (2019) estimate a model that measures the differences in some prescription opioids. The point of that analysis was to show that use of some prescription opioids differed between triplicate and non-triplicate states and that difference varied over time. This is exactly what I suggest to do (my equation 2).⁹

In sum, all the parts of the instrumental variables approach I recommend were recognized by the authors, but it was not estimated. The instrumental variables approach I recommend is consistent with the AELP (2022) conceptualization of the problem. The data are in the authors' hand, and the suggested IV approach could be carried at small additional effort to them (though not to others). So why

9. However, Alpert et al.'s (2019) analysis differed from my suggested model in an important way. For some inexplicable reason, Alpert et al. (2019) omitted state fixed effects from their model (equation 3 that produced estimates in Table 2 of their article). No justification for this deviation from best practice is given.

wasn't it done? My suspicion is that the authors recognized that such an analysis would contradict their basic argument that the introduction of OxyContin changed the time pattern of prescription opioid use that in turn caused the time pattern in deaths from drugs. As described in detail earlier, the descriptive data strongly suggest that this is not likely.

Replication

While I believe the arguments above are sufficient to raise doubts about the likely veracity of the claim that the introduction of OxyContin was the origin and chief persistent cause of the opioid epidemic through 2017, it is also worthwhile to assess the reliability of the statistical model used by AELP (2022), and results from that model. After all, it is the statistical model that must do the heavy lifting to support the conclusion, as little theory was provided. However, before presenting results from my re-analysis, it is worth pointing out the considerable evidence of a faulty research design presented in the AELP (2022) article itself.

Table I of the article (AELP 2022, 1161) contains much evidence suggesting a faulty research design. If the analysis was a bona fide experiment then results from it are apt to be true even if difficult to explain, although without theory it would still be considered exploratory. But AELP (2022) do not conduct an experiment. They exploit a supposed natural experiment, namely the presence of triplicate prescription programs in some states and not others. Evidence that this bit of history is not such a great experiment is in Table I, for all to see.

As is standard practice, AELP (2022) conduct a series of sequential models, adding additional control variables to the basic pre- and post-test with comparison group design that characterizes true experiments. In a true experiment, adding additional controls usually has almost no effect on results. In this case, however, adding controls changes results markedly. AELP (2022, 1162) interpret these marked changes as supportive, “robust” evidence, which gives new meaning to the expression “the glass is half full.” Comparing estimates in columns 2 and 4 of top panel of AELP’s Table I, which pertain to deaths from all drugs, shows that the addition of control variables to the model reduces the estimate of the effect of not being a triplicate state on deaths between 2001 to 2010 by 29 percent, and reduces the estimate of the effect of not being a triplicate state on deaths between 2011 to 2017 by 40 percent. The analogous changes in estimates in the analysis of opioid deaths are 23 percent and 44 percent. Table I also reports that a test of whether the three estimates of the effect of being a non-triplicate state on opioid deaths are jointly zero cannot be rejected at the 0.11 level of significance, which is above the commonly used thresholds of statistical significance at 0.05 or 0.10. Overall,

an experiment this is not. Similarly, in an earlier version of the article, the authors conducted an analysis in which they allowed covariates to have different effects by year (Alpert et al. 2019, Appendix Table B1; see Jaeger et al. 2020 for a similar application). Here too the test that all three estimates of the effect of being a non-triplicate state on opioid deaths cannot be rejected.

Perhaps no more evidence of the fragility of the statistical model is needed, but I provide additional analyses to augment the evidence already reported by the authors (to their credit). In this section, I estimate models identical to those in columns 1 and 2 of Table I in AELP (2022, 1161). I use the same data as AELP (2022), but the public-use versions of the data, which is accessible through the Centers for Disease Control Wonder database ([link](#)). AELP (2022) had access to restricted-use data. There are two differences between my data and that used by AELP (2022). The first is that in cases when there were fewer than 10 deaths in a state and year, the number of deaths is suppressed. I know only that the actual number of deaths is somewhere between 1 and 9. Second, prior to 1999, I cannot identify all deaths from opioids that AELP (2022) used because I do not have access to one ICD-9 code related to cause of death (N695). Despite these differences, I am largely able to replicate the estimates in AELP (2022).

