Opioid Overdose Deaths and Florida's Crackdown on Pill Mills

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Objectives. We examined the effect on opioid overdose mortality of Florida state laws and law enforcement operations targeting "pill mills."

Methods. We collected 2003 to 2012 mortality data from the Florida Department of Health and the North Carolina State Center for Health Statistics (the comparison state) to estimate changes in the rates of death from prescription opioid, heroin, or any opioid overdose.

Results. Florida's actions were associated with an estimated 1029 lives saved from prescription opioid overdose over a 34-month period. Estimated reductions in deaths grew over the intervention period, with rates per 100 000 population that were 0.6 lower in 2010, 1.8 lower in 2011, and 3.0 lower in 2012 than what would have been expected had the changes in mortality rate trends in Florida been the same as changes in trends in North Carolina. Florida's mortality rates from heroin and total opioid overdose were also lower than anticipated relative to changes in trends in North Carolina.

Conclusions. Findings from this study indicate that laws regulating pain clinics and enforcement of these laws may, in combination, reduce opioid overdose deaths. (*Am J Public Health.* 2016;106:291–297. doi:10.2105/AJPH.2015.302953)

See also Galea and Vaughan, p. 201.

From 2003 to 2010, Florida experienced a proliferation of "pill mills," a category that includes physicians, pain clinics, and other providers that dispense large quantities of prescription drugs, typically for cash only, outside the scope of standard medical practice.[1] These pill mills initially operated with limited state oversight.[2,3] By 2010, 90 of the 100 doctors purchasing the most oxycodone nationwide were practicing in Florida.[4] Accompanying increases in pill mills and opioid prescribing was a rapid rise in mortality from prescription opioid overdoses in Florida.[3,5]

Florida adopted several measures to rein in the negligent practices of pill mills. These included 2 new state laws in 2010 and 2011, which substantially restricted prescribers' ability to dispense opioids at the site of care, and law enforcement initiatives during 2010 and 2012, which led to the arrest and prosecution of persons operating the pill mills violating these new laws.

Since 2010, Florida has experienced substantial reductions in oxycodone-purchasing physicians,[6] opioid prescribing,[7] and prescription drug diversion.[8] A descriptive study by the Centers for Disease Control and Prevention showed dramatic reductions in overdose deaths following Florida's policy changes. However, that study did not use a comparison group or employ statistical techniques to account for potential confounding factors or secular trends.[5] We addressed this gap by using a quasi-experimental study design and rigorous analytic techniques to estimate the cumulative effect of these laws and enforcement activities on Florida's mortality rates from prescription opioid, heroin, and total opioid overdose. We estimated these effects under assumptions about the counterfactual—that is, what would have occurred in the absence of these interventions.

We hypothesized that Florida's interventions directed at pill mills would be associated with a decrease in mortality from prescription opioid overdose. The implications of restrictions on prescription opioid supply for heroin overdose risk are uncertain. Most new heroin users first used prescription opioids.[9] Although some individuals with problematic prescription opioid use will respond to reduced availability of prescription opioids by substituting with heroin,[10] if fewer individuals become addicted to prescription opioids because of limited supply, fewer also will be vulnerable to heroin use and overdose. Given the lower baseline rate of deaths from heroin than from prescription opioids, we hypothesized that Florida's actions would be associated with a reduction in the total opioid (i.e., prescription opioid and heroin) overdose death rate.

METHODS

We assessed the overall effect of the combination of Florida's interventions targeting pill mills on opioid overdose deaths. The first significant action was an initiative led by the US Drug Enforcement Agency (DEA) in late February 2010, dubbed Operation Oxy Alley. It resulted in the arrest of 32 pill mill owners, doctors, and other staff associated with clinics that were some of the largest dispensers of oxycodone in the country at that time.[11] The DEA also coordinated Operation Pill Nation, with major activities taking place

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in February 2011 and August 2012. It yielded the arrest of 47 pill mill owners, physicians, and other staff, $18.9 million in asset seizures, and the suspension of 92 DEA registrations.[2,12]

In October 2010, a new state law went into effect in Florida that required pain clinics to identify a licensed physician as responsible for clinic operations, limited dispensing of opioids to a 72-hour supply for a patient, and prohibited advertising of controlled substances.[13] A second law, which took effect in July 2011, was more robust: it prohibited physicians from dispensing most narcotic medications on-site and increased criminal penalties for doctors and clinics involved in drug diversion.[14]

