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Association Between State Laws Facilitating Pharmacy Distribution of Naloxone and Risk of Fatal Overdose

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IMPORTANCE Given high rates of opioid-related fatal overdoses, improving naloxone access has become a priority. States have implemented different types of naloxone access laws (NALs) and there is controversy over which of these policies, if any, can curb overdose deaths. We hypothesize that NALs granting direct authority to pharmacists to provide naloxone will have the greatest potential for reducing fatal overdoses.

OBJECTIVES To identify which types of NALs, if any, are associated with reductions in fatal overdoses involving opioids and examine possible implications for nonfatal overdoses.

DESIGN, SETTING, AND PARTICIPANTS State-level changes in both fatal and nonfatal overdoses from 2005 to 2016 were examined across the 50 states and the District of Columbia after adoption of NALs using a difference-in-differences approach while estimating the magnitude of the association for each year relative to time of adoption. Policy environments across full state populations were represented in the primary data set. The association for 3 types of NALs was associated: NALs providing direct authority to pharmacists to prescribe, NALs providing indirect authority to prescribe, and other NALs. The study was conducted from January 2017 to January 2019.

EXPOSURES Fatal and nonfatal overdoses in states that adopted NAL laws were compared with those in states that did not adopt NAL laws. Further consideration was given to the type of NAL passed in terms of its association with these outcomes. We hypothesize that NALs granting direct authority to pharmacists to provide naloxone will have the greatest potential for reducing fatal overdoses.

MAIN OUTCOMES AND MEASURES Fatal overdoses involving opioids were the primary outcome. Secondary outcomes were nonfatal overdoses resulting in emergency department visits and Medicaid naloxone prescriptions.

RESULTS In this evaluation of the dispensing of naloxone across the United States, NALs granting direct authority to pharmacists were associated with significant reductions in fatal overdoses, but they may also increase nonfatal overdoses seen in emergency department visits. The effect sizes for fatal overdoses grew over time relative to adoption of the NALs. These policies were estimated to reduce opioid-rated fatal overdoses by 0.387 (95% CI, 0.119-0.656; $P = .007$) per 100 000 people in 3 or more years after adoption. There was little evidence of an association for indirect authority to dispense (increase by 0.121; 95% CI, −0.014 to 0.257; $P = .09$) and other NALs (increase by 0.094; 95% CI, −0.040 to 0.227; $P = .17$).

CONCLUSIONS AND RELEVANCE Although many states have passed some type of law affecting naloxone availability, only laws allowing direct dispensing by pharmacists appear to be useful. Communities in which access to naloxone is improved should prepare for increases in nonfatal overdoses and link these individuals to effective treatment.

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Supplemental content

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Drug overdose fatalities in the United States today, associated with fentanyl, heroin, and prescription analgesic use, exceed those from any prior drug epidemic on record.[1] The number of deaths each year after 2014 surpasses the number of deaths associated with the HIV epidemic of the 1980s in its peak year,[2] and as of 2009, exceeds that of deaths from car crashes and gun violence.[3] The upward trends in mortality over the past 2 decades have affected both men and women, and no age group or geographic region of the United States has been exempt.[1,4]

States and the federal government have tried multiple strategies aimed at curbing the supply of opioids, the misuse of them, and the mortality associated with their misuse and addiction. Distribution of naloxone to potential witnesses of an opioid overdose is a core strategy for accomplishing the latter and now serves as 1 of the 5 key components of the Department of Health and Human Services' comprehensive strategy for addressing the opioid epidemic.[5] Efforts to expand naloxone access, which has generally occurred through harm reduction organizations, have been pursued in many states.[6] Today, naloxone formulations are distributed through different mechanisms. Depending on the jurisdiction, they can be prescribed by a physician directly to patients or indirectly through standing orders, or distributed without a prescription through Overdose Education and Naloxone Distribution programs,[7] opioid overdose prevention programs,[8] and pharmacies in states that legally permit it.[6]

Expansion of naloxone distribution has its critics.[9,10] Concerns about the message that such life-saving drugs might send regarding reduced risk of abuse have been fueled by a recent working paper suggesting that state policies expanding naloxone distribution were potentially positively associated with opioid-related mortality.[11] The results from the study described in that article stand in contrast to findings from 3 other recent studies, which also examined the association of naloxone laws with opioid mortality, with 2 suggesting a decrease in opioid mortality[12,13] and the other finding no effect.[14] These divergent observations may be the result of differences in how the state laws were operationalized. Herein, we estimate the outcome of different types of state naloxone distribution laws on naloxone availability, opioid mortality, and emergency department (ED) visits for nonfatal overdoses. Our hypothesis is that laws that facilitate greater distribution of naloxone will result in greater decreases in opioid mortality.

Key Points

Question Are state laws regarding naloxone access associated with reductions in fatal overdoses involving opioids?

Findings In this population-based study of data from the 2005-2016 National Vital Statistics System, a difference-in-differences design to evaluate 50 states and the District of Columbia, found that states adopting naloxone access laws granting direct authority to pharmacists experienced statistically significant declines in fatal opioid-related overdoses. Other types of naloxone access laws appear not to be associated with decreases or increases in mortality.

Meaning Naloxone access laws have the potential to improve naloxone access and save lives, but the details of the laws matter; permitting pharmacists to dispense directly and under their own authority appears to maximize the potential benefits of these policies.

Methods

Data Sources and Measures

To assess whether state laws enabling pharmacy distribution of naloxone are associated with pharmacies distributing the drug, we used quarterly data from the 2010-2016 State Drug Utilization Data, which record outpatient drug use information for covered drugs paid for by state Medicaid agencies, including Medicaid managed-care organizations. Medicaid covers 40% of nonelderly adults with an opioid addiction.[15] Distribution of naloxone was identified through the dispensing of naloxone in all forms, except buprenorphine and naloxone combinations, which would be used for treatment. We generated a quarterly rate of naloxone prescribed per 1000 Medicaid beneficiaries. The study was conducted from April 2018 through January 2019. The RAND Corporation Institutional Review Board determined that this research was exempt from approval and acquiring written or oral informed consent.

Opioid-related mortality data were obtained from the National Center for Health Statistic's National Vital Statistics System for 2005-2016. The data set includes all deaths in the United States with causes specified using the *International Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*). Opioid overdose deaths are identified using codes X40-X44, X60-X64, X85, or Y10-Y14. We examined all opioid-involved deaths (T40.1-T40.4), and in sensitivity analyses also considered deaths for natural and semisynthetic (T40.2), methadone (T40.3), other synthetic opioids (T40.4), and heroin (T40.1) separately. We aggregated the data by state and month using geocoded data and constructed rates per 100 000 residents.

We used state-level quarterly data on nonfatal opioid-related ED visits from the Agency for Healthcare Research and Quality's Healthcare Cost Utilization Project State Emergency Department Databases for 2005-2016. These data included ED visits that did not result in hospital admissions. Opioid-related ED visits were identified based on *International Classification of Diseases, Ninth Revision*, and *ICD-10* codes. There were 45 states participating in this survey during the period of our study, although they did not necessarily all report in each period.

Information on state naloxone access laws (NALs) was obtained from the Prescription Drug Abuse Policy Surveillance System as well as academic[16] and legal sources.[17,18] Naloxone access laws provide immunity from civil and/or criminal prosecution to prescribers, dispensers, and/or laypersons who administer naloxone to individuals who have overdosed on an opioid. Three policy indicators are constructed from these legal data: (1) an indicator if a state provides pharmacists with explicit permission to distribute naloxone either by providing them prescriptive authority or by explicitly allowing pharmacies to dispense naloxone without a prescription (direct

authority), (2) an indicator if a state indirectly provides pharmacists the ability to dispense naloxone either through a standing order (ie, a professional group authorizes general dispensing to people who meet specific criteria) or a statewide protocol/standing order issued by a state health official for all licensed pharmacists (indirect authority), and (3) an indicator if a state has passed any other type of naloxone law providing legal protections other than laws captured in the first 2 categories. We refer to the laws in this latter category as weak NALs.

The Prescription Drug Abuse Policy Surveillance system also contains information describing other state opioid policies that we included in our analysis, such as Good Samaritan laws, which provide further immunities from drug-related charges to individuals who report an opioid overdose, and Prescription Drug Monitoring Programs (PDMPs). For PDMPs, we included 2 measures in our analyses. The first is an indicator for when the state adopted any type of PDMP and the second is an indicator for when a state adopted a must-access PDMP, requiring prescribers to check the system before writing a prescription for a patient.[19]

In light of research suggesting an association with opioid mortality, we also included an indicator of whether the state had passed a medical marijuana law[20] and whether the state had an open dispensary that was legally protected.[21,22] Given our examination of naloxone distribution within Medicaid, we also included indicators for state expansions of Medicaid associated with the Affordable Care Act, starting with the 6 states that expanded early in 2010 and followed by several states in 2014 and after.