First, I begin by replicating, as best I can, the results of AELP (2022). Table 1 below shows the estimates of AELP (2022) and my replication attempts. Because I do not have access to restricted data, I am missing deaths for some states and years. For all drug deaths, I am missing only 9 out of 1377 observations. I am missing 209 out of 1377 observations in the case of opioid deaths. Deaths are missing when there are fewer than 10 and so missing observations are from small population states and from earlier years when deaths were relatively low. To address this issue, I alternately assign missing deaths to be equal to 1 or 9, which are the lowest and highest possible deaths, respectively. To assess whether the missing data matters, I estimate models using the imputed deaths rates in addition to models that use the observed data. It makes little difference, as can be observed below.

The top panel of Table 1 reports estimates for deaths from all drugs and the bottom panel reports estimates for deaths from opioids. The first two columns reprint estimates from Table I of AELP (2022). Starting with the top panel, my estimates (in columns K1 and K2) are almost identical to those reported in AELP (2022). In both analyses, estimates indicate that deaths from all drugs were significantly higher in non-triplicate states and this difference grows with time. Estimates using the imputed death rates (columns K3 and K4) are virtually identical to those using the observed data, which is not surprising because there are only nine imputed values.

Estimates in the bottom panel also demonstrate that I can replicate the results related to opioid deaths reported by AELP (2022). In this case, my estimates

(in columns K1 and K2) differ somewhat quantitatively—by 20 percent to 30 percent—but not qualitatively. The difference between my estimates and AELP (2022) estimates is likely due to the missing observations on opioid deaths and that, prior to 1999, my data does not include all opioid deaths (missing those with ICD-9 code N965.0). Despite these differences, like estimates in AELP (2022), my estimates indicate that deaths from opioids were significantly higher in non-triplicate states and this difference grows with time. Estimates using the imputed death rates (columns K3 and K4) are virtually identical to those using the observed data. My estimates show a slightly steeper gradient with respect to time of the effect of being a non-triplicate state.

TABLE 1. Estimates of the effect of being a non-triplicate state on drug deaths

	AELP (2022)		Kaestner			
	(AELP1)	(AELP2)	(K1)	(K2)	(K3)	(K4)
Non-triplicate ×	Deaths from all drugs					
1996–2000	1.17** [0.39,2.37]	1.29** [0.42,2.45]	1.25** [0.48,2.02]	1.30** [0.60,2.00]	1.30** [0.60,2.00]	1.28** [0.59,1.99]
2001–2010	3.67** [1.52,6.21]	4.49** [2.20,6.40]	3.79** [1.94,5.63]	4.51** [2.81,6.20]	4.51** [2.81,6.20]	4.49** [2.79,6.18]
2011–2017	6.06** [2.81,9.37]	7.81** [4.02,10.44]	6.17** [3.49,8.86]	7.82** [5.15,10.48]	7.82** [5.15,10.48]	7.80** [5.13,10.46]
Impute missing deaths=9	No	No	No	No	Yes	No
Impute missing deaths=1	No	No	No	No	No	Yes
Weighted	No	Yes	No	Yes	Yes	Yes
Mean 1991–1995	3.89	4.44	3.96	4.45	4.45	4.43
N	1377	1377	1368	1348	1377	1377
Non-triplicate ×	Deaths from opioids					
1996–2000	0.63** [0.09,1.57]	0.62** [.112,1.61]	0.64 [-0.18,1.45]	0.50 [-0.07,1.08]	0.34 [-0.14,0.81]	0.38 [-0.08,0.86]
2001–2010	2.61** [1.12,4.38]	2.94** [1.23,4.25]	3.60** [2.09,5.11]	3.59** [2.17,5.02]	3.36** [2.10,4.63]	3.47** [2.20,4.73]
2011–2017	5.00** [1.48,8.29]	5.90** [1.76,8.90]	6.02** [3.66,8.37]	6.90** [4.23,9.59]	6.68** [4.17,9.18]	6.78** [4.28,9.28]
Impute missing deaths=9	No	No	No	No	Yes	No
Impute missing deaths=1	No	No	No	No	No	Yes
Weighted	No	Yes	No	Yes	Yes	Yes
Mean 1991–1995	1.19	1.48	0.8	0.8	0.76	0.42
N	1377	1377	1168	1168	1377	1377
<i>Notes:</i> All regression models include state and year fixed effects. Standard errors are constructed allowing for non-independence of observations within a state (i.e., robust-cluster method). Confidence intervals are shown in brackets. ** indicates statistical significance at the 5% level.						