Study Design and Data

North Carolina served as a comparison state for Florida in our analyses because, for most of the preintervention period, North Carolina experienced similar trends in mortality rates from prescription opioid overdose. During the period in which Florida was implementing its interventions, North Carolina passed no new laws regulating pain clinics or restricting physician dispensing of prescription opioids.[15] In addition, both states are in the southeastern region of the United States and have similar poverty levels and median household incomes.[16]

We collected 2003 to 2012 mortality data from the Florida Department of Health and the North Carolina State Center for Health Statistics. We identified opioid deaths as poisoning deaths according to *International Classification of Diseases, 10th Revision* (*ICD-10*)[17] codes for external cause of injury (codes X40–X44, X60–X64, X85, and Y10–Y14) and underlying cause of death (codes T40.0 [opium], T40.1 [heroin], T40.2 [other opioids], T40.3 [methadone], and T40.4 [synthetic narcotic]).[18,19]

Measures

The 3 dependent variables were the monthly rates of overdose death from (1) prescription opioid, (2) heroin, and (3) any opioid (prescription opioid, heroin, or both). Model predictors included measures for month, state, and a month–state interaction. We also tested models that controlled for state unemployment rates, but found that including this variable did not improve model fit; other research has not shown a significant association between state unemployment rates and mortality rates from opioid overdose.[20] We defined March 2010 as the beginning of the intervention period because Florida's first DEA crackdown took place at the end of the prior month, February.

Analytic Approach

We used multivariate adaptive regression spline (MARS) models to estimate trends in the outcomes in the 2 states. Although the states' trends in their mortality rates for prescription opioid overdose tracked each other closely during most of the preintervention period, during the 16 months preceding the initiation of Florida's policy changes, the rate of increase of North Carolina's mortality rate from prescription opioid overdose slowed, whereas Florida's rates continued to ascend rapidly. These divergent trends in the study groups just prior to the intervention period violate a key assumption of standard interrupted time-series models incorporating nonintervention control groups—namely, that the trends are approximately equal prior to the treatment period. Because a parametric model did not fit these complex time trends well, we used the MARS model to compare the observed outcomes in Florida with the trend for the predicted counterfactual, in which we estimated what would have happened in Florida in the absence of the interventions. The predicted counterfactual was informed by changes in North Carolina's trends in mortality rates from opioid overdose.

MARS models fit flexible, continuous, piece-wise linear functions to the data, identifying change or "hinge" points simultaneously with slopes.[21] Model identification of these change points and slopes simultaneously minimizes the residual sum of squares error for the study sample; cross-validation prevents overfitting of the data. We used the earth package[22] in R (R Foundation for Statistical Computing, Vienna, Austria) to implement these models.

Change points identified in MARS models delineate differences in the fitted slopes. Although these change points can be interpreted as indicating statistically significant changes in the trend, MARS models do not produce standard errors or *P* values to accompany the coefficient estimates. Therefore, we used bootstrapping to produce estimates of the uncertainty surrounding the fitted slopes and estimates of the interventions' effects.[23] We bootstrapped the data on individual deaths to produce variations in aggregate month–state units. To preserve the original MARS change point structure, we fixed the change point locations at those estimated with the original data and allowed the slopes to vary in each bootstrap iteration.

We predicted what Florida's mortality rates from prescription opioid overdose would have been absent the state's interventions, based on the MARS fitted slopes and change points for North Carolina. The counterfactual's point of departure from the observed trends in the mortality rate for prescription opioid overdose occurs at the change point that the MARS model identified as most proximate to the intervention period and the point at which the largest change occurred in Florida's trends in mortality rates from prescription opioid overdose.

To estimate the counterfactual, we assumed that the shift in the rate of monthly change (i.e., magnitude of change in the slope) in Florida's mortality rates from prescription opioid overdose at the change point identified near the beginning of the intervention period would have been the same as the shift in the slope of North Carolina's rates at that time. This means that, at this critical change point, we assumed that Florida would have experienced a change in slope equal to the change in slope for North Carolina, an approach that is consistent with traditional difference-in-difference estimation of intervention effects on slopes. We estimated the effects of Florida's interventions by calculating the differences between the mortality rates predicted in this counterfactual and Florida's actual rates during the intervention period. We did not generate independent effect estimates for the individual components of Florida's intervention (e.g., new state laws or DEA operations) because the MARS models did not identify significant change points in Florida's trends in mortality rates from prescription opioid overdose later during the intervention period.

