Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix to:

State Legal Restrictions and Prescription Opioid Use among Disabled Adults

AUTHORSHIP

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METHODS

To access a spreadsheet of data on controlled substance laws by state and year, and information on each opioid related outcome used in our study summarized by state and year, as described below, please visit dartmouthdiffusion.org.

Study sample

For each calendar year 2006 to 2012, from a 40% random sample of the Medicare Master Beneficiary Summary File, we identified Medicare beneficiaries age 21 to 64 who were alive throughout the calendar year and continuously enrolled in fee-for-service Medicare parts A, B, and a stand-alone Part D prescription drug plan. Medicare Prescription Drug Event files do not contain enrollee data for HMO enrollees (those in Medicare Advantage); thus, we excluded these beneficiaries. Median HMO penetration for Medicare beneficiaries under age 65 grew from 8.2% to 17.7% during the study period. HMO penetration ranged from less than 0.4% in Alaska to 37.4% in Arizona in 2006 with a 2012 range of 0.6% in Alaska to 46% in Arizona.

The random 40% sample, the largest sample available to us for prescription drug fills in Medicare Part D, is provided by the Centers for Medicare and Medicaid Services on the basis of the final, randomly assigned, digits of beneficiaries' claims account number. The random assignment is independent of state, and we confirm that we have 40% of each state's Medicare beneficiaries and demographics that are similar to those that would be obtained if a random 40% sample had been drawn within each state. After exclusion restrictions for age and 12 calendar months alive with continuous enrollment in fee-for-service Medicare parts A, B and D, our final sample ranged from 3,900 unique beneficiaries in Wyoming to 196,432 unique beneficiaries in California.

We required beneficiaries to have 12 months continuous enrollment (and thus they had to be alive for the entire calendar year to be in the sample in that year). Sample characteristics differed little with less stringent requirements (3 months continuous enrollment in fee-for-service parts A, B, and D). Comparing our sample (based on the continuous enrollment and alive for full calendar year) to a sample with a 3-month requirement, average age, percent female, and racial composition were nearly identical. The 3-month sample was slightly less likely to have diagnoses of depression (22.9% vs. 23.6%) and serious mental illness (6.9% vs. 7.2%), but differences were small in magnitude.

Sample time period and impact of first year of Medicare Part D on study sample

In 2006, the first year of Medicare's Part D program (prescription benefits), the prolonged open enrollment period (through June) could, in theory lead to non-representative study samples in 2006, especially in studies that include in annual cohorts only beneficiaries enrolled for 12 full months. Beneficiaries dually eligible for Medicaid and Medicare (75% of our study population) were automatically enrolled in Part D on January 1, 2006. This resulted in a higher proportion of dually-eligible patients (those enrolled in both Medicaid and Medicare) in our

2006 study data; despite this, outcome measures and demographics are very stable over the study period.

Morphine Equivalent Dose

The Medicare Prescription Drug Event and Pharmacy Characteristics files include the National Drug Code (NDC), the date the prescription was filled, the quantity dispensed, and the number of days of supply. The Lexi-Data Basic database (Lexicomp) was used to obtain the drug name, dose, and active ingredient according to the NDC. To create measures of the intensity of opioid prescribing, we converted the dose of opioid products into a morphine equivalent dose (MED) according to opioid conversion factors in Table S2.[1,2] The conversion factors and our measure of MED includes methadone. Although methadone is used for addiction management, it is commonly used for pain treatment as well. Methadone use exclusively for opioid addiction management will not appear in retail pharmacy claims, and thus is not covered in our data, because opioid treatment centers (methadone maintenance clinics) dispense this product directly to patients on a daily basis. While it is possible that some observed methadone consumption reflects unlawful prescribing on the part of clinicians treating opioid addiction outside the setting of an opioid treatment program, we believe the volume of such prescribing is likely to be trivial.

Defining Treatment for Nonfatal Prescription Opioid Overdose

For each beneficiary in each calendar year, we coded treatment for nonfatal overdose in emergency department or inpatient settings according to *International Classification of Disease, Ninth Revision* diagnosis codes following codes used in prior studies[3,4] (Table S3). Because we limit the sample to those alive throughout a calendar year, in practice, these reflect only non-fatal overdose events.

State Controlled Substance Laws

We assembled an original data set of controlled substance prescribing restrictions in all fifty states and DC. First, using the Westlaw State Statutes databases and a number of pre-existing surveys of state laws,[5-9] we researched current statutes in 2014 to determine whether each state had any of the eight categories of laws shown in Table S4. We consulted an existing Centers for Disease Control and Prevention (CDC) database of laws as well as other sources, but relied largely on our primary research because the CDC database only included laws up to 2010.[10] In addition, in its coverage of state laws, the CDC also considered immunity laws, but we exclude immunity laws from our analyses, because of our focus on prescribing and dispensing behavior. We used hard copies of the statutes to verify changes in language over time and dates of passage and revision of statutes.

Second, using the Westlaw State Regulations databases and state administrative law registers where electronically available to verify dates and language of changes over time, we conducted the same search in state regulations. At least one research assistant and a law librarian with an expertise in health law and regulation reviewed each source. In cases in which the meaning of the text was unclear, we conducted additional research to clarify the meaning and the lawyers on the team came to agreement about the meaning.

We conducted primary research and did not rely on existing datasets because a number of sources needed to be updated, and those sources were based only on whether a state had a statute, which is an incomplete measure of state prescribing restrictions. Moreover, because we were interested in whether the laws restrict behavior, we thoroughly examined the content of the restrictions. In the case of PDMPs, which require considerable development in terms of bureaucracy and infrastructure, we did additional research on the implementation of those laws. We consulted the website of the organization formerly known as the Prescription Monitoring Program Alliance, an organization of state PDMP regulators that has since been folded into the National Association of State Controlled Substances Authorities.[5] In several cases, we coded a state as not having a PDMP despite the fact that there exist statutes indicating a PDMP might exist. These states were: Arkansas, Georgia, Maryland, Montana, Nebraska, South Dakota, and Wisconsin. These programs were never established or were established later than the listed effective date.

Based on the approach described above, we created a state by year database that indicates whether a state had each of the relevant opioid-related laws in place in a given year. We required a law to be in place for the entire calendar year before coding a law as in place in that year. If a law regarding quantitative prescription limits became effective in the middle of the year, for example, that year was treated as not having any prescription limits. Our results are insensitive to treatment of laws in place for partial years.

Based on available information from state websites in 2014 and early 2015, we coded 2009 as the first full year of PDMP operