Analysis

Chronic Opioid Therapy Utilization Following an Acute Pain Prescription Supply Restriction Law: An Interrupted Time Series Analysis

Yun Shen, MPH[1,2], Juan M. Hincapie-Castillo, PhD[1-3], Scott M. Vouri, PhD[1,2,4], Marvin A. Dewar MD[4,5], Jill M. Sumfest, MD[6], and Amie J. Goodin, PhD[1,2]

From: [1]Department of Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, FL; [2]Center for Drug Evaluation and Safety, University of Florida, Gainesville, FL; [3]Pain Research and Intervention Center of Excellence, University of Florida, Gainesville, FL; [4]University of Florida Health Physicians, Gainesville, FL; [5]College of Medicine, University of Florida, Gainesville, FL; [6]GatorCare Health Plan, Gainesville, FL

Address Correspondence:
Amie Goodin, PhD, MPP
P.O. Box 100496
University of Florida
Gainesville, FL 32610-0496
E-mail: amie.goodin@ufl.edu

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-29-2021
Revised manuscript received: 08-02-2021
Accepted for publication: 08-31-2021

Free full manuscript: www.painphysicianjournal.com

Background: Florida House Bill 21 (HB21) was implemented in July 2018 to limit Schedule II opioids prescriptions for patients with acute pain to a 3-day supply. Little is known about the potential unintended effects that such opioid restriction policies may have on chronic pain patients, who are exempt from the law.

Objective: We aimed to evaluate the effect of HB21 on opioid utilization measures among a cohort of chronic opioid therapy (COT) patients.

Study Design: A quasi-experimental design with interrupted time series analyses.

Setting: Pharmacy claims from January 1, 2015 to June 31, 2019 from a large employer-based health plan in Florida.

Methods: COT patients were those who received a ≥ 70 days' supply of opioids in the prior 90 days, representing 15,310 patients. Interrupted time series analyses were conducted to compare the following monthly measures among COT patients before and after HB21 implementation: 1) number of COT patients, 2) daily Morphine Milligram Equivalents [MMEs], 3) days' supply of prescriptions.

Results: There was a significant 25% reduction in the trend (pre-HB21 RR: 0.95, 95% CI: 0.93, 0.96 versus post-HB21 RR: 0.70, 95% CI: 0.65, 0.76) and an 8% immediate decrease (RR: 0.92, 95% CI: 0.88, 0.97) in the monthly prevalence of COT patients after HB21 implementation. However, no significant change was observed in trends for monthly number of days supplied per prescription, monthly MMEs per COT patient-day, or total MMEs per prescription.

Limitations: Our study used data from employer-based private health insurance and did not include a longer post-policy period to adjust for implementation lag.

Conclusion: Fewer patients received COT after HB21; however, patients who continued to receive COT experienced no significant changes in their regimen. The study did not assess whether COT patients were appropriately tapered or if therapeutic alternatives were initiated for new chronic pain patients.

Key words: Prescription opioids, health policy evaluation, chronic opioid therapy, drug utilization

Pain Physician 2021: 24:417-424

Chronic pain is recognized as a common and significant public health problem that affects approximately 20-30% of people worldwide and more than 100 million people in the United States (US) (1-3). Chronic opioid therapies (COT) are pharmacotherapeutic treatment options prescribed for the treatment of chronic pain related to palliative care, active cancer, and end of life care (4,5); however, the use of COT to alleviate or manage chronic non-cancer pain remains controversial, due

to debate about efficiency and increased risks of transition to opioid use disorder, overdose, and other opioid-related adverse events (5). Opioid medications remain a mainstay for the long-term management of chronic pain despite these risks (6-8). The importance of considering risks of adverse outcomes from COT reflected in the 2016 Centers for Disease Control and Prevention guideline (9). This guideline provided recommendations for prescribing opioids for chronic pain regarding, when to initiate or continue opioids, dose initiation and escalation, and reevaluation of benefits and harms, as based on the most recent evidence at that time (9).

National and state-level legislation to restrict prescription opioid supply has been introduced as one supply-side strategy to mitigate opioid-related adverse effects. To date, more than half of states have enacted laws or adopted guidelines to restrict either opioid prescribing, or dispensing for the treatment of acute pain, and several insurers and health-systems have followed suit by implementing their own restrictions (10). In Florida, House Bill 21 (HB21) represents one of the most stringent of these opioid restriction policies in the nation. HB21 limits Schedule II opioid prescriptions for patients with acute pain to a 3-day supply, unless a medically necessary exemption is declared. HB21 also includes provisions that require prescribers to query the state prescription drug monitoring program for initiating or continuing most controlled substance prescriptions (11). Prescriptions for Schedule II opioids may be extended up to a 7-day supply if the prescriber indicates an "acute pain exception" (11); however, the restrictions of HB21 Schedule II opioids were not applied to patients with chronic pain, nor are they intended to apply to prescription supply for Schedule III opioids for either acute or chronic pain (11).

In a prior study, we demonstrated that there was an immediate and significant reduction in the number of opioid units and days' supply per prescription as well as a decline in the number of new opioid users after the implementation of Florida HB21 among acute pain patients (12); however, that study did not evaluate the impact of this policy change on opioid prescribing and dispensing patterns among patients who are treated for chronic pain. A recent study conducted in another state with similar restrictions (Tennessee) evaluated the impact of opioid restriction policy on opioid prescription days' supply among COT patients and found that the policy change was associated with reductions in number of monthly prescriptions and the average days' supply. However, a significant increase in the average Daily MME was observed (13).

We hypothesize that restrictions on opioid prescriptions for acute pain conditions potentially impact prescription patterns of COT despite exemptions for chronic pain. The purpose of this study was to assess opioid prescribing patterns among patients receiving COT following a policy change that restricted opioid supply for acute conditions.

Methods

Study Population

We analyzed prescription claims data for opioid medications dispensed from January 1, 2015 to June 31, 2019 from a private health insurer representing an employer-based health plan for a large university and affiliated health system in Florida, which provides insurance for over 40,000 individuals. Our study period started on January 1, 2015 to avoid contamination with the rescheduling of hydrocodone-containing products implemented in October 2014. The first day of each month during the study period was used as the index date for each patient. COT episodes were defined as having opioid prescription claims totaling ≥ 70 days' cumulative supply in the prior 90 days before each index date (14) (Supplemental Fig. 1). The 70 days' supply cut-off point has been used in previous research to define COT episodes and is among the most widely used COT definitions in recent years (14-18). Both single-entity and combination products of prescription opioids were identified by generic names and assessed, including: hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, codeine, tramadol, meperidine, fentanyl, pentazocine, and tapentadol.

Intervention

The intervention was operationalized as the effective date for Florida HB21, which was July 1, 2018. All outcomes were operationalized as monthly prescription measures, and so the pre-intervention period consisted of all months between January 2015 through June 2018 and the post-intervention period consisted of all months between July 2018 through June 2019.

Outcome Measurement

A total of 4 monthly indicators were used to assess the effect of HB21 on COT patients: 1) the proportion of plan enrollees receiving COT; 2) the average number of days supplied per prescription among COT patients;

3) the average morphine milligram equivalents (MME) per day per COT patient; and 4) the average total of MMEs per prescription among COT patients. MMEs were calculated using the conversion factors from the Center for Disease Control's National Center for Injury Prevention and Control.

Study Design and Statistical Analyses

Descriptive analyses were preformed to assess each of the 4 indicators described with means and standard deviations in aggregate for the total period before and after HB21 implementation. Monthly counts were defined as the mean number of each indicator that were identified in the pre- and post-policy time periods (where indicators were: number of patients, number of days supplied, MMEs per day, and Total MMEs). Monthly rates were defined as the mean counts per respective denominator unit in the pre- and post-policy time periods (i.e., number of patients with a COT episode per 1,000 patients; number of days supplied per prescription; MMEs per day per COT patient; and total MMEs per prescription).

Interrupted time series (ITS) models were used to compare monthly indicators for monthly opioid prescription indicators for COT in Florida before and after HB21 implementation on July 1, 2018. ITS study designs are quasi-experimental designs that are particularly suited to evaluate population-level interventions (e.g., pre- and post- policy changes) because ITS models also account for secular trends (19). In the ITS analysis, the series of monthly opioids prescription indicators prior to the implementation of the bill were used to establish an underlying trend, which was then "interrupted" by the implementation of HB21 on July 1, 2018.

We used the pre-intervention trends to model the counterfactual of post-intervention trends (if the law was not implemented). Impacts of the new prescribing policy was assessed by comparing actual utilization to the post-intervention counterfactual. Segmented quasi-poisson regression models were then used to estimate effect sizes (i.e., risk ratios [RRs]) after taking underlying trends into account by analyzing trends in both periods. The population size was used as the offset. Harmonic terms were used to control for seasonal effects and residual autocorrelations were tested using the Ljung-Box test (20,21). When there are significant autocorrelations ($P < 0.1$ in the Ljung-Box test), conservative estimates were generated using the robust standard errors with a sandwich estimator (22). In addition, the effect of HB21 on the average monthly number of prescription opioids per 1,000 enrolled patients were examined by dosage form among patients with COT and all patients, both unstratified and stratified, by receipt of prescriptions for short-acting and long-acting opioids.

We hypothesized the potential impact of the HB21 intervention as an immediate change since it was a legal requirement affixed at one time point. Analyses were repeated for each of the 4 indicators. For each indicator, we started with a step change impact model (i.e., without an interaction term between time and policy enactment), followed by a step and slope change model (i.e., with an interaction term between time and policy enactment). Both models were compared using ANOVA and the best model was selected based on the F-statistic. Relative risks (RRs) and 95% confidence internals (95% CIs) were reported. All statistical analyses were conducted in R 3.5.1 (R Project for Statistical Computing). This study was reviewed and approved by the Institutional Review Boards from the University of Florida.

Results

Overall, there were a total of 56,544 individual opioid prescriptions dispensed to 15,310 patients who met our definition of having at least 1 COT episode from January 1, 2015 to June 31, 2019. The descriptive results of the 4 indicators (Table 1) shows that there was a decrease in the average monthly rate of COT per 1,000 patients (pre-HB21: 7.70 versus post-HB21: 5.54), MME per day per COT patient (pre-HB21: 94.31 versus post-HB21: 76.64), and total MME per prescription (pre-HB21: 2125.59 versus post-HB21: 1866.00) after the enactment of HB21. A slight increase was observed in the average monthly rate of days supplied per prescription (pre-HB21:28.66 vs. post-HB21: 29.18).