We applied a similar approach to estimate the cumulative effect of Florida's interventions on mortality rates for total opioid overdose. For this outcome, the MARS model identified 2 key change points during the intervention period (at April and November 2010); we identified the second change point in North Carolina's trends only. We predicted the counterfactual by applying the same magnitude of change that occurred in North Carolina's trends at these change points to estimate the shifts in Florida's trends in the mortality rate for total opioid overdose that would have occurred if the interventions had not been implemented.

We also conducted 2 sensitivity analyses under more conservative assumptions about the counterfactual. In the first sensitivity analysis, we assumed that there would have been no change (slope = 0) in Florida's mortality rates from prescription opioid and total opioid overdose following the critical change points identified by the MARS models. In the second sensitivity analysis, we assumed that Florida's slope for each outcome would have mirrored that of North Carolina after the critical change points.

Because Florida's and North Carolina's trends in heroin overdose death rates differed during much of the preintervention period, we did not use North Carolina's postintervention trends to estimate intervention effects as we did for the other 2 outcomes explored in this study. Rather, we plotted the separate MARS models estimating Florida's and North Carolina's heroin overdose death rates and assessed the implications of these differences in trends.

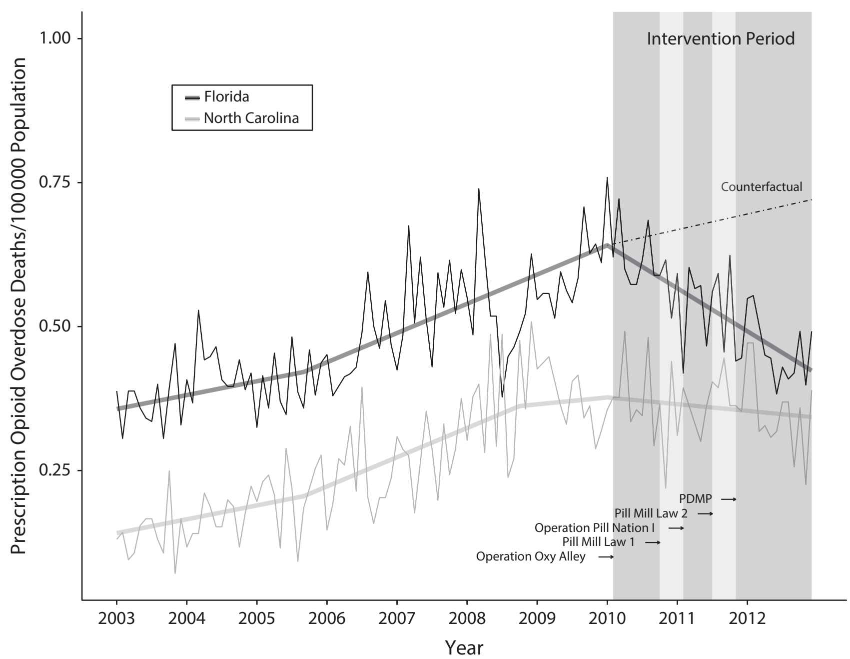
RESULTS

Table A (available as a supplement to the online version of this article at http://www.ajph.org) displays the characteristics of individuals dying from opioid overdoses in the 2 states during the period 2003 through 2012. The large majority of opioid overdose deaths were attributable solely to prescription opioids (91.6% in Florida, 82.2% in North Carolina). In Florida, a smaller proportion of all opioid overdose deaths during this period were attributable solely to heroin compared with North Carolina (7.2% vs 16.0%).

Mortality From Prescription Opioid Overdose

Figure 1 displays the plotted MARS model estimates of the mortality rates for prescription opioid overdose in both states as well as the counterfactual prediction. The model identified the key change point in both states at January 2010, immediately before Florida began its crackdown on pill mills. Although this change point was identified the month before Florida began implementing its interventions, the MARS model would not have identified this change point if not for the sustained downward trajectory of this outcome through the end of the study period. Florida's prescription opioid overdose mortality rates per 100 000 population were increasing by 0.004 per month prior to this change point, at which point Florida's rates began falling by −0.006 per month, a steep rate of decline sustained through the end of the study period. The trend in Florida's mortality rates for prescription opioid overdose shifted downward by −0.010 (95% confidence interval [CI] = −0.012, −0.009) at this January 2010 change point, the largest shift associated with any of the change points identified in Florida's trends.