Statistical Analysis

We adopted a difference-in-differences strategy, controlling for national time effects (month or quarter) and state fixed effects by exploiting the longitudinal nature of the data. This approach assumes that adopting states would have followed the same trends as the nonadopting states if they had not passed the policies of interest. We estimated a linear specification using ordinary least squares, modeling the rate of opioid-involved deaths (and other outcomes) as a linear function of state fixed effects, year-month or year-quarter fixed effects, indicator variables related to NAL adoption for all 3 dimensions, and other covariates. These other covariates included an indicator for Good Samaritan law adoption, our 2 measures of medical marijuana laws, the 2 measures of state PDMPs, the state unemployment rate, population age shares (0-17, 18-34, 35-54, ≥65; 55-64 years served as the reference group) and Medicaid expansion indicators. Standard errors were adjusted for within-state dependence. All analyses were weighted by population.

We tested the parallel trends assumption, which is necessary for obtaining unbiased estimates using the difference-in-differences framework, through event study analyses, which is recommended when evaluating health policies.[23] In the event study specification, the temporal effects of the main policy variables (direct authority to dispense, indirect authority to dispense, and weak NALs) are estimated for 8 points in time relative to adoption of those policies. This approach permits us to test for preexisting trends in the outcome. Small and statistically nonsignificant estimates before adoption suggest that the parallel trends assumption was satisfied. We also estimated postadoption outcomes by year relative to passage of the law. This flexibility is important because we may expect these policies to have lagged results if implementation takes time or pharmacies responded with a lag. Although we had monthly or quarterly data, we estimated year-relative-to-adoption outcomes to improve the precision of the estimates. We defined first year post adoption as beginning in the first month (quarter) following the adoption of the policy.

Specifically, we included separate indicators equal to 1 for 4 or more years, 3 years, 2 years, and 1 year before adoption of the NALs. Each indicator is equal to 0 for nonadopters. We normalized all coefficients to 0 in the year of adoption, so this indicator was excluded. We also included separate indicators equal to 1 in the year after adoption, the second year post adoption, and 3 or more years post adoption. We estimated the 3 event studies (1 for each NAL dimension) jointly in the same specification, conditioning on the covariates and policy variables discussed above. We show these results graphically and include 95% CIs for each of the point estimates.

We considered statistical significance to be a 2-sided P value <.05. All analyses were conducted using Stata, version 14.2 (StataCorp).

Table 1. Number of States With NAL by Type, 2005-2016[a]

Year of Adoption	Any NAL	Weak NAL[b]	Indirect Authority[c]	Direct Authority[d]
2005	2	2	0	0
2006	3	3	0	0
2007	3	3	0	0
2008	4	4	0	0
2009	4	4	0	0
2010	6	5	1	0
2011	6	5	1	0
2012	8	7	1	0
2013	18	12	5	1
2014	28	10	15	3
2015	42	6	30	6
2016	47	0	38	9

Abbreviation: NAL, naloxone access law.

[a] Sources of data were Prescription Drug Abuse Policy Surveillance,[16] academic sources,[16] and legal sources.[17,18]

[b] Weak NAL indicates states with NALs but without providing indirect or direct authority to pharmacists.

[c] Statewide protocol or standing order.

[d] Dispensing without prescription or prescriptive authority.

Results

Although few states had any type of NAL before 2010, there has been rapid adoption since then (**Table 1**; eAppendix in the Supplement provides the dates that the bills were passed). Provisions granting indirect authority to pharmacists to distribute naloxone were uncommon until 2013, at which point 5 states had adopted policies that did so. This number increased to 15 states in 2014. State laws providing direct

