Received: 25 May 2017 | Revised: 10 January 2018 | Accepted: 18 January 2018

DOI: 10.1002/pds.4404

ORIGINAL REPORT

WILEY

Impact of Florida's prescription drug monitoring program and pill mill law on high-risk patients: A comparative interrupted time series analysis

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Funding information
Centers for Disease Control and Prevention, Grant/Award Number: U01CE002499; Robert Wood Johnson Foundation, Grant/Award Number: U01CE002499

Abstract

Purpose: We quantified the effects of Florida's prescription drug monitoring program and pill mill law on high-risk patients.

Methods: We used QuintilesIMS LRx Lifelink data to identify patients receiving prescription opioids in Florida (intervention state, N: 1.13 million) and Georgia (control state, N: 0.54 million). The preintervention, intervention, and postintervention periods were July 2010 to June 2011, July 2011 to September 2011, and October 2011 to September 2012. We identified 3 types of high-risk patients: (1) concomitant users: patients with concomitant use of benzodiazepines and opioids; (2) chronic users: long-term, high-dose, opioid users; and (3) opioid shoppers: patients receiving opioids from multiple sources. We compared changes in opioid prescriptions between Florida and Georgia before and after policy implementation among high-risk/low-risk patients. Our monthly measures included (1) average morphine milligram equivalent per transaction, (2) total opioid volume across all prescriptions, (3) average days supplied per transaction, and (4) total number of opioid prescriptions dispensed.

Results: Among opioid-receiving individuals in Florida, 6.62% were concomitant users, 1.96% were chronic users, and 0.46% were opioid shoppers. Following policy implementation, Florida's high-risk patients experienced relative reductions in morphine milligram equivalent (opioid shoppers: −1.08 mg/month, 95% confidence interval [CI] −1.62 to −0.54), total opioid volume (chronic users: −4.58 kg/month, CI −5.41 to −3.76), and number of dispensed opioid prescriptions (concomitant users: −640 prescriptions/month, CI −950 to −340). Low-risk patients generally did not experience statistically significantly relative reductions.

Conclusions: Compared with Georgia, Florida's prescription drug monitoring program and pill mill law were associated with large relative reductions in prescription opioid utilization among high-risk patients.

KEYWORDS

chronic opioid users, concomitant users of benzodiazepines and opioids, long-term opioid therapy, opioid shoppers, pharmacoepidemiology, pill mill law, prescription drug abuse, prescription drug monitoring program, time series analysis

1 | INTRODUCTION

Injuries and deaths from opioids have soared over the past 2 decades.[1-5] In 2016, an estimated 64,000 Americans died from drug overdoses, with most succumbing to prescription opioids, heroin, or illicit fentanyl.[6] The epidemic has also manifest in various ways, ranging from strains on the foster system[7] and large increases in neonatal abstinence syndrome[8] to local outbreaks of HIV and hepatitis C.[9]

The epidemic is so far-reaching that drug overdoses are now 1 of the leading causes of death among Americans under 50 years of age,[10,11] despite evidence suggesting the prevalence of pain has not substantially changed.[12,13]

Many policies have been developed to address opioid-related morbidity and mortality.[14-18] In the United States, states have increasingly implemented prescription drug monitoring programs (PDMPs) and "pill mill" laws.[16,17,19,20] Prescription drug monitoring programs are databases that aggregate information about individuals' controlled substance prescribing history; they can be queried by health-care providers and certain stakeholders.[17,21,22] In contrast, pill mill laws establish regulatory oversight of pain management clinics—such as creating penalties for those who do not comply with state registration, ownership requirements, or limitations on physician dispensing—to mitigate problematic prescribing practices such as cash-for-pill exchanges.[23]

Many studies suggest that these policies can reduce prescription opioid utilization[16,20,24,25] and deaths.[26] However, some studies fail to identify such impact.[27-30] Primarily focused on Florida given its role as an epicenter of nonmedical prescription opioid use, our work found that Florida's PDMP and pill mill law were associated with modest declines in overall opioid sales[20] and that these declines were concentrated among the highest prescribing physicians.[25]

Previous studies do not answer how policies may affect patients at differing levels of risk of addiction and death. Not all opioid users have identical likelihood of experiencing morbidity or mortality, and clinical characteristics of patients, such as their combined use of benzodiazepines and opioids, or long-term high-dose opioid use, have been consistently associated with a substantially elevated risk.[31-35] In this study, we sought to (1) describe the characteristics of high-risk patients and their counterparts in Florida and (2) compare opioid utilization in Florida with Georgia to quantify the effect of Florida's PDMP and pill mill law on their opioid utilization by patients' risk status.