The origin of digestive and respiratory deaths

I have emphasized that the AELP (2022) analysis is based on little theory and lacks specific hypotheses. It is largely a statistical model that is exploratory. Given this, I apply the same statistical model to explore the role of the introduction of OxyContin in the presence of triplicate and non-triplicate states in deaths from causes other than drugs. In fact, AELP (2022) examined two other causes of death: suicide and alcohol-related liver disease. The authors conclude that they do not find any significant effects of the introduction of OxyContin (i.e., being a non-triplicate state) on these two causes of death.¹⁰ Here I apply the statistical model used by AELP (2022) to several other causes of death: cancer, circulatory, digestive, metabolic and respiratory.¹¹ These illnesses were selected because they are most of the major causes of death among adults. Data on these deaths comes from the CDC Wonder database ([link](#)).

Estimates for these causes of death are presented in Table 2. For two of the five causes of death, estimates are statistically significant and the pattern of estimates is similar to that for all drugs and opioids (which were shown above in Table 1). Deaths due to digestive illnesses and respiratory causes are higher in non-triplicate states than triplicate states and the difference grows with time, which is a pattern exactly like that found for drugs. The magnitudes of the estimates are modest (e.g., 10 percent effect size).¹² There may be some reason to believe that the introduction of OxyContin had a causal effect on deaths from these causes, but it is not obvious, nor is it obvious why the time pattern of deaths would differ between states with and without a triplicate prescription program. Overall, estimates in Table 2 highlight the atheoretical and statistical nature of the AELP (2022) article. Applying the same statistical model yields estimates of the effect of the 1996 introduction of OxyContin that lack plausibility. For example, the 22 per 100,000-unit decline in deaths from respiratory causes in non-triplicate states subsequent to the introduction of OxyContin is almost twice the 20-year change (−12) in deaths from respiratory causes between 2000 and 2020 (see the CDC Wonder database).

In the last two columns, I add the death rates from the five illnesses to the model of deaths from all drugs and opioids. This is appropriate under the assumption that the introduction of OxyContin has no causal effect on these other

10. However, when the same statistical model used in the main analysis is estimated for these alternative causes of death, there is evidence of a divergence between triplicate and non-triplicate states in suicides. Only after controlling for differential prior trends by detrending the data does the difference become statistically zero.

11. I used the death rates for those ages 35 to 85.

12. The huge increase in deaths from drugs over time makes the comparison of magnitudes challenging, as there is no similar increase in other causes of death.

causes of death, but that these death rates are correlated with unmeasured confounders, which is demonstrated by the significant estimates for non-drug causes of death. Including these variables reduces the magnitudes of the effects of being in a non-triplicate state by from 22 percent to 38 percent in the case of all drugs, and by from 20 percent to 28 percent in the case of opioids.

TABLE 2. Estimates of the effect of being a non-triplicate state on several causes of death

Non-triplicate ×	Kaestner						
	Cancer	Circulatory	Digestive	Metabolic	Respiratory	All drugs	Opioids
1996–2000	5.34 [−0.02,10.7]	1.4 [−25.3,28.1]	2.8** [0.9,4.6]	0.8 [−2.9,4.5]	5.5** [2.5,8.5]	0.8 [−0.1,1.7]	0.09 [−1.0,1.2]
2001–2010	11.4 [−0.9,23.7]	−5.9 [−48.4,36.7]	4.6** [1.7,7.5]	0.4 [−7.1,8.0]	12.0** [0.8,23.1]	3.4** [1.7,5.2]	2.6** [0.6,4.6]
2011–2017	14.8 [−1.2,30.8]	7.0 [−45.2,59.1]	6.9** [2.9,11.0]	2.6 [−10.0,15.2]	22.8** [4.9,40.6]	6.1** [4.2,8.1]	5.5** [2.8,8.1]
Include other causes of death	No	No	No	No	No	Yes	Yes
Weighted	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mean 1991–1995	421	735	61	58	165	4.44	0.76
N	1377	1377	1377	1377	1377	1368	1168
<i>Notes.</i> All regression models include state and year fixed effects. Standard errors are constructed allowing for non-independence of observations within a state (i.e., robust-cluster method). ICD-10 codes for each cause of deaths are as follows: cancer (C00-D48); circulatory (I00-I99); digestive (K00-K92); metabolic (E00-E88); and respiratory (J00-J98). ** indicates statistical significance at the 5% level.							