Table 2 and Fig. 1A illustrate the impact of HB21 on the number of COT-receiving patients per 1,000 enrolled patients. After accounting for underlying trend, we found a significant 25% reduction in the trend (pre-HB21 RR: 0.95, 95% CI: 0.93, 0.96 versus post-HB21 RR: 0.70, 95% CI: 0.65, 0.76) and a significant 8% immediate decrease (RR: 0.92, 95% CI: 0.88, 0.97) for the monthly prevalence of COT per 1,000 enrolled patients after HB21 implementation.

Table 2 and Fig. 1B show the impact of HB21 on number of days supplied per prescription. There was a significant 1% immediate increase in monthly number of days' supply per prescription (RR: 1.01, 95% CI: 1.00, 1.02) after the implementation of HB21; however,

no significant change in the trend was observed for monthly number of days supplied per prescription (overall RR trend: 1.00, 95% CI: 1.00, 1.01).

Table 2 and Fig. 1C show the impact of HB21 on MMEs per COT patient-day. A significant 8% increase in monthly MMEs per COT patient-day (RR: 1.08, 95% CI: 1.02, 1.14) was observed, while no significant change in the trend was observed for monthly MME per COT patient-day (overall RR trend: 0.88, 95% CI: 0.87, 0.90) after HB21 implementation.

Table 2 and Fig. 1D show the impact of HB21 on total MMEs per prescription. There was a significant 10% increase in total MMEs per prescription (RR: 1.10, 95% CI: 1.04, 1.15) after the implementation of HB21; however, no significant change in the trend was observed for total MMEs per prescription (overall RR trend: 0.91, 95% CI: 0.89, 0.92).

Supplemental Tables 1 show the effect of HB21 on the mean monthly number of prescription opioids per 1,000 enrolled patients with COT by dosage form. Large reductions in the mean number of prescriptions among COT patients were observed for codeine, oxymorphone, and tapentadol tablets, and a slightly increased trend for hydromorphone, morphine, and oxycodone tablets. Supplemental Table 2 shows the effect of HB21 on the mean monthly number of prescription opioids per 1,000 enrolled patients by dosage from among all patients. We found that there was a decreasing mean number of prescription opioids for all patients except for morphine/naltrexone tablet.

Supplemental Tables 3 and 4 present the effect of HB21 on the mean monthly number of prescription opioids per 1,000 enrolled patients with COT and all patients, stratified by receipt of prescriptions for short-acting and long-acting opioids. After the introduction of HB21, there was a decreasing mean number of prescription opioids for all patients except for morphine/naltrexone (long-acting). A declining average number of prescriptions was also observed among COT patients for particular opioid types, such as, large reductions in codeine (short-acting: from 14.27 to 2.09), oxymor-

Table 1. *Impact of HB21 (enacted on July 1, 2018), Florida, 2015-2019.*

	Before and After HB21 Policy Implementation		
	Before (mean ± SD)	**After (mean±SD)**	***P* value**
Number of patients with a COT episode			
Monthly Count	299.00 ± 20.86	229.33 ± 29.66	< 0.001
Monthly Rate (per 1,000 enrolled patients)	7.70 ± 0.66	5.54 ± 0.72	< 0.001
Number of days supplied			
Monthly Count	32,127.17 ± 2,911.94	22,975.17 ± 3,144.59	< 0.001
Monthly Rate (per prescription)	28.66 ± 0.33	29.18 ± 0.26	< 0.001
MME* per day			
Monthly Count	2,413,621.00 ± 468,231.20	1,493,031.00 ± 230,355.30	< 0.001
Monthly Rate (per Chronic Opioid Therapy patient)	94.31 ± 13.69	76.64 ± 2.65	< 0.001
Total MME*			
Monthly Count	2,403,013.00 ± 467,288.70	1,471,644.00 ± 226,974.20	< 0.001
Monthly Rate (per prescription)	2,125.59 ± 251.51	1,866.00 ± 73.24	< 0.001

*MME: Morphine Milligram Equivalents

Table 2. *Risk ratio (95% CI) from the Interrupted Time Series (ITS) models to examine the impact of HB21 (enacted on July 1, 2018), Florida, 2015-2019.*

	Trend (per year)						Step Change	*P* value
	Overall[1]	***P* value**	**Before[2]**	***P* value**	**After[2]**	***P* value**		
Number of patients with a COT episode [a]	-	-	0.95 (0.93,0.96)	< 0.001	0.70 (0.65,0.76)	< 0.001	0.92 (0.88,0.97)	0.001
Number of days supplied [b]	1.00 (1.00,1.01)	0.113	-	-	-	-	1.01 (1.00,1.02)	0.018
MME* per day [c]	0.88 (0.87,0.90)	< 0.001	-	-	-	-	1.08 (1.02,1.14)	0.005
Total MME [b]	0.91 (0.89,0.92)	< 0.001	-	-	-	-	1.10 (1.04,1.15)	< 0.001