KEY POINTS

- Among 1.1 million patients filling a prescription opioid in Florida prior to policy implementation, 6.6% were concomitant users, 2.0% were chronic users, and 0.5% were opioid shoppers.
- The concentration of total opioid prescriptions among high-risk patients decreased by approximately 17% from the prepolicy to the postpolicy period.
- Compared with Georgia, Florida's prescription drug monitoring program and pill mill law were associated with large relative reductions in prescription opioid utilization among 3 high-risk opioid groups.
- There were generally no statistically significant policy effects on nonhigh-risk patients.

2 | METHODS

2.1 | Data

We used QuintilesIMS LifeLink Longitudinal Prescription (LRx) data, which consists of anonymized, individual-level prescription drug dispensing data. The database includes payer, patient, and prescriber information derived from approximately 75% of all retail prescription transactions in the United States. Each transaction record includes the National Drug Code, quantity dispensed, days supplied, quantity dispensed, zip code of the dispensing pharmacy, encrypted prescriber identifiers, patient sex, and date of birth.

2.2 | Time segments and group derivation

We included a 12-month pre- and postintervention observation period. The preintervention period was from July 2010 to June 2011. The policy implementation period extended from July 2011 (pill mill law) to September 2011 (PDMP). The postintervention period ranged from October 2011 through September 2012.

We identified approximately 2.76 million individuals who (1) lived in Florida or Georgia, (2) had at least 1 pharmacy claim each within the first and last 3 months of the study period, and (3) filled prescriptions from stores reporting data to QuintilesIMS within the first and last 3 months. After excluding records outside of the study period and records with missing state of prescriber, 2.65 million patients remained. We further restricted to patients with at least 1 nonextreme opioid prescription (not among top 1% prescriptions in morphine milligram equivalents [MMEs], days supplied, or quantities dispensed) during the pre- or postimplementation periods. A total of 1.67 million patients reflecting about 12 million opioid prescriptions were included in our study (Florida/Georgia: 1.13/0.54 million patients).

We defined 3 types of patients at elevated risks of adverse events.[36] First, we defined "concomitant users" as patients filling more than 30 days (not necessarily continuous) of concomitant opioids and benzodiazepines in a year. The coadministration of benzodiazepines and opioids may lead to more adverse events, with benzodiazepines associated with ~30% of overdose deaths involving prescription opioids.[34,35] Second, we defined "chronic users" as those consuming more than 100 MMEs per day for more than 90 consecutive days, as there is a strong dose-response association between the opioid dose and the overdose death risk.[31,33] Finally, we defined "opioid shoppers" as patients visiting >3 pharmacies and >3 prescribers to acquire opioids during any 90-day period because using multiple concurrent prescribers and pharmacies is related to a 600% increase in opioid overdose.[37,38] Patients not meeting the criterion were considered "low-risk" by the definition. These 3 groups were not mutually exclusive. Total prescriptions were not used as a measure of high-risk as they do not account for product or dose.

2.3 | Outcomes

We examined 4 outcomes, derived on a monthly basis and summarized by risk group and state. First, we calculated the average MME per transaction. Risk of opioid-related morbidity and mortality increases

as MME per transaction increases.[39] Second, we computed total opioid volume across all prescriptions by using MMEs. This measure standardizes opioid prescriptions by accounting for differences in molecules, quantity, and strength of doses.[35,40] Third, we quantified average days supplied per transaction given many opioids are ultimately diverted.[41,42] Fourth, we examined the total number of opioid prescriptions dispensed.

We also examined the overlap of 3 high-risk groups (concomitant users, chronic users, and opioid shoppers) and the degree to which total opioid volume was concentrated within these groups. In addition, we compared the prevalence of 3 high-risk groups between 2 states.