What the results in Table 2 suggest is that estimates of AELP (2022) are confounded by unmeasured factors. Death rates from illnesses with little direct connection to drug and opioid use, digestive and respiratory causes, and more importantly, to the introduction of OxyContin and whether a state had a triplicate program, follow the same general time path as death rates from all drugs and opioids. These results underscore that the AELP (2022) article was not an experiment and that the premise of a natural experiment was not valid. It was an observational study using regression methods that was at best exploratory. Its results and conclusions, particularly the claim that the introduction of OxyContin explains 79 percent of the change in opioid deaths from 1996 to 2017, should not be accepted. The claim is based on evidence that is unreliable. Even if we confine ourselves to the supply-side explanations of the opioid tragedy, AELP do not provide a particularly believable alternative to the conventional explanation, that changing attitudes and new treatment guidelines encouraged doctors to treat patients’ pain more aggressively with opioids.

Differential pre-trends in triplicate and non-triplicate states

Close inspection of Figure I in AELP (2022, 1141) suggests that, between triplicate and non-triplicate states, there may be differential trends in deaths from all drugs and opioids prior to 1996. That might suggest those sets of states differed systematically, which especially would undermine the claim of AELP's approach to be a natural experiment. This was a major concern of the authors and they conducted a variety of analyses that demonstrate the problem including one similar to what I present next.

First, to investigate whether there were differential pre-trends, I estimated a regression of all drug deaths on state fixed effects and a separate quadratic time trend for triplicate and non-triplicate states using only data prior to 1996. The results of that regression indicate that, prior to 1996, triplicate and non-triplicate states had different trends in deaths for all drugs and the difference was statistically significant.¹³ I used these regression results to predict the time trend in deaths due to all drugs for the entire 1983 to 2017 period and subtracted that predicted value from the actual death rate for all drugs. Then, to control for the possibility of differential pre-trends, which would bias estimates of the difference-in-differences design, I used the detrended death rate to re-estimate the models in Table 1 (Bacon-Goodman 2021). This is the same procedure used by AELP (2022) in their analyses of deaths due to suicides and alcohol-related liver disease, and in their Appendix Figure A20 for drug and opioid deaths. There is one major difference between my approach and theirs, however: I used a quadratic time trend instead of a linear trend. The quadratic trend prior to 1996 is visually observable in Figure 1, although not pronounced. However, as noted, the trends were statistically different.

Estimates from this procedure are shown in Table 3. For clarity, I included the original estimates from AELP (2022), my estimates using the untransformed data, and estimates when the detrended data were used. Controlling for differential pre-trends in this way substantially reduces estimates of the effect of being a non-triplicate state.¹⁴ The estimate for the 1996–2000 period is reduced by 17 percent; the estimate for the 2001–2010 period is reduced by 30 percent; and the estimate for the 2011–2017 period is reduced by 46 percent. These large reductions in estimates when controls for pre-trends are included raise further doubts about the

13. I calculated the slope of the quadratic trend at various points in time for triplicate and non-triplicate states and tested whether those slopes differed.

14. Standard errors of estimates are likely biased because the construction of these ignores the fact that the dependent variable is predicted and not the actual value.

validity of the AELP (2022) statistical approach.

This evidence of a likely invalid research design adds to that reported by the authors and evidence in Table 2 above. There are clearly unmeasured factors that are causing the trends in drug deaths to differ in triplicate and non-triplicate states. Whether the estimates that address this issue, either those in AELP (2022), in Table 2 from models that include additional death rates, or those in Table 3 from models using detrended data, are enough to eliminate the problem is unknown. What is known is that the validity of the statistical approach used by AELP (2022) is suspect. Given this, AELP’s conclusions and causal claims are suspect and should be interpreted accordingly.

TABLE 3. Estimates of the effect of being a non-triplicate state on detrended all drug deaths

	AELP (2022)	Kaestner	
		Original	Detrended
Non-triplicate ×	Deaths from all drugs		
1996–2000	1.29** [0.42,2.45]	1.30** [0.60,2.00]	1.08** [0.39,1.78]
2001–2010	4.49** [2.20,6.40]	4.51** [2.81,6.20]	3.17** [1.48,4.87]
2011–2017	7.81** [4.02,10.44]	7.82** [5.15,10.48]	4.27** [1.61,6.93]
Weighted	No	Yes	Yes
Mean 1991–1995	4.44	4.45	4.43
N	1377	1368	1368
<i>Note.</i> ** indicates statistical significance at the 5% level.			

Synthetic control

Another approach used by AELP (2022) to address differential pre-trends between triplicate and non-triplicate states was the synthetic control method. The synthetic control method compares the time pattern of deaths from drugs in triplicate states as a whole, or in each triplicate state separately, to the time pattern of deaths from drugs in a composite group of non-triplicate states that are the best match for the triplicate states or state. The best match is chosen purely on a statistical basis and is not necessarily a good match—just the best that a statistical algorithm can select.