[a] per 1,000 enrolled patients; [b] per prescription; [c] per Chronic Opioid Therapy patient; *MME: Morphine Milligram Equivalents; [1] From the ITS level change model; [2] From the ITS level and slope change model

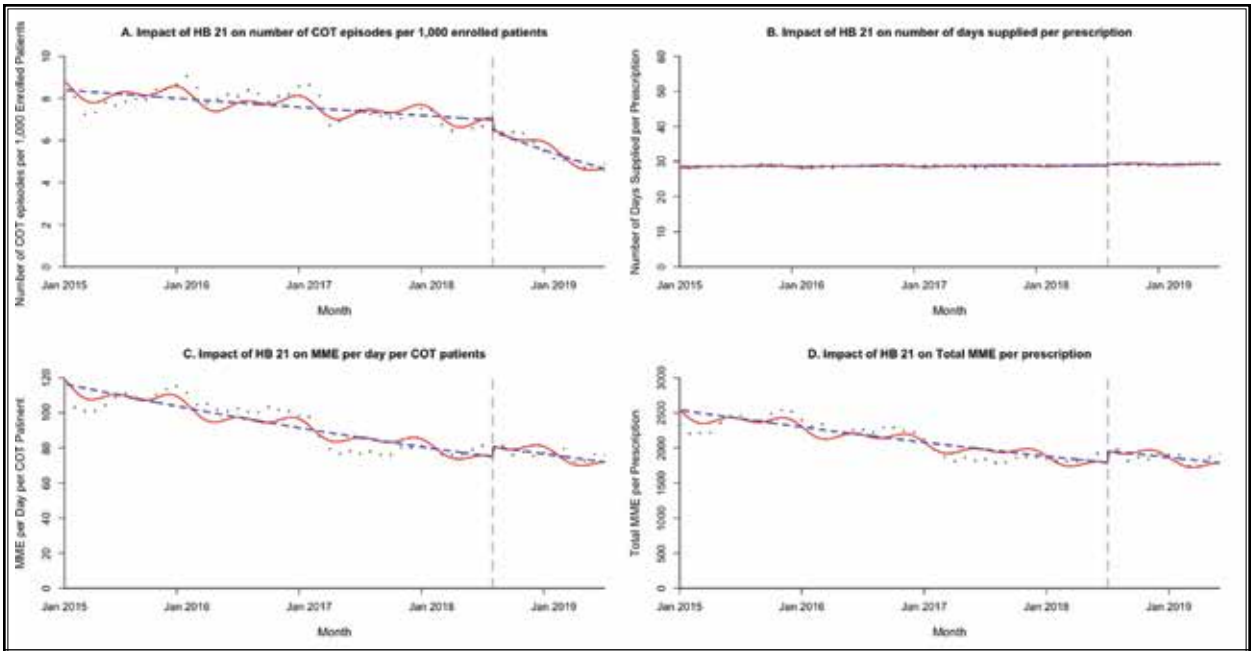


Fig 1. *Impact of HB 21 on four monthly indicators for the prescription patterns of opioids among COT patients, Florida, 2015-2019 (Black Dot: the observed value by each month, Red Solid Line: the model adjusted for seasonality, Blue dashed line: the deseasonalized trend).*

phone (short-acting: from 6.46 to 0.34, long-acting: from 26.5 to 4.72) and tapentadol (short-acting: from 6.55 to 3.33, long-acting: from 1.94 to 0.00), while non-significant increased trend were observed in fentanyl (short-acting), hydromorphone (long and short-acting), meperidine (short-acting), morphine (long-acting), morphine/naltrexone (long-acting), oxycodone (short-acting) and tramadol (long-acting).

Discussion

In this study, we found significant reductions in both the trend and immediate (i.e., "level") monthly prevalence of patients receiving COT following the implementation of an acute opioid prescription supply restriction law in Florida. There was a significant, but small, immediate increase (i.e., a "step change") in monthly number of days supplied per prescription, MME per day per COT patient, and total MME per prescription, with no significant change observed in trends. These results suggested that HB21 had a potential downward impact on the number of patients receiving COT; however, those patients that continued to receive COT retained similar quantities and strengths of their opioid therapy.

The potential reduction in patients receiving COT may be due in part to the increased awareness among prescribers, since the law requires continuing education on controlled substance prescribing (i.e., completing mandatory courses) (11); however, it is also possible that the reduction in patients receiving COT is due to what has been described as a "chilling effect," which is prescriber reluctance to initiate and/or maintain COT, due to either perceived increases in prescribing practice scrutiny or unwillingness to further engage in chronic pain care. This particular Florida law had other provisions in addition to the days' supply limit and the continuing education requirement that may have also impacted findings; namely, the mandate that prescribers query the state prescription drug monitoring program (PDMP) for initiations of new controlled substance prescriptions. While the literature on PDMP provisions and prescribing outcomes has yielded mixed results, there is at least one study from another state (Ohio) suggesting that a prescriber query mandate for PDMPs prior to controlled substance prescribing is associated with reduced opioid prescribing (23), so it is possible that the PDMP mandate provision of the Florida law had an overlapping, attenuating, or amplifying effect on the days' supply provision.