Table 2. Summary Statistics for 2005-2016

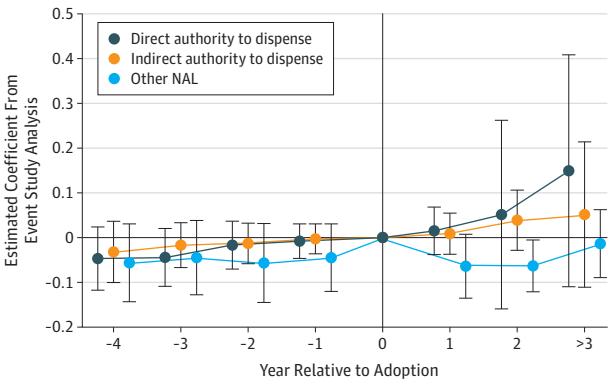
Variable	Mean (SD)[a]
Naloxone access laws (n = 7344)	
Weak, %[b]	16.2 (36.8)
Indirect authority (standing/protocol order), %	15.0 (35.7)
Direct authority, %	2.8 (16.4)
Economic conditions and other policies (n = 7344)	
Medicaid expansion, %	13.7 (34.3)
PDMP, %	84.7 (35.0)
Must access PDMP, %	6.1 (23.2)
Good Samaritan law, %	22.7 (41.9)
Medical marijuana law, %	30.8 (46.2)
Active and legal dispensaries, %	17.5 (38.0)
Unemployment rate	6.673 (2.263)
Monthly fatal overdoses per 100 000 people (n = 7344)	
Heroin	0.165 (0.190)
Natural/semisynthetic opioids	0.278 (0.197)
Methadone	0.116 (0.085)
Synthetic opioids	0.130 (0.225)
Opioids	0.469 (0.238)
Opioids or heroin	0.590 (0.387)
Quarterly nonfatal overdoses (n = 1920)	
ED visits per 100 000	198.3 (93.65)
Quarterly prescriptions (2010-2016, n = 1428)	
Medicaid naloxone prescriptions per 1000 beneficiaries	0.046 (0.128)

Abbreviations: ED, emergency department; PDMP, Prescription Drug Monitoring Programs.

[a] All means are population-weighted. Mean policy values refer to the percentage of population over the sample period subject to those policies.

[b] Naloxone access laws were considered weak in states with the policies but without providing indirect or direct authority.

Figure 1. Event Study Results of Naloxone Access Laws (NALs) on Naloxone Distribution, 2010-2016



Outcome was naloxone prescriptions per 1000 Medicaid beneficiaries. Vertical bars represent 95% CIs, adjusted for state-level clustering. All values in the figure were estimated jointly, along with state fixed effects, time fixed effects, and coefficients associated with policy variables and other covariates discussed in the text. Event study estimates were normalized to 0 in the year of adoption. Times to the left of zero refer to periods before adoption of NALs (−4 refers to periods ≥4 years before adoption); times to the right indicate periods after adoption of NALs (3+ refers to periods ≥3 years after adoption).

authority were even slower to emerge, with only 6 states granting these legal allowances by 2015 and 9 states by 2016.

Rates of monthly fatal overdoses were high between 2005 and 2016 (0.59 per 100 000 people each month), as were opioid-involved ED visits (mean [SD], 198.3 [93.65]) (**Table 2**). The quarterly rate of Medicaid prescribing of naloxone, however, was not substantial, with only 0.046 prescriptions per 100 000 beneficiaries over the shorter 2010-2016 period (Table 2).

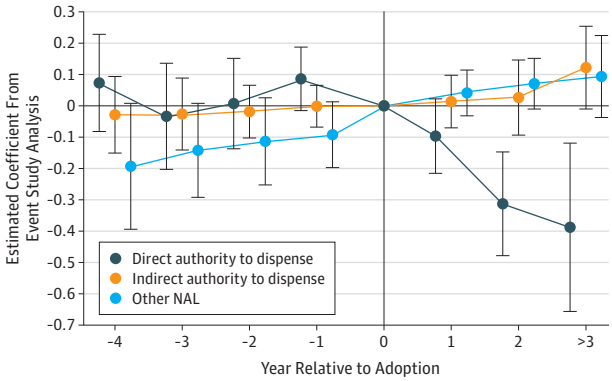
Results showing the association between NALs and naloxone prescribing among Medicaid patients are presented in **Figure 1** (full lists of coefficients and 95% CIs for all results are included in eAppendix in the Supplement). For the NALs providing indirect authority and weak NALs, there was little evidence of trend changes in naloxone prescribing after adoption. In contrast, states passing laws providing direct authority demonstrated an increase in the naloxone prescribing rate compared with the preadoption trend. We observed increases throughout the postadoption period. Although the association with direct authority was large, it was not statistically significant at the 5% level.