Consider results reported in AELP (2022) for California. California is the most important triplicate state in terms of the magnitude of its impact and its contribution to the overall estimate of the effect of being a triplicate state. When

California is dropped from the analysis, estimates of the effect of being a triplicate state on deaths from drugs declines by 30 percent (Figure C3 in AELP 2022). The synthetic control analysis for California produces a surprising result: There are only two states out of 46 including Washington DC that form the composite group of non-triplicate states that are the best match, or counterfactual ‘outcome in California if it did not have triplicate status.’ Those two states are Nevada, which contributes 5 percent to the composite outcome and Washington (state), which contributes 95 percent to the composite outcome. Thus, the synthetic control analysis of the effect of California’s triplicate program is basically a comparison of California and Washington. There might be some reason to see Washington as representing the right counterfactual outcome for California—maybe something about being on the Pacific Ocean?—but it is more likely that Washington was chosen purely because the statistical algorithm couldn’t come up with anything better.

I used the synthetic control approach for California to assess its reasonableness. My analysis differs from AELP (2022) in one way: I used annual data whereas they used quarterly data. It is the only time that AELP (2022) used quarterly data. They argue that quarterly data provides more information than annual data. That may be true, but reason suggests that the use of quarterly versus annual data should not make too much of a difference for selecting a comparison group of states. If it does, it reveals the fragility of the approach.

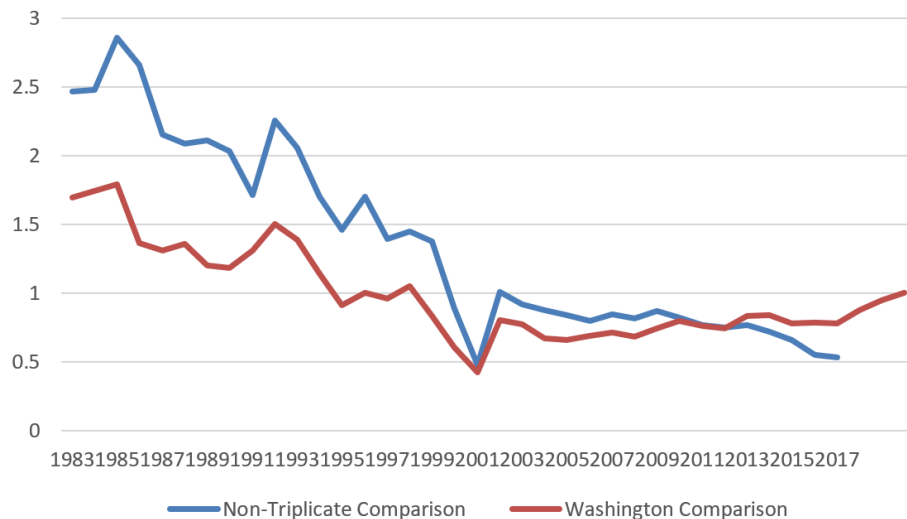
My results yield an equally surprising finding vis-à-vis that reported in AELP (2022). Like AELP (2022) only two states contribute to the composite comparison group, but these two states are Nevada, which now contributes 84 percent (compared to 5 percent in AELP 2022), and the other Washington, that is, the District of Columbia, which contributes 16 percent. Just using annual instead of quarterly data changes the comparison group radically. Would Nevada and the District of Columbia be likely candidates to use as counterfactuals for California? It strains the imagination to believe that any theoretically driven approach would choose these two states. To illustrate the arbitrariness of the synthetic control approach, I re-estimated the model using only data from 1989 (seven years prior to the introduction of OxyContin). In this iteration, the states that contribute to the composite comparison group are New Mexico (50 percent), Rhode Island (31 percent) and the District of Columbia (19 percent)—Washington and Nevada are nowhere to be found. Again, we have an unintuitive and shifting cast of comparison states.

Remarkably, all estimates obtained using the synthetic control method, those from AELP (2022) and my two, show that deaths from drugs were substantially lower in California than in any of these other synthetic comparison groups after 1996. This may be because of the triplicate program and its unknown and

unspecified effect on the time pattern of prescription opioid use, or it may simply reflect the fact that California is an outlier with a pattern of death rates that is idiosyncratic, as indicated by the analysis that left out California.