There are potential advantages of this and similar laws, such as: promoting clinically optimal pain management practices in primary care settings in the

absence of specialists, mitigating risk for prescription opioid-related adverse events, and improvement of continuing medical education opportunities for up-to-date best-practices for prescribing of controlled substances in general. However, the potential limitations and negative unintended consequences of this and other similar laws are significant and require further scrutiny. Supply-side laws and restrictions such as these do not address the prevailing demand for pain therapy, and, critically, this particular law was not intended to impact or apply to therapies prescribed to patients with chronic nonmalignant pain. Because this study was not able to examine in-depth medical records of patients before and after the law implementation, we are unable to ascertain whether the observed decrease in number of patients receiving COT was clinically appropriate for each of their cases.

The findings observed in our study are consistent with previous studies that evaluate opioid prescription restriction laws. Lainie et al (24), reported that the implementation of Florida's Prescription Drug Monitoring Program and "pill mill" law was associated with modest reductions in opioid prescribing overall and among patients receiving opioids long-term. A recent study assessed the impact of another state opioid restriction policy change (Tennessee Prescription Regulatory Act) on opioid prescription days' supply among COT patients, and found that the policy change was associated with reductions in number of monthly prescriptions (-1.3%, 95% CI: -3%, -0.07%) and the average days' supply (-5.30 days, 95% CI: -5.64, -4.96), while a significant increase in the average Daily MME was observed (1.41, 95% CI: 0.37, 2.45) (13); however, this study used a cut-point (> 30 days' supply) to define long-term opioid users that is not a typical clinical representation of COT, with a recent review finding that only 7 out of 227 studies defined patients as receiving COT using this more relaxed criterion (18). Additionally, the pre-policy period in that study was only 1 year and may not be sufficient to fully capture the pre-intervention secular trend of patients' opioid prescription patterns in an ITS model. In contrast, Meara et al (25), reported that there were no significant associations between implementation of controlled-substance supply restriction laws and reductions for the percentages of long-term receipt of opioids, multiple opioid prescribers, and daily morphine-equivalent dose > 120 mg, compared with states that adopted no such restriction laws among disabled Medicare beneficiaries. However, these results may only be generalized to adults with disabilities and the effect may be more pronounced after the law has been implemented over a longer period of time .

In our prior work, significant decreases of 4,250 total opioid units and 55,499 MMEs were observed in aggregate, in acute pain patients after the implementation of HB21 (26). The evidence accumulating from these policy evaluations supports that supply restriction policies likely impact initial opioid prescribing patterns and prescription duration among patients with acute conditions; however, uncertainty still remains whether these initial decreases in opioid supply observed within acute pain patients were a spillover effect or whether they were also driving change in observed prescribing patterns for patients treated with long-term opioid therapies (i.e., changes in percentages of long-term receipt of opioids, the number of unique opioid prescribers, and daily morphine-equivalent dose). Our findings indicated that fewer patients received COT overall following HB21 implementation, but we were unable to discern the diagnosis or treatment histories of these patients in the data source, so it is unclear for what conditions patients were receiving COT (26). Furthermore, the mandated supply restrictions on opioid prescriptions intended to be applied to acute pain patients do not directly address adverse opioid-related events (i.e., problematic use of prescription opioids, transition to nonmedical opioids, overdose, and opioid-related deaths) potentially contributed to by COT with imbalanced risk-benefit, as there is no explicit provision or program from such policies to clarify how prescribers and patients should 'navigate' perceived risks differently for patients with acute pain versus patients in need of long-term pain management.

Previous studies suggest that policy change to restrict prescription of opioid therapy could potentially cause worsening outcomes for patients receiving COT for pain management (27); namely, reduced access to prescription therapies for patients with stable pain management increases risks of nonmedical use of opioid prescriptions, or alternatives with unfavorable risk, as well as risk for worsening quality of life and suicide (28,29). We found that although HB21 likely reduced the number of patients receiving COT, those patients who continued to receive COT retained similar quantities and dosage strengths of opioid therapy.

In the face of such restriction policies, both physicians and pharmacists face additional burden to ensure the safety of patients when such legislative restrictions on opioids supply come into effect (30). Pharmacists may have delayed or limited access to health care infor-

mation regarding diagnosis for prescription of opioids (31), but retain responsibility for patient safety at the point of prescription dispensing; therefore, it is critical to have effective communication between physicians (or other prescribers) and pharmacists to ensure compliance with the specific guidance for policy change, as it relates to pain management among patients with chronic and acute conditions. Despite numerous state and insurer policies to mitigate potential opioid-related adverse events, such as opioid overdose, the impact of these policies on outcomes for long-term opioid treatment for pain management among chronic pain patients are only recently emerging. In the future, to assist clinicians and policymakers to make informed decisions on the safe use of opioids among patients with acute and chronic pain, comprehensive and nuanced benefit-risk assessments are needed to guide treatment recommendations for both improving pain management and reducing adverse health outcomes.