Table 1 displays the estimated differences between the mortality rates for prescription opioid overdose predicted by the counterfactual and the observed mortality rates in Florida during the intervention period. We estimated 1029 fewer deaths in Florida from prescription opioid overdoses associated with the intervention period. The estimated reduction in death rates grew over time, with death rates from prescription opioid overdose per 100 000 population that were 0.5 lower for 2010 (95% CI = −0.8, −0.3), 1.8 lower in 2011 (95% CI = −2.5, −0.9), and 3.0 lower in 2012 (95% CI = −4.3, −1.6). These reductions represent declines of 7.4% in 2010, 20.1% in 2011, and 34.5% in 2012. Under the counterfactual scenarios estimated in our sensitivity analyses (Figure A and Table B, available as a supplement to the online version of this article at http://www.ajph.org), we estimated similar patterns of increasing



Note. PDMP = prescription drug monitoring program. The figure overlays the fitted multivariate adaptive regression spline (MARS) model on the observed prescription opioid overdose mortality rates in Florida and North Carolina. Under the counterfactual, we assumed that the rate of change in Florida's prescription opioid overdose mortality rates would have changed by the same amount that North Carolina's slope changed at the change point most proximate to the intervention period (January 2010). Note that the year labels indicate the start of each year (January) rather than the midpoint of each year.

FIGURE 1—Changes in Prescription Opioid Overdose Mortality Rates: Florida and North Carolina, 2003–2012

TABLE 1—Trends in Mortality Rates From Prescription Opioid and Total Opioid Overdose and Estimated Number of Lives Saved by Interventions: Florida, March 2010–December 2012

	Reduction in Mortality Rate[a] (95% CI)	No. of Lives Saved (95% CI)	% Change in Overdose Mortality Rate
Estimated changes in prescription opioid overdose mortality			
Mar[b]–Dec 2010	−0.55 (−0.79, −0.29)	104 (54, 149)	−7.4
Jan–Dec 2011	−1.79 (−2.55, −0.93)	342 (177, 487)	−20.1
Jan–Dec 2012	−3.02 (−4.31, −1.57)	583 (302, 832)	−34.5
Estimated changes in total opioid overdose mortality			
Mar–Dec 2010	−0.02 (−0.02, −0.01)	3 (2, 4)	−0.3
Jan–Dec 2011	−1.49 (−1.95, −1.07)	284 (205, 373)	−18.2
Jan–Dec 2012	−3.87 (−5.08, −2.79)	747 (539, 981)	−40.1

Note. CI = confidence interval. Changes in mortality trends in North Carolina were used as a comparison.

[a]Deaths per 100 000 population.

[b]The intervention period begins at March 2010, the month after the first major US Drug Enforcement Agency crackdown on pill mills, Operation Oxy Alley. We only estimate differences in mortality rates predicted by the counterfactual (based on changes in North Carolina's trends) and Florida's observed data during this period (March 2010–December 2012).

reductions in death rates throughout the intervention period, although the magnitudes were lower than in the main analysis.