2.4 | Analysis

We first described the characteristics of high-risk patients, including age, sex, prevalence, and overlap with other high-risk groups; persistence from the pre- to postperiod; and chronic disease score. The chronic disease score, using pharmacy claims only, is a validated measure of morbidity and has been linked to patient's health status, expenditures, and death.[43,44] We used a χ^2 test to examine whether being a high-risk patient by 1 definition in the preintervention period was more likely to (1) be a high-risk patient by another definition in the preintervention period and (2) be a high-risk patient by all 3 definitions in the postintervention period.

We used a comparative interrupted time series approach to quantify the impact of Florida's laws on our outcomes while accounting for secular trends as well as the autocorrelated nature of the data.[20,25,45-47] We used Georgia as a control state because of its geographical proximity, the absence of similar policy implementation during the study period, and its similarity in baseline opioid utilization trends (of note, Georgia's PDMP became operational in 2013).

Our unit of analysis was a monthly measure derived by aggregating all of the transactions associated with a specific group in a given state during that month. For example, we aggregated all transactions that occurred in December 2011 from all concomitant users who resided in Florida to obtain total opioid volume of concomitant users in Florida in December 2011. We had 25 observations for each outcome and patient subgroup in each state: 12 observations each in the pre- and postimplementation period and 1 aggregate observation from the 3 policy-intervention months. We used linear regression to evaluate the comparative changes in the outcomes of the interest before and after the implementation of Florida's PDMP and pill mill legislation. We included a state indicator (FL or GA) in the model, a period indicator (pre or post), a month indicator, a postintervention month indicator, an interaction term of the state and month, and 2 additional interaction terms. The first interaction term was the interaction between the state and period indicator which reflected the effect of the policies on the level of the outcome. The second was the interaction between state and postintervention month indicator, which represented the effect of the policies on the rate of change (trend). Six models were executed for each outcome (1 for each patient subgroup). We tested for autocorrelation across time by using the generalized Durbin-Watson test and included the appropriate autocorrelation orders in the final models. We also evaluated the impact of the policy implementation by calculating the model-based predicted outcomes, assuming the policies were not implemented. We presented the accumulative difference between the observed and predicted at the 6th and 12th month post intervention. The equation and detailed information are provided in Online Appendix 1.

The R^2 was higher than 0.80 across all models, a reflection of large sample sizes and little variation in the outcomes of interest over time. All analyses were performed by using SAS version 9.4 (proc autoreg command with nlag function).

3 | RESULTS

3.1 | Characteristics of high-risk patients

Approximately 7% (6.6%) of the 1.13 million Florida individuals in the prepolicy period were concomitant users, 2.0% were chronic users, and 0.5% were opioid shoppers (Table 1). Among 0.54 million Georgia individuals, the prevalence was lower at 4.4%, 1.2%, and 0.4%, respectively. More than three-fifths of concomitant users (64.8%) and opioid shoppers (60.4%) were female, while slightly more chronic users (51%) were male. Concomitant users were the oldest (mean age: 54.4 years), while chronic users were slightly younger (50.8 years) and opioid shoppers were the youngest (41.9 years).

3.2 | Opioid concentration and prevalence of high-risk patients

The concentration of total opioid prescriptions among high-risk patients decreased by approximately 17% from the prepolicy to the postpolicy period (Table 1). For example, the proportion of opioid prescriptions accounted for by high-risk patients ranged from 40.2% among chronic users to 3.3% among opioid shoppers in the prepolicy period; these numbers decreased to 33.2% and 2.7% in the postpolicy period. In the prepolicy period, the concentration of total opioid volume within high-risk patients was somewhat lower, ranging from 23.3% (chronic users) to 2.4% (opioid shoppers); this also declined following policy implementation, ranging from 19.4% to 1.8%.

The overlap across the 3 high-risk groups was low; for example, the highest was 45% of chronic users being concomitant users. In addition, approximately two-thirds of concomitant users (62%) and chronic users (59%) remained similarly high-risk following policy implementation, while fewer (25%) opioid shoppers continued to be classified as such following policy implementation. Compared with low-risk patients, high-risk patients by 1 definition (ie, chronic users) in the preintervention period were statistically significantly more likely to be high-risk patients by another definition (ie, concomitant users) in the same period (Online Appendix 2; $P < .05$) and stay high-risk by all 3 definitions (ie, concomitant, chronic, and opioid shoppers) in the postintervention period (Online Appendix 3; $P < .05$). For example, 38% of opioid shoppers were also concomitant users compared with just 6% of nonopioid shoppers.