Our study has several strengths. First, this is the first study to evaluate the impacts of an acute pain opioid supply restriction law on opioid prescriptions among exempt patients receiving chronic opioid therapies in Florida. Few studies have evaluated the effect of restrictive acute pain policies on COT patients. The Florida HB21 was more restrictive than all acute pain opioid prescription policies that have been evaluated from other states (i.e., New York, Massachusetts, and Connecticut) (11). Second, by using a quasi-experimental design and ITS analysis technique, we also account for secular trends, which are not controlled for in simple pre-/post- study designs. In spite of these strengths, there are several limitations to our study. First, the findings of this study come only from a discrete set of individuals receiving employer-based private health insurance. Second, our study only included a limited time period after law implementation, which may under- or overestimate the longer-term effect of policy change on patients receiving COT. Third, we do not have diagnosis information and minimal information regarding patient clinical and sociodemographic characteristics in these data and so cannot examine indications or draw conclusions about particular conditions in which COT regimens were prescribed. Relatedly, we are unable to quantify access to COT for incident chronic pain patients in the absence of diagnosis data, so monthly proportions have been calculated using the total monthly health plan enrollment, with the assumption that new and extant chronic pain patients comprise a relatively stable proportion of enrollees over time. Fourth, methadone and buprenorphine were excluded since these have indications for the treatment for opioid use disorder (OUD). Without diagnosis information, we were unable to discern the treatment purpose for either pain or for OUD. Further research with longer post-policy period to adjust for implementation lag and using all-payer data with the availability of diagnosis date are warranted confirm and expand our findings.

Conclusion

Fewer patients received COT following a prescription opioid restriction law for acute pain; however, those patients that continued to receive COT experienced no significant changes in days' supply or MMEs per patient day following policy change. In the future, more research is warranted to assess whether the patients who were removed from COT underwent appropriate tapering or were converted to appropriate opioid-alternative pain management therapies, as well as if reduced initiation of COT signals improvements in alternative pain management strategies or in reduced access to care for chronic pain patients.

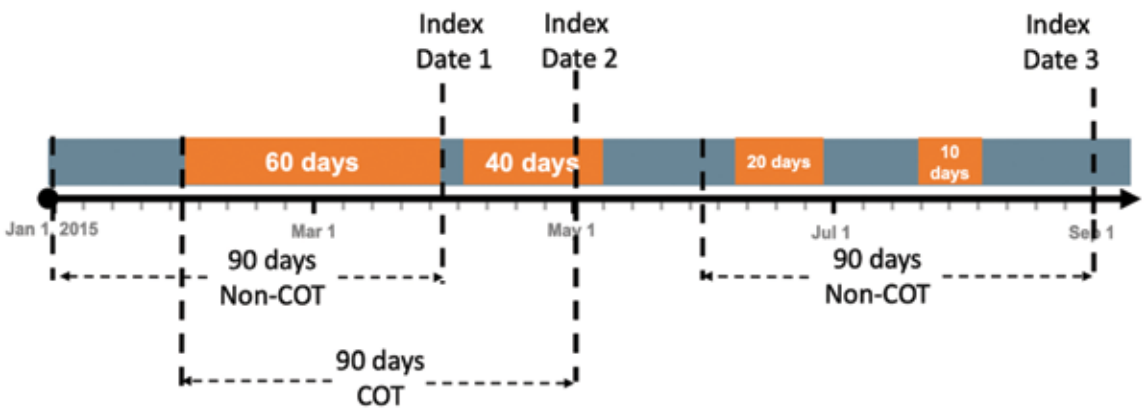
Supplemental material available at www.painphysicianjournal.com

References

1. Reuben DB, Alvanzo AA, Ashikaga T, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. *Ann Intern Med* 2015; 162:295-300.
2. Dansie E, Turk DC. Assessment of patients with chronic pain. *Br J Anaesth* 2013; 111:19-25.
3. Simon LS. Relieving pain in America: A blueprint for transforming prevention, care, education, and research. *J Pain Palliat Care Pharmacother* 2012; 26:197-198.
4. Portenoy RK. Treatment of cancer pain. *Lancet* 2011; 377:2236-2247.
5. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009; 10:113-130.e122.
6. Sullivan MD, Edlund MJ, Fan M-Y, et al. Trends in use of opioids for noncancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: The TROUP study. *Pain* 2008; 138:440-449.
7. Von Korff M, Kolodny A, Deyo RA, et al. Long-term opioid therapy reconsidered. *Ann Internal Med* 2011; 155:325.
8. Olsen Y, Daumit GL, Ford DE. Opioid

prescriptions by US primary care physicians from 1992 to 2001. *J Pain* 2006; 7:225-235.

9. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 2016; 315:1624-1645.
10. Davis CS, Lieberman AJ, Hernandez-Delgado H, et al. Laws limiting the prescribing or dispensing of opioids for acute pain in the United States: A national systematic legal review. *Drug Alcohol Depend* 2019; 194:166-172.
11. Florida Statutes. TITLE XXVII. 2018. www.flsenate.gov/Session/Bill/2018/21/BillText/er/PDF
12. Hincapie-Castillo J, Goodin A, Possinger M, et al. Changes in opioid use after florida's restriction law for acute pain prescriptions. *JAMA Netw Open* 2020; 3:e200234.
13. Yenerall J, McPheeters M. The effect of an opioid prescription days' supply limit on patients receiving long-term opioid treatment. *Intern J Drug Policy* 2020; 77:102662.
14. Turner JA, Saunders K, Shortreed SM, et al. Chronic opioid therapy urine drug testing in primary care: Prevalence and predictors of aberrant results. *J Gen Intern Med* 2014; 29:1663-1671.
15. Masters ET, Ramaprasan A, Mardekian J, et al. Natural language processing–identified problem opioid use and its associated health care costs. *J Pain Palliat Care Pharmacother* 2018; 32:106-115.
16. Thakral M, Walker RL, Saunders K, et al. Impact of opioid dose reduction and risk mitigation initiatives on chronic opioid therapy patients at higher risk for opioid-related adverse outcomes. *Pain Med* 2018; 19:2450-2458.
17. Von Korff M, Dublin S, Walker RL, et al. The impact of opioid risk reduction initiatives on high-dose opioid prescribing for patients on chronic opioid therapy. *J Pain* 2016; 17:101-110.
18. Shen Y, Bhagwandass H, Branchcomb T, et al. Chronic opioid therapy: A scoping literature review on evolving clinical and scientific definitions. *J Pain* 2020; 22:246-262.
19. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; 27:299-309.
20. Ljung GM, Box GE. On a measure of lack of fit in time series models. *Biometrika* 1978; 65:297-303.
21. Box GE, Pierce DA. Distribution of residual autocorrelations in autoregressive-integrated moving average time series models. *J Am Stat Assoc* 1970; 65:1509-1526.
22. Andrews DW. Heteroskedasticity and autocorrelation consistent covariance matrix estimation. *Econometrica* 1991; 59:817-858.
23. Winstanley EL, Zhang Y, Mashni R, et al. Mandatory review of a prescription drug monitoring program and impact on opioid and benzodiazepine dispensing. *Drug Alcohol Dep* 2018; 188:169-174.
24. Rutkow L, Chang H-Y, Daubresse M, et al. Effect of Florida's prescription drug monitoring program and pill mill laws on opioid prescribing and use. *JAMA Int Med* 2015; 175:1642-1649.
25. Meara E, Horwitz JR, Powell W, et al. State legal restrictions and prescription-opioid use among disabled adults. *N Eng J Med* 2016; 375:44-53.
26. Hincapie-Castillo J, Goodin A, Vouri S, et al. Pdg33 changes in Schedule II oral opioid volume dispensed in a private payer following Florida's Acute Pain Opioid Restriction Law. *J Manag Care Spec Pharm* 2021; 27:779-784.
27. Mojtabai R. National trends in long-term use of prescription opioids. *Pharmacoepidemiol Drug Saf* 2018; 27:526-534.
28. Alpert A, Powell D, Pacula RL. Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids. *Am Econ J Econ Policy* 2018; 10:1-35.
29. Scholl L, Seth P, Kariisa M, et al. Drug and opioid-involved overdose deaths—United States, 2013–2017. *Morb Mortal Wkly Rep* 2019; 67:1419.
30. Norwood CW, Wright ER. Integration of prescription drug monitoring programs (PDMP) in pharmacy practice: Improving clinical decision-making and supporting a pharmacist's professional judgment. *Res Soc Adm Pharm* 2016; 12:257-266.
31. Schiff G, Seoane-Vazquez E, Wright A. Incorporating indications into medication ordering—time to enter the age of reason. *N Eng J Med* 2016; 375:306-309.



Supplemental Fig. 1. *The Selection of Study Population (Patients with COT vs. without COT)*

Supplemental Table 1. *Mean monthly number of prescription opioids per 1,000 enrolled patients by dosage form before and after HB21 among patients with COT.*

	Form (mean)				
	Tablet	**Capsule**	**Solution**	**Patch**	**Sublingual**
Codeine					
Before	14.12	0.00	0.15	N/A	N/A
After	2.09	0.00	0.00	N/A	N/A
p-value	< .001		.160		
Fentanyl					
Before	N/A	N/A	N/A	17.60	0.08
After	N/A	N/A	N/A	11.47	0.00
P-value				.006	.323
Hydrocodone					
Before	349.18	0.00	0.31	N/A	N/A
After	309.84	0.00	0.00	N/A	N/A
P-value	< .001		.044		
Hydromorphone					
Before	11.83	0.00	0.00	N/A	N/A
After	12.91	0.00	0.00	N/A	N/A
P-value	.578				
Meperidine					
Before	0.15	0.00	0.00	N/A	N/A
After	0.00	0.00	0.00	N/A	N/A
P-value					
Morphine					
Before	84.04	0.36	0.08	N/A	N/A
After	88.87	0.00	0.00	N/A	N/A
P-value	.160	.044	.323		
Morphine/Naltrexone					
Before	0.00	0.00	0.00	N/A	N/A
After	0.00	0.85	0.00	N/A	N/A
P-value		.168			
Oxycodone					
Before	444.01	0.40	2.87	N/A	N/A
After	476.30	0.00	1.37	N/A	N/A
P-value	.012	.024	.044		
Oxymorphone					
Before	33.97	0.00	0.00	N/A	N/A
After	5.05	0.00	0.00	N/A	N/A
P-value	< .001				
Tapentadol					
Before	8.49	0.00	0.00	N/A	N/A
After	3.33	0.00	0.00	N/A	N/A
P-value	< .001				
Tramadol					
Before	208.69	0.08	0.00	N/A	N/A
After	182.93	0.00	0.00	N/A	N/A
P-value	< .001	.323			