In fact, as shown in Figure 2, California’s mortality rate from drugs starts out 2.5 times higher than that of all non-triplicate states in 1983 and declines relative to non-triplicate states continuously and, generally, smoothly until 2017 (except for the likely data problem in 2001). The figure clearly shows a differential pre-trend prior to 1996. In 1995, the ratio of drug deaths in California to drug deaths in non-triplicate states is 1.5—40 percent lower than it was in 1983. Even if the comparison to non-triplicate states is limited to just Washington state, which is virtually the only comparison state used by AELP (2022), there is still marked evidence of a significant pre-trend. Indeed, the line in Figure 2 that pertains to the difference between California and Washington is virtually the synthetic control result obtained by AELP (2022). The drug death rate in Washington state was rising relative to that in California prior to 1996 and it continued to rise relative to California post-1996. In sum, California seems to be an outlier and the synthetic control approach unreliable.

Figure 2. Ratio of drug death rate in California to non-triplicate states and California to Washington state by year

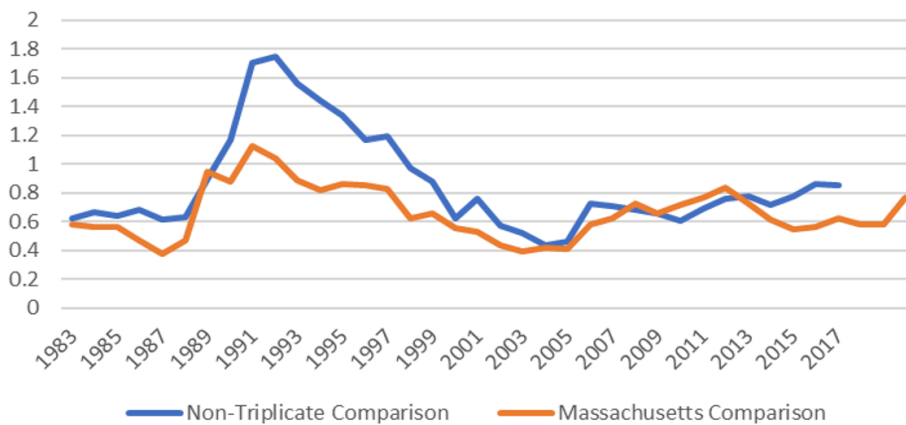


Another important triplicate state is New York, which also had one of the largest estimates of the effect of the introduction of OxyContin (see Appendix Figure D2 in AELP 2022). I also used the synthetic approach for New York. AELP (2022) reported that the non-triplicate states that constitute the comparison group are: New Mexico (42 percent), Connecticut (34 percent), Massachusetts (13

percent), Rhode Island (6 percent), West Virginia (5 percent) and the District of Columbia (1 percent). While several of these states seem intuitive as comparators, others are not. When I estimate the model using annual data, the states that constitute the comparison group are: New Mexico (25 percent), Connecticut (42 percent), Wyoming (17 percent) and New Hampshire (15 percent). When I limit the pre-period to 1989 to 1995, the comparison states consist of Massachusetts (79 percent), New Hampshire (20 percent) and New Mexico (1 percent). These shifting comparison states in terms of both whether they are included or excluded in the synthetic control unit, and the weight they contribute to the counterfactual synthetic group, seems problematic. A true experiment, which is what all the analyses conducted by AELP (2022) intend to mimic, would not support a shifting composition of the comparison group that changes seemingly randomly. And as with California, all these synthetic control analyses indicate that deaths from drugs in New York grew significantly slower than in the synthetic comparison groups after 1996.

The same question applies in this case: is the lower drug death rate because New York is an outlier, or is it because of its triplicate status? Figure 3 shows the strange pattern of deaths from drugs in New York versus all other non-triplicate states and versus Massachusetts—one of the important states in the synthetic comparison group. There is a large relative increase in deaths from drugs in New York between 1989 and 1992, which was almost surely due to the crack epidemic. While limiting the comparison to Massachusetts improves this a bit, the differential pre-trends persist in this comparison. This makes New York an outlier.

Figure 3. Ratio of drug death rate in New York to non-triplicate states and New York to Massachusetts by year



Overall, the statistical nature of the synthetic control approach and its fragility to small changes in model specification (e.g., length of pre-period) and unit of analysis (annual versus quarterly data) undermine its reliability and value as a solution to differential pre-trends that I have demonstrated bias estimates obtained by AELP (2022). Figures 2 and 3 show that in the two states in which the introduction of OxyContin had the largest effects, California and New York, there are clear differences in pre-trends between the triplicate and non-triplicate states further eroding confidence in all the results from AELP (2022).