Prevalence of high-risk patients by state and period are presented in Figure 1. The prevalence of concomitant users slightly increased from 6.62% in the prepolicy to 6.66% in the postpolicy period in

TABLE 1 Characteristics of high-risk patients defined in the prepolicy period (July 2010 to June 2011) in Florida

	Concomitant Users	Chronic Users	Opioid Shoppers
N: 1,126,797	74,603	22,071	5,200
100.00%	6.62%	1.96%	0.46%
Female, %	64.82%	48.75%	60.40%
Age, year	54.35 ± 14.53	50.78 ± 12.76	41.88 ± 12.75
Chronic disease score, score	2.21 ± 1.44	2.23 ± 1.51	2.00 ± 1.24
Number of opioid prescription	11.39 ± 7.67	19.26 ± 9.19	16.99 ± 10.56
Opioid prescription concentration, %			
Prepolicy period	37.51	40.19	3.32
Postpolicy period	31.72	33.18	2.70
Total opioid volume concentration, %			
Prepolicy period	23.32	11.67	2.43
Postpolicy period	19.40	9.74	1.76
Overlap in the preperiod			
Concomitant users	–	45.10%	37.96%
Chronic users	13.34%	–	19.48%
Opioid shoppers	2.65%	4.59%	–
Persistence into the post period			
Concomitant users	61.83%	38.75%	29.76%
Chronic users	10.52%	58.93%	14.39%
Opioid shoppers	1.40%	2.21%	24.90%

Source: QuintilesIMS Lifelink LRx data, 2010 to 2012.

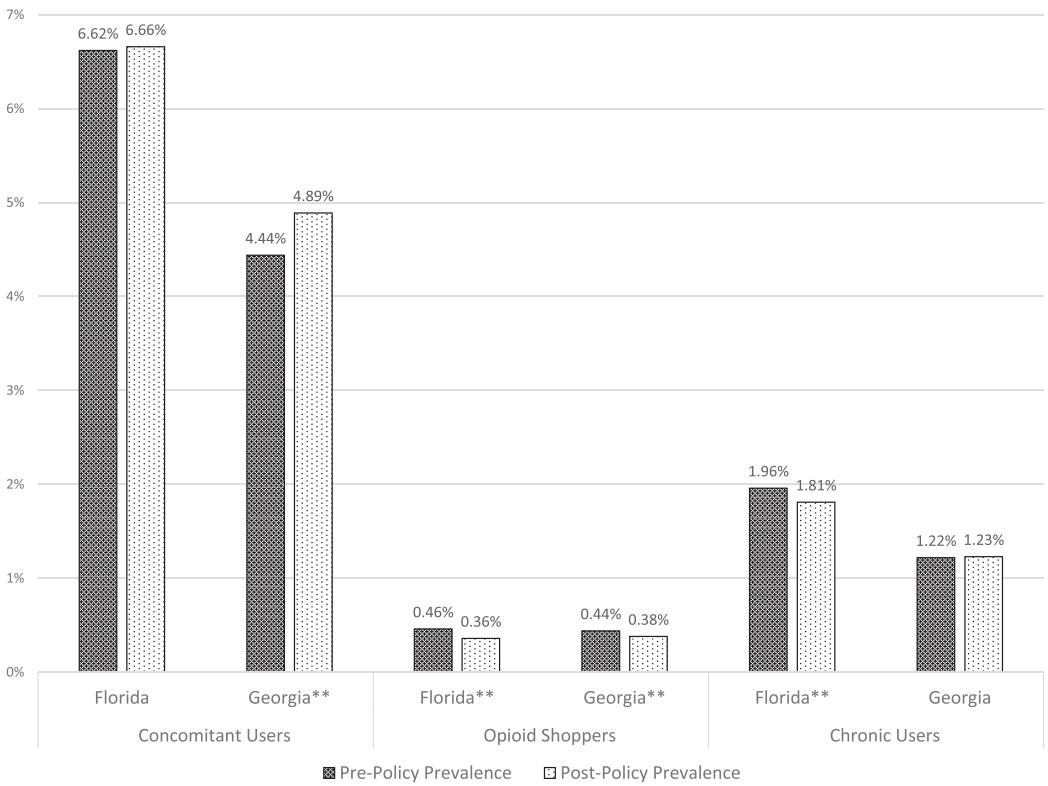

FIGURE 1 Policy impact on the prevalence of high-risk patients by period and state