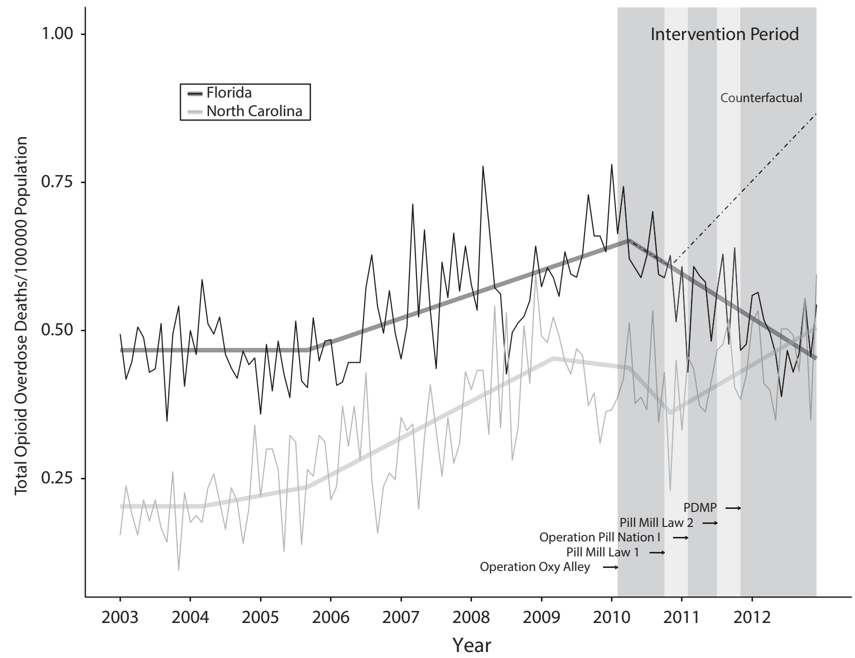
Mortality From Total Opioid Overdose

Figure 2 displays the plotted MARS model estimates for the mortality rate for total opioid overdose and the counterfactual prediction. The change point associated with the largest shift in the trend in mortality rates for total opioid overdose during the study period was at April 2010 in Florida and North Carolina, at which point both states' slopes changed by –0.011 (95% CI = –0.012, –0.009). At the second change point at November 2010, North Carolina's slope reversed course and began an upward trajectory.

We estimated that Florida's interventions were associated with a cumulative 1034 fewer deaths from any opioid overdose (Table 1). After minimal changes in 2010 (–0.3% difference), we estimated 1.5 fewer opioid overdose deaths per 100 000 population in 2011 (95% CI = –1.9, –1.1) and 3.9 fewer deaths per 100 000 in 2012 (95% CI = –5.1, –2.8). These estimates represent rate reductions of 18.2% in 2011 and 40.1% in 2012. Our sensitivity analyses estimated less substantial, but still large, reductions in the mortality rates for total opioid overdose (Figure B and Table B, available as a supplement to the online version of this article at http://www.ajph.org).

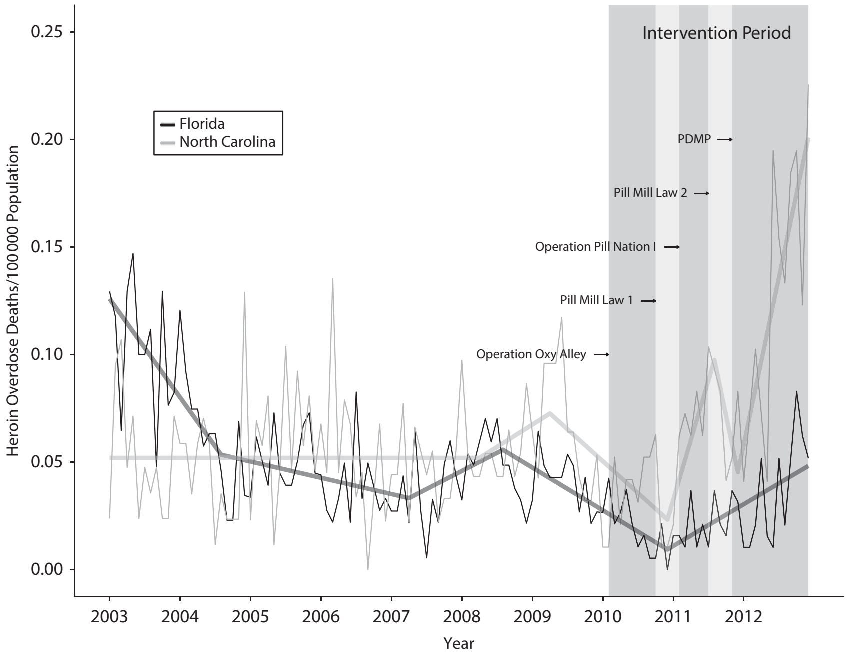
Mortality From Heroin Overdose

Figure 3 displays the changes in the mortality rates for heroin overdose in Florida and North Carolina during the period 2003 through 2012. Mortality rates for heroin overdose rose sharply in each state at the beginning of 2011. During the first half of 2011, North Carolina's rate of heroin



Note. PDMP = prescription drug monitoring program. The figure overlays the fitted multivariate adaptive regression spline (MARS) model on the observed total opioid overdose mortality rates in Florida and North Carolina. Under the counterfactual, we assumed that the rate of change in Florida's prescription opioid overdose mortality rates would have changed by the same amount that North Carolina's slope changed at the change points during the intervention period (April and November 2010). Note that the year labels indicate the start of each year (January) rather than the midpoint of each year.