Conclusion

There is a widely accepted explanation for the opioid epidemic, as described in numerous places (Humphreys et al. 2022; De Weerd 2019; Congressional Budget Office 2022). That conventional wisdom points to changes in physician opioid prescribing behavior caused by a greater concern to effectively treat pain. The standard explanation also argues that opioid manufacturers, including but not limited to Purdue Pharma, increased prescribing through aggressive marketing efforts. Jonathan Marks writes in the *Journal of Bioethical Inquiry*:

Most of the media attention has focused on Purdue Pharma—and on members of the Sackler family who are major shareholders. However, it is important to keep in mind that this company was only one of several drug companies that promoted their opioids by building webs of relationships with a variety of public health agencies, academic institutions, and public health NGOs, as well as thousands of individual health professionals. A recent trial in Oklahoma shed light on the activities of Johnson & Johnson, a family of companies that has not only sold its own opioids but also supplied the active ingredients to several other opioid companies, including Purdue Pharma (Hoffman 2019a, 2019b). For that reason, Johnson & Johnson had an additional incentive to engage (and did engage) in the unbranded promotion of opioids. The criminal trial of the former executives of another company, Insys, also shed light on its fraudulent marketing practices (Emanuel and Thomas 2019). We know more about the “webs of influence” woven by these companies than about the strategies of other companies that have been more successful, thus far, at keeping evidence out of the public domain—often by settling cases before they go to trial. But there is clear evidence that aggressive promotion strategies were widespread, to varying degrees, across the opioid industry. (Marks 2020, 174)

In addition, the marketing of a branded drug by Purdue Pharma was not out of the ordinary (Ma et al. 2003; Schwartz and Woloshin 2018). Promotional efforts

by pharmaceutical companies predated the introduction of OxyContin and have continued, and promotional spending on narcotic analgesics was an order of magnitude lower than promotional spending on other drug classes around the time of OxyContin's introduction (Ma et al. 2003).

In fact, AELP (2022) do not really take on the question of what was the origin and enduring cause of the opioid epidemic. Instead, the analysis of AELP (2022) is intended to answer a much narrower research question. That objective is to estimate the effect of triplicate prescription programs, which applied to all Schedule II prescription opioids, on deaths from drugs (opioids). Triplicate prescription programs plausibly reduced prescription opioid use for Schedule II drugs such as oxycodone including OxyContin, although given that hydrocodone and propoxyphene, which dominated the prescription opioid market until about 2010, were not affected by the triplicate programs, it is unclear whether and by how much the triplicate prescription programs affected total prescription opioid use. Triplicate prescription programs also predated the introduction of OxyContin and presumably impacted opioid prescribing prior to 1996 (Department of Health and Human Services 1992). While the mix of prescription opioids changed with the rapid rise of OxyContin from 1996 to 2001, data on total prescription opioid sales does not indicate a sharp increase in all prescription opioids in 1996 (Food and Drug Administration 2018). Such an increase would seem necessary if the origin of the opioid epidemic was the introduction of OxyContin given that there are 46 non-triplicate states including Washington DC that were (more) affected by the introduction of OxyContin. This basic fact suggests that the combination of triplicate prescription programs and introduction of OxyContin is unlikely to be a particularly important part of the explanation of the opioid epidemic.

However, the value of the more limited objective of AELP (2022) is diminished by the absence of any direct assessment of the effect of prescription opioids on drug deaths and the considerable evidence that the presence of a triplicate prescription program is not a valid natural experiment. In the end, the empirical analysis is a good old fashioned observational study with all the usual associated pitfalls. Thus, AELP's conclusions about the effects of the triplicate prescription program are suggestive at best. The article's title and packaging are regrettably audacious and its conclusions are inappropriately advanced by publication in the *Quarterly Journal of Economics*.