Florida and statistically significantly increased from 4.44% to 4.89% in Georgia. Prevalence of opioid shoppers decreased statistically significantly in both states, but the magnitude was larger in Florida (0.08% in Florida vs 0.06% in Georgia). The prevalence of chronic users decreased significantly from 1.96% to 1.81% in Florida but remained stable in Georgia (1.22% to 1.23%).

Characteristics of nonhigh-risk patients from Florida are presented in Online Appendix 4.

3.3 | Effect of policy changes by types of patient risk

Table 2 demonstrates the impact of Florida's policies on high-risk patients, as compared with Georgia. Across 3 high-risk groups and 4 outcomes, comparative changes in *levels* pre- and postpolicy implementation were generally statistically significant among chronic users, but not concomitant users and opioid shoppers. By contrast, clinically significantly comparative reductions in monthly *trends* in 3 of the 4 outcomes were observed across all 3 high-risk groups. For volume-based outcomes such as total opioid volume and the number of opioid prescriptions, the policy effects were largest for concomitant and chronic users and were smaller for opioid shoppers. For example, there was a monthly relative decline in total opioid volume of 2.61 kg/month (95% confidence interval [CI], −1.67 to −3.56) among concomitant users, 4.58 kg/month (CI, −5.41 to −3.76) among chronic users, and 0.55 kg/month (CI, −0.44 to −0.65) among opioid shoppers. By contrast, each of the 3 high-risk groups experienced a similar, statistically significant comparative reduction in MME. Across 3 nonhigh-risk groups, generally no statistically significant effects on the level or trend were identified across all outcomes examined (Online Appendix 5).

3.4 | Observed versus predicted outcomes without policy implementation

Table 3 shows the difference between the observed and the predicted outcomes had Florida's policies not been implemented. There was a greater difference between the observed and predicted outcomes

TABLE 2 Impact of Florida's prescription drug monitoring programs and pill mill law on monthly outcomes among high-risk patients

	Concomitant Users	Chronic Users	Opioid Shoppers
N: 1,126,797	6.62%	1.96%	0.46%
Comparative change in level			
Morphine milligram equivalent, mg	0.23 (−1.85, 2.31)	−0.23 (−1.89, 1.43)	−0.03 (−3.10, 3.04)
Total opioid volume, kg	−5.25 (−12.01, 1.52)	−7.65* (−13.56, −1.75)	−1.19** (−1.92, −0.47)
Days supplied	0.07 (−0.14, 0.29)	0.32** (0.11, 0.52)	0.03 (−0.72, 0.78)
Opioid prescriptions, thousand	−4.39 (−6.72, −2.06)	−1.74* (−3.12, −0.36)	−0.74* (−1.29, −0.19)
Comparative change in trend			
Morphine milligram equivalent, mg	−1.07** (−1.42, −0.72)	−1.20** (−1.46, −0.95)	−1.08** (−1.62, −0.54)
Total opioid volume, kg	−2.61** (−3.56, −1.67)	−4.58** (−5.41, −3.76)	−0.55** (−0.65, −0.44)
Days supplied	0.02 (−0.01, 0.05)	0.00 (−0.03, 0.03)	−0.10 (−0.21, 0.02)
Opioid prescriptions, thousand	−0.64** (−0.95, −0.34)	−0.71** (−0.90, −0.52)	−0.19** (−0.17, −0.11)

*$P < .05$.

**$P < .01$.

Source: QuintilesIMS Lifelink LRx data, 2010 to 2012.