Figure 2 shows the coefficient estimates and 95% CIs of NAL policies on all opioid mortality, including heroin, both before and after policy adoption. For weak NAL laws and those providing indirect authority to pharmacists, we observed little evidence of a trend break at time of adoption or post adoption. There was little evidence of association for indirect authority to dispense (increase by 0.121; 95% CI, −0.014 to 0.257; P = .09) and other NALs (increase by 0.094, 95% CI, −0.040 to 0.227, P = .17).

We estimated reductions in opioid overdose fatalities related to NALs providing direct authority. There was no evidence of any preexisting trends in the event study results shown in Figure 2 for this dimension, as in 2012—the year prior to passage of any direct authority NALs—the future direct authority states had relatively similar annual overdose rates on average as the nonadopters. In the second full year after adoption, we estimated that direct-authority NALs were associated with 0.313 (95% CI, 0.148-0.478; P = .001) fewer opioid deaths per 100 000 people relative to the year before adoption. In the following years, we estimate even greater reductions, implying 0.387 (95% CI, 0.119-0.656; P = .007) fewer opioid deaths per 100 000 people. Relative to the mean number of opioid deaths in the 2016 states without direct-authority NALs (1.14 per 100 000 people), these estimated reductions imply decreases of 27% in the second postadoption year and 34% in subsequent years. We replicated our analysis separately for overdoses involving natural and semisynthetic opioids, heroin, methadone, and synthetic opioids. We found less evidence of association between direct-authority NALs and heroin or methadone overdoses, but the patterns for the other opioids were similar to those presented herein (eAppendix in the Supplement).

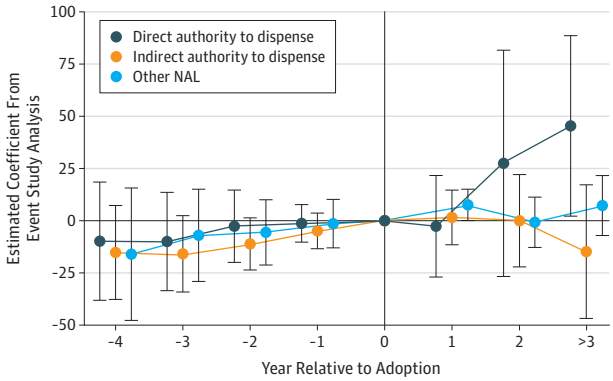
For nonfatal opioid-related ED visits, we found no evidence of meaningful trend breaks for weak NALs and those providing indirect authority to pharmacists (**Figure 3**). However, we estimated increases associated with NALs providing

Figure 2. Event Study Results for the Outcome of Naloxone Access Law (NAL) Policies on All Opioid Mortality, 2005-2016



Outcome was opioid-related fatal overdoses per 100 000 people. Vertical bars represent 95% CIs, adjusted for state-level clustering. All values in the figure were estimated jointly, along with state fixed effects, time fixed effects, and coefficients associated with policy variables and other covariates discussed in the Methods section. Event study estimates were normalized to 0 in the year of adoption. Times to the left of zero refer to periods before adoption of NALs (−4 refers to periods ≥4 years before adoption); times to the right indicate periods after adoption of NALs (3+ refers to periods ≥3 years after adoption).

Figure 3. Event Study Results for the Association Between Naloxone Access Law (NAL) Policies and Nonfatal Opioid Overdoses, 2005-2016



Outcome was opioid-related emergency department visits per 100 000 people. Vertical bars represent 95% CIs, adjusted for state-level clustering. All values in the figure were estimated jointly, along with state fixed effects, time fixed effects, and factors associated with policy variables and other covariates discussed in the Methods section. Event study estimates were normalized to 0 in the year of adoption. Times to the left of zero refer to periods before adoption of NALs (−4 refers to periods ≥4 years before adoption); times to the right indicate periods after adoption of NALs (3+ refers to periods ≥3 years after adoption).

direct authority. In 3 or more years post adoption, opioid-related ED visits per quarter increased by 45.446 (95% CI, 2.189-88.709; P = .045) per 100 000 people, representing a 15% increase compared with the mean in nonadopting states in 2016. This increase translates to approximately 15 more opioid-related ED visits per month.