FIGURE 2—Changes in Total Opioid Overdose Mortality Rates: Florida and North Carolina, 2003–2012



Note. PDMP = prescription drug monitoring program. The figure overlays the fitted multivariate adaptive regression spline (MARS) models for Florida and North Carolina's heroin overdose mortality rates on the observed data. The MARS models identified 3 change points during the intervention period (March 2010–December 2012): December 2010, August 2011, and December 2011; the latter 2 change points occurred in North Carolina only. Note that the year labels indicate the start of each year (January) rather than the midpoint of each year.

FIGURE 3—Changes in Heroin Overdose Mortality Rates: Florida and North Carolina, 2003–2012

overdose deaths increased by an average of 18% per month, compared with an average increase of 8% each month in Florida. Although fluctuating, the increase in North Carolina's mortality rates from heroin overdose rose more than fourfold from early 2011 to late 2012, well above the state's mean rate during the study period. By contrast, Florida's increase in mortality rates from heroin overdose during this period was substantially less: by late 2012, the state's death rate from heroin overdose had leveled off to near its mean for the study period. During 2012, North Carolina's heroin overdose mortality rates increased by about 10% each month (monthly increase of 0.013 per 100 000) whereas Florida's increased by approximately 6% per month (monthly increase of 0.002 per 100 000).

DISCUSSION

Previous results from descriptive research have suggested that interventions in Florida targeting harmful prescribing and dispensing practices for prescription opioids produced life-saving benefits.[5] This study used a comparison state and statistical methods appropriate for analyzing complex trend data to estimate the impact of policies implemented in Florida on mortality from opioid overdoses. Even using conservative assumptions about what would have happened to opioid overdose mortality rates in Florida had the state not implemented significant legislative changes and law enforcement operations targeting pill mills, we estimated large declines in the rates of mortality from prescription opioid overdose associated with the intervention period. These declines were substantial and grew over the period 2010 through 2012.

There is evidence that, in the current epidemic of opioid overdose deaths, some individuals addicted to prescription opioids transition to heroin.[24,25] Some have inferred from this shift that supply-side interventions to reduce prescription opioid misuse are likely to be ineffective in stemming the tide of deaths from opioid overdoses because individuals addicted to these drugs will substitute prescription opioids with heroin.[10,26,27] On the basis of our finding that the initiation of Florida's interventions was associated with minimal reductions in mortality rates for total opioid overdose in 2010, substitution from opioid medications to heroin may have occurred initially, following the crackdown on pill mills. However, given our estimates of large reductions in mortality rates for total opioid overdose in 2011 and 2012—after the second major DEA enforcement operation and the more stringent 2011 state law restricting prescriber dispensing of opioids—our data contradict the claim that supply-side interventions for prescription opioids are ineffective.

If the statutory restrictions and law enforcement operations targeting pill mills in Florida simply shifted people with an addiction from prescription opioids to heroin, there should have been little net change in opioid overdose deaths in Florida and a more prominent shift from prescription opioids to heroin in Florida relative to North Carolina. Yet we estimate that the combined interventions in Florida were associated with 1034 fewer deaths attributable to overdoses from any opioid during a 34-month period—very similar to the estimated number of deaths prevented from prescription opioids—with these reductions growing over time. Furthermore, increases in heroin overdose mortality in Florida were less than one fourth as large as the increases observed in North Carolina, where there were no major state-specific supply-side actions during the intervention period and lower baseline mortality rates for prescription opioid overdoses. Florida's increase in mortality rates from heroin overdose during the 2010 to 2012 period was also less than that of the average southern state (181%).[28] In 2012, Florida's heroin overdose rates were within the state's norm for the 10-year study period, whereas North Carolina's 2012 heroin overdose rates reached unusually high levels.

By strengthening the regulation of pill mills and by targeting providers whose practices contributed to prescription opioid misuse, Florida may have prevented overdose deaths from heroin as well as from prescription opioids. If the interventions prevented new cases of prescription opioid addiction, fewer individuals would be at heightened risk for heroin overdose. More research is needed to identify the pathways by which some prescription opioid users transition to heroin, and to evaluate how restrictions on prescription opioid access and supply affect heroin overdose risk—both for current users of prescription opioids and those not currently using prescription opioids but at potential risk if in environments with large quantities of easily accessible opioid medications.