TABLE 3 Difference between monthly observed and predicted outcomes without policy implementation among high-risk patients in Florida

	First Half-Year After Policy			Second Half-Year After Policy			Cumulative 1-year After Policy		
	Actual	Predicted w/o Law	Diff, %	Actual	Predicted w/o Law	Diff, %	Actual	Predicted w/o Law	Diff, %
Concomitant users									
MME, mg	70.77	74.99	5.97%	67.39	78.12	15.92%	69.08	76.55	10.82%
Total opioid volume, kg	106.50	124.22	16.64%	92.60	124.95	34.93%	99.55	124.58	25.15%
Days supplied	24.60	24.39	−0.85%	24.55	24.28	−1.07%	24.57	24.34	−0.96%
Opioid prescriptions, N	59,927	67,499	12.64%	55,144	66,211	20.07%	57,535	66,855	16.20%
Chronic users									
MME, mg	136.62	142.38	4.21%	129.60	142.61	10.04%	133.11	142.49	7.05%
Total opioid volume, kg	114.61	143.83	25.50%	93.70	149.25	59.29%	104.15	146.54	40.70%
Days supplied	26.94	26.61	−1.25%	26.60	26.26	−1.26%	26.77	26.43	−1.26%
Opioid prescriptions, N	30,854	35,990	16.65%	26,921	36,076	34.01%	28,888	36,033	24.74%
Opioid shoppers									
MME, mg	77.15	81.22	5.28%	73.80	85.11	15.33%	75.47	83.17	10.19%
Total opioid volume, kg	9.50	13.27	39.72%	7.45	14.35	92.65%	8.48	13.81	62.99%
Days supplied	19.97	20.05	0.38%	20.00	20.99	4.95%	19.98	20.52	2.67%
Opioid prescriptions, N	5,673	7,439	31.12%	4,741	7,395	55.98%	5,207	7,417	42.44%

MME, morphine milligram equivalent; Diff, difference.

Source: QuintilesIMS Lifelink LRx data, 2010 to 2012.

during the second 6 months after the policy changes than during the first 6 months. For example, during the second 6 months, the observed total opioid volume was 34.9% less and 6.2% more than the predicted values among concomitant and nonconcomitant users, respectively. We estimate that at 1 year, the policies were associated with a 25% reduction in opioid volume among concomitant users, a 40.7% reduction among chronic users, and a 63.0% reduction among opioid shoppers; they were also associated with a 16.2% reduction in opioid prescriptions among concomitant users, a 24.7% reduction among chronic users, and a 42.4% reduction among opioid shoppers. Smaller reductions (eg, a 0.5% reduction among nonopioid shoppers on opioid prescriptions) or sometimes increases (eg, a 12.9% increase among chronic users on total opioid volume) were observed to be associated with the policies at 1 year among nonhigh-risk patients (Online Appendix 6).

4 | DISCUSSION

Among 1.1 million patients filling a prescription opioid in Florida prior to policy implementation, 6.6% were concomitant users, 2.0% were chronic users, and 0.5% were opioid shoppers; the prevalence of these 3 high-risk groups was lower in Georgia. Across all 3 high-risk groups, these policies were associated with statistically significant comparative reductions in monthly trends of morphine equivalent dose, total opioid volume, and number of opioid prescriptions. In general, no statistically significant effects on nonhigh-risk patients were observed.

In so far as Florida's policies were designed to target those at greatest risk of opioid-related adverse events, our study suggests that the policies had their intended effect. However, the impacts seemed to be larger among high-risk patients than high-risk prescribers. For example, about 80% of high-risk prescribers remained so following policy implementation while at most 60% of high-risk patients persisted. Similarly, we estimate larger policy effects among high-risk patients than high-risk prescribers at 1 year as well; for example, we estimate a 25% to 70% reduction in total opioid volume among high-risk patients compared with a 13.5% reduction among high-risk prescribers.[25] Further study is necessary to evaluate these differential effects.

Prescription drug monitoring programs and pill mill laws are rapidly evolving state-level policies to address prescription opioid abuse and diversion. Prescription drug monitoring programs have been implemented in all but 1 state, representing nearly complete policy diffusion, with particularly rapid uptake during the last 15 years. Because PDMPs vary extensively across states, they present a natural policy-making experiment, for which rigorous evaluation has only recently begun.[16,20,25,26,29] For example, states house PDMPs in different agencies (eg, health department and pharmacy board), require PDMPs to capture information about different drug schedules, and vary in the extent to which law enforcement officials can access their data.[48,49]

One of the more controversial—and heterogeneous—aspects of PDMPs is whether prescribers are legally required to register with and subsequently query them. Approximately half of the states do not have such registry requirement; the other states vary in requiring prescribers and/or dispensers to enroll.[50] Importantly, registration does not guarantee use of the PDMP, which is why 30 states now require prescribers to query the PDMP in at least some circumstances (eg, when initially prescribing an opioid; for prescriptions related to noncancer chronic pain).[51] Evaluations of these mandates, while early, suggest that they increase use of PDMPs and decrease prescribing of opioids, at least among certain groups of providers.[52,53] Because these mandates were generally implemented simultaneously as other measures intended to address prescription drug abuse, it is difficult to ascertain their individual contribution to any reduction in morbidity and mortality. Opinions also differ regarding whether PDMPs and other policies to reduce nonmedical opioid use may have unintended consequences such as stimulating the use of heroin or illicit fentanyl.[54,55] This is a complicated issue, and further research is necessary.

Our study has several limitations. First, given the lack of diagnosis and death information, we cannot assess whether transactions were clinically indicated or associated with opioid-related morbidity or mortality. Second, we could not evaluate the independent effects of Florida's PDMP and pill mill laws as they were enacted within 3 months of each another. In addition, activities related to the implementation of these policies (eg, increased law enforcement activity and media coverage of pill mill closures) are not specifically accounted for, although they may have influenced our findings. Third, PDMPs are heterogeneous in their structure and function, and our findings may not be generalizable to all PDMPs.[19] Fourth, our dataset contained only the retail prescription claims; those occurring in institutional settings such as hospitals, or through direct physician dispensing (partially banned by the pill mill law starting in July 2011), were not captured. The absence of data capturing physician dispensing may lead us to underestimate the effect of Florida's policies. Fifth, people can cross the state lines to obtain opioid prescriptions, although in prior analyses, we found that fewer than 1% of opioid prescriptions by Florida residents were filled in Georgia. Sixth, we did not evaluate whether these policies had a differential impact on different types of opioids. Seventh, we did not examine whether the policies have a differential effect on cash versus noncash transactions. Lastly, we used 1 set of thresholds to examine high-risk opioid patients; additional analyses might examine the effect of PDMPs and pill mill laws by using alternative thresholds.

5 | CONCLUSIONS

Despite the concerted efforts of many stakeholders, morbidity and mortality continue to accrue from prescription and illicit opioids. Prescription drug monitoring programs and pill mill laws remain an important component of states' policies to address the nonmedical use and diversion of prescription opioids. While there is evidence from an increasing number of sources that state's policies have a positive impact on both opioid prescribing as well as related injuries, addiction, and deaths, evaluations of specific state's interventions will continue to be important given the heterogeneity of these programs across states and their continued evolution.

ETHICS STATEMENT

This study was exempt from IRB review.

ACKNOWLEDGEMENTS

The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated information service(s): QuintilesIMS Health LifeLink LRx Database® (2010-2012), QuintilesIMS Health Incorporated. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of QuintilesIMS Health Incorporated or any of its affiliated or subsidiary entities. This work was funded by the Robert Wood Johnson Foundation Public Health Law Research Program and the Centers for Disease Control and Prevention under cooperative agreement U01CE002499. The funding sources had no role in the design and conduct of the study, analysis, or interpretation of the data and preparation or final approval of the manuscript prior to publication. The opinions and conclusions expressed are solely of the author(s) and should not be construed as representing the opinions of CDC or any agency of the federal government.

CONFLICT OF INTEREST

Dr Alexander is chair of the FDA's Peripheral and Central Nervous System Advisory Committee; serves on the Advisory Board of MesaRx Innovations; holds equity in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and serves as a member of OptumRx's P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following QuintilesIMS Health Incorporated information service(s): QuintilesIMS Health LifeLink LRx Database® (2010-2012), QuintilesIMS Health Incorporated. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of QuintilesIMS Health Incorporated or any of its affiliated or subsidiary entities.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Chang H-Y, Murimi I, Faul M, Rutkow L, Alexander GC. Impact of Florida's prescription drug monitoring program and pill mill law on high-risk patients: A comparative interrupted time series analysis. *Pharmacoepidemiol Drug Saf*. 2018;27:422–429. https://doi.org/10.1002/pds.4404