Discussion

Our results suggest that naloxone laws providing direct authority to pharmacists may be associated with reductions in opioid-related mortality. Our results extend the findings of a few recent studies,[11-13] although these studies did not look specifically at direct-authority NALs. We found evidence that the outcomes of these laws grow in magnitude over time. The lagged results of the pharmacy access laws are not surprising since these policies take time before they are fully implemented in the real-world setting.[24] However, we found less evidence that other types of NALs matter, including standing orders. Most NALs providing indirect authority to prescribe and dispense naloxone, such as standing orders, provide limited immunity to pharmacists specifically. Standing orders also may apply to only certain settings—usually EDs[25]—suggesting that they should not have as widespread an association as direct-authority NALs, which affect pharmacy access. Our results are consistent with this fact.

We found suggestive complementary evidence of an increase in naloxone prescriptions among the Medicaid population. The noisiness of the estimated effects post policy adoption is likely driven by the relatively short period (2010-2016) and the limited population represented in the data. Given the high cost of naloxone,[26] suggestive evidence of an association with distribution for Medicaid is important since Medicaid is responsible for a large share of these high costs. The results are consistent with improved access to naloxone.

We also found evidence that ED visits for nonfatal overdoses increased, more so than the decline in fatal overdoses. While one might interpret this finding as evidence that naloxone access encourages opioid misuse by reducing the potential risks associated with an overdose, other plausible interpretations exist. For example, it may be that the same people present repeatedly to the ED with multiple nonfatal overdoses rather than more people using opioids. Alternatively, improvements in naloxone access may lead to a more supportive environment for seeking medical help for opioid-related poisonings or more education about overdoses, promoting medical care after near overdoses rather than resistance to naloxone. The ratio of the nonfatal overdose to the fatal overdose outcome was not significantly different from 1 so we cannot reject the null hypothesis that each saved life results in 1 additional ED visit.

These results highlight the importance of coupling naloxone laws with useful interventions and connections to treatment for patients seen in EDs for overdoses, as this is the location where such programs may be the most effective.

Limitations

Although this study provides what we believe to be some of the first evidence of the role of pharmacists in the distribution of naloxone and its association with opioid overdoses, there are some limitations. First, our dispensing data included only the Medicaid population, which is a limited proxy for overall changes in naloxone prescribing and may not reflect statewide changes in naloxone access for everyone. State

Drug Utilization Data information before 2010 does not include managed care organizations so we relied on a shorter timeframe for this outcome. Given concerns about the inclusion of managed care organizations in 2010, we replicated this analysis excluding 2010 and found similar results (eAppendix in the Supplement).

Second, we were limited by the number of states that had passed these laws during the study period. In addition, while we are interested in differences across naloxone policies, it is difficult to disentangle all dimensions of these policies. We studied variations of the policy that we believe are important based on the literature[6,25] and for which enough states have adopted to permit proper analysis. Third, our estimates should be interpreted as short-term outcomes given that these policies have primarily been adopted in recent years. Pharmacies may take time to institute these policies such that the long-term results differ from the short-term results.

Fourth, there is evidence that opioid-related mortality is not necessarily coded consistently across states and over time.[27] Our assumption is that passage of NALs is not correlated with changes in the accuracy of coding opioid deaths. Our event study framework pinpoints the timing of the outcome, so these changes would have to occur at the same time as adoption of direct-authority NALs but be uncorrelated with adoption of all other types of NALs. We consider such a coincidence unlikely. However, we also replicated the results presented in Figure 2 while using a correction discussed in the literature.[27,28] This correction imputes opioid involvement in cases in which the death certificate only indicates unspecified drugs (T50.9). The results from this analysis are presented in the eAppendix in the Supplement and are similar to the main estimates described in the article.

In addition, we cannot rule out that states passing NALs with prescriptive authority simultaneously improved substance abuse treatment access or passed other policies that reduced opioid-related overdoses. The timing of the outcomes suggests that any such improvements were adopted around the same time as the prescriptive authority law but were not adopted at the same time as other types of NALs. We have not found any such policies, but we cannot rule out the possibility. In the eAppendix in the Supplement, we report that our results are similar if we do not control for other policy variables, suggesting that other state-level policies did not affect our results. However, our main models controlled for only a small set of other policy variables.

Conclusions

Our research highlights the value of naloxone distribution as a tool in the fight against the rise in fatal opioid overdoses, but it also suggests that the type of policy is important for making the tool useful. Enabling distribution through various sources, or requiring gatekeepers, will not be as beneficial. We suggest that future work seeking to understand the value of these distribution policies consider the likely scope they could have when gatekeepers are removed.

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