References

Alpert, Abby, William N. Evans, Ethan M. J. Lieber, and David Powell. 2019. Origins of the Opioid Crisis and Its Enduring Impacts. *NBER Working Paper* 26500. National

- Bureau of Economic Research (Cambridge, Mass.). [Link](#)
- Alpert, Abby, William N. Evans, Ethan M. J. Lieber, and David Powell** (AELP). 2022. Origins of the Opioid Crisis and Its Enduring Impacts. *Quarterly Journal of Economics* 137(2): 1139–1179. [Link](#)
- Case, Anne, and Angus Deaton**. 2015. Rising Morbidity and Mortality in Midlife Among White Non-Hispanic Americans in the 21st Century. *Proceedings of the National Academy of Sciences* 112: 15078–15083.
- Case, Anne, and Angus Deaton**. 2017. Mortality and Morbidity in the 21st Century. *Brookings Papers on Economic Activity* 48: 397–443.
- Congressional Budget Office**. 2022. The Opioid Crisis and Recent Federal Policy Responses. September. Congressional Budget Office (Washington, D.C.). [Link](#)
- Department of Health and Human Services, Office of Inspector General**. 1992. Multiple Copy Prescription Programs: State Experiences. June. Department of Health and Human Services (Washington, D.C.). [Link](#)
- DeWeerd, Sarah**. 2019. Tracing the US Opioid Crisis to Its Roots. *Nature* 573: S10–S12. [Link](#)
- Emanuel, Gabrielle, and Katie Thomas**. 2019. Top Executives of Insys, an Opioid Company, Are Found Guilty of Racketeering. *New York Times*, May 2. [Link](#)
- Food and Drug Administration**. 2018. FDA Analysis of Long-Term Trends in Prescription Opioid Analgesic Products: Quantity, Sales, and Price Trends. March 1. Food and Drug Administration (Silver Spring, Md.). [Link](#)
- General Accounting Office**. 2003. Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem. GAO-04-110. General Accounting Office (Washington, D.C.). [Link](#)
- Goodman-Bacon, Andrew**. 2021. Difference-in-Differences With Variation in Treatment Timing. *Journal of Econometrics* 225(2): 254–277.
- Hoffman, Jan**. 2019a. Johnson & Johnson Ordered to Pay \$572 Million in Landmark Opioid Trial. *New York Times*, August 26. [Link](#)
- Hoffman, Jan**. 2019b. Whoops: Judge Reduces J&J Opioid Fine After Mistaking Thousands for Millions. *New York Times*, November 15. [Link](#)
- Humphreys, Keith, Chelsea L. Shover, Christina M. Andrews, Amy S. B. Bohnert, Margaret L. Brandeau, Jonathan P. Caulkins, Jonathan H. Chen, Mariano-Florentino Cuéllar, Yasmin L. Hurd, David N. Juurlink, Howard K. Koh, Erin E. Krebs, Anna Lembke, Sean C. Mackey, Lisa Larrimore Ouellette, Brian Suffoletto, and Christine Timko**. 2022. Responding to the Opioid Crisis in North America and Beyond: Recommendations of the Stanford–Lancet Commission. *Lancet* 399(10324): P555–P604. [Link](#)
- Jaeger, David A., Theodore J. Joyce, and Robert Kaestner**. 2020. A Cautionary Tale of Evaluating Identifying Assumptions: Did Reality TV Really Cause a Decline in Teenage Childbearing? *Journal of Business & Economic Statistics* 38(2): 317–326. [Link](#)
- Jones, Mark R., Omar Viswanath, Jacquelin Peck, Alan D. Kaye, Jatinder S. Gill, and Thomas T. Simopoulos**. 2018. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain and Therapy* 7: 13–21. [Link](#)
- Kolodny, Andrew, David T. Courtwright, Catherine S. Hwang, Peter Kreiner, John**

- L. Eadie, Thomas W. Clark, and G. Caleb Alexander.** 2015. The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. *Annual Review of Public Health* 36: 559–574. [Link](#)
- Ma, Jun, Randall S. Stafford, Iain M. Cockburn, and Stan N. Finkelstein.** 2003. A Statistical Analysis of the Magnitude and Composition of Drug Promotion in the United States in 1998. *Clinical Therapeutics* 25(5): 1503–1517.
- Marks, Jonathan H.** 2020. Lessons from Corporate Influence in the Opioid Epidemic: Toward a Norm of Separation. *Journal of Bioethical Inquiry* 17(2): 173–189. [Link](#)
- Quinones, Sam.** 2015. *Dreamland: The True Tale of America's Opiate Epidemic*. New York: Bloomsbury Publishing.
- Schwartz, Lisa M., and Steven Woloshin.** Medical Marketing in the United States, 1997–2016. *JAMA* 321(1): 80–96. [Link](#)
- Van Zee, Art.** 2009. The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy. *American Journal of Public Health* 99: 221–227.
- Volkow, Nora D.** 2014. America's Addiction to Opioids: Heroin and Prescription Drug Abuse. May 14. National Institutes of Health, Department of Health and Human Services (Bethesda, Md.). [Link](#)

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