Supplemental Table 2. *Mean monthly number of prescription opioids per 1,000 enrolled patients by dosage form before and after HB21 among all patients.*

	Form (mean)				
	Tablet	**Capsule**	**Solution**	**Patch**	**Sublingual**
Codeine					
Before	0.77	0.00	0.06	N/A	N/A
After	0.48	0.00	0.02	N/A	N/A
P-value	< .001		< .001		
Fentanyl					
Before	N/A	N/A	N/A	0.20	0.00
After	N/A	N/A	N/A	0.09	0.00
P-value				< .001	.160
Hydrocodone					
Before	10.29	0.00	0.17	N/A	N/A
After	6.55	0.00	0.01	N/A	N/A
P-value	< .001	.323	< .001		
Hydromorphone					
Before	0.30	0.00	0.00	N/A	N/A
After	0.18	0.00	0.00	N/A	N/A
P-value	< .001				
Meperidine					
Before	0.05	0.00	0.00	N/A	N/A
After	0.04	0.00	0.00	N/A	N/A
P-value	< .001				
Morphine					
Before	0.82	0.00	0.00	N/A	N/A
After	0.57	0.00	0.00	N/A	N/A
P-value	< .001	.024	< .001		
Morphine/Naltrexone					
Before	0.00	0.02	0.00	N/A	N/A
After	0.00	0.00	0.00	N/A	N/A
P-value		.172			
Oxycodone					
Before	9.36	0.02	0.23	N/A	N/A
After	6.97	0.01	0.14	N/A	N/A
P-value	< .001	.206	.018		
Oxymorphone					
Before	0.27	0.00	0.00	N/A	N/A
After	0.04	0.00	0.00	N/A	N/A
P-value	< .001				
Pentazocine					
Before	0.03	0.00	0.00	N/A	N/A
After	0.00	0.00	0.00	N/A	N/A
P-value	< .001				
Tapentadol					
Before	0.11	0.00	0.00	N/A	N/A
After	0.03	0.00	0.00	N/A	N/A
P-value	< .001	.160			
Tramadol					
Before	5.85	0.00	0.00	N/A	N/A
After	3.77	0.00	0.00	N/A	N/A
P-value	< .001				

Supplemental Table 3. *Mean monthly number of prescription opioids per 1,000 enrolled patients by short-acting and long-acting opioids before and after HB21 among patients with COT.*

	Type of Opioids (mean)	
	Short-Acting	**Long-Acting**
Codeine		
Before	14.27	N/A
After	2.09	N/A
P-value	< .001	
Fentanyl		
Before	0.08	17.60
After	0.00	11.47
P-value	.323	< .001
Hydrocodone		
Before	349.49	0.00
After	309.84	0.00
P-value	< .001	
Hydromorphone		
Before	11.49	0.34
After	12.46	0.45
P-value	.564	.820
Meperidine		
Before	0.15	N/A
After	0.00	N/A
P-value	.160	
Morphine		
Before	15.49	68.98
After	14.12	74.76
P-value	.533	.329
Morphine/Naltrexone		
Before	N/A	0.00
After	N/A	0.85
P-value		.168
Oxycodone		
Before	371.84	75.44
After	392.01	85.66
P-value	.119	.034
Oxymorphone		
Before	6.46	26.50
After	0.34	4.72
P-value	< .001	< .001
Tapentadol		
Before	6.55	1.94
After	3.33	0.00
P-value	< .001	< .001
Tramadol		
Before	186.97	21.81
After	163.73	19.21
P-value	< .001	.210

Supplemental Table 4. *Mean monthly number of prescription opioids per 1,000 enrolled patients by short-acting and long-acting opioids before and after HB21 among all patients.*

	Type of Opioids (mean)	
	Short-Acting	**Long-Acting**
Codeine		
Before	0.83	N/A
After	0.50	N/A
P-value	< .001	
Fentanyl		
Before	0.00	0.20
After	0.00	0.09
P-value	.160	< .001
Hydrocodone		
Before	10.46	0.00
After	6.57	0.00
P-value	< .001	.323
Hydromorphone		
Before	0.30	0.00
After	0.18	0.00
P-value	< .001	.083
Meperidine		
Before	0.05	N/A
After	0.04	N/A
P-value	.101	
Morphine		
Before	0.17	0.66
After	0.12	0.45
P-value	< .001	< .001

	Type of Opioids (mean)	
	Short-Acting	**Long-Acting**
Morphine/Naltrexone		
Before	N/A	0.00
After	N/A	0.02
P-value		.172
Oxycodone		
Before	8.88	0.73
After	6.61	0.51
P-value	< .001	< .001
Oxymorphone		
Before	0.06	0.22
After	0.00	0.04
P-value	< .001	< .001
Pentazocine		
Before	0.03	N/A
After	0.00	N/A
P-value	< .001	
Tapentadol		
Before	0.08	0.03
After	0.03	0.00
P-value	< .001	< .001
Tramadol		
Before	5.65	0.21
After	3.65	0.12
P-value	< .001	< .001