Limitations

This study had several limitations. First, we were unable to parse out the unique effects of each of Florida's new laws strengthening oversight of opioid prescribers and dispensers and law enforcement crackdowns on overdose deaths. Although we cannot determine whether regulation without substantial enforcement would have been effective in reducing death rates, we suspect that the synergistic combination of these efforts contributed to the sustained declines in opioid overdose deaths in Florida. Second, we did not account for all local and national interventions that may have influenced opioid overdose deaths. For instance, North Carolina's Project Lazarus, an overdose prevention program,[29,30] may have biased our findings very slightly toward the null hypothesis, but it was implemented in only one sparsely populated county. Other interventions occurring at the national level (e.g., introduction of abuse-deterrent OxyContin, changes in prescribing practices) likely would not have affected the states differentially. Although Florida implemented a prescription drug monitoring program during our intervention period, we suspect that the reductions in opioid overdose mortality rates may be related more to Florida's activities targeting pill mills. Research has not shown prescription drug monitoring programs to be associated with lower mortality from opioid overdose.[20,31]

Third, we used only one comparison state to produce our estimates of the counterfactual. However, North Carolina was the most appropriate candidate given the similarity of long-term trends in mortality rates from opioid overdose during most of the preintervention period. Fourth, we assessed mortality rates from opioid overdose only through 2012. It is unclear if the effects of Florida's interventions were sustained beyond the study period. Fifth, we could not account for the potential displacement effects of the interventions on individuals addicted to prescription opioids, some of whom may have responded to new restrictions on access by traveling to other states, where they could have overdosed. Alternatively, other states may have seen declines in overdose deaths not measured by this study among residents who had been traveling to Florida pill mills. These limitations suggest important areas for future research.

Finally, the MARS model we estimated for mortality rates from prescription opioid overdose identified the change point associated with the largest shift in trends in Florida at January 2010, slightly preceding the start of Florida's interventions. It is possible that the model's identification of this change point immediately prior to the initiation of Florida's interventions targeting pill mills is a sign of omitted variable bias. We cannot explain the unexpectedly falling mortality rates from prescription opioid overdose predicted by the model in the first 2 months of 2010. Given the large sustained and increasing effects estimated by our models during the 34 months of the intervention period, however, the most likely explanation for the decline in deaths is Florida's statutory changes and law enforcement crackdowns.

Conclusions

Opioid overdose is a complex problem requiring multifaceted solutions. In addition to targeting pill mills, other interventions, such as broader naloxone distribution and expanded addiction treatment services, may reduce overdose deaths.[30,32,33] Our analyses indicate that Florida's actions targeting pill mills were associated with significant declines in mortality rates for prescription opioid and total opioid overdose during the period of implementation. These declines grew over time as additional interventions were adopted to address inappropriate prescribing and dispensing practices. During this time, Florida passed 2 laws regulating pill mills and enforced those laws, prosecuting pill mill operators and physicians operating outside the bounds of standard medical practice. Our study suggests that this approach was associated with a major decline in opioid overdose mortality, potentially saving around 1000 lives during the 34-month period of March 2010 through December 2012. In addition, our findings suggest that actions to reduce prescription opioid misuse may reduce heroin overdose deaths in the long term. Future research should assess whether these trends have continued since the end of our study period and examine the interrelationship between policies targeting prescription opioid misuse and heroin use and overdose. AJPH

CONTRIBUTORS

A. Kennedy-Hendricks helped to design the study, oversaw the statistical analyses, interpreted findings, and drafted the article. M. Richey helped to design the study, conducted the statistical analyses, interpreted findings, and provided critical review of the article. E. E. McGinty and D. W. Webster conceptualized and designed the study, oversaw the data collection and statistical analyses, interpreted findings, and provided critical review of the article. E. A. Stuart and C. L. Barry helped to conceptualize the study, oversaw the statistical analyses, interpreted findings, and provided critical review of the article. All authors approved the final version submitted for publication and have agreed to be responsible for the integrity of the research.

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HUMAN PARTICIPANT PROTECTION

This study was approved by the institutional review boards of the Johns Hopkins Bloomberg School of Public Health and deemed not to be human participant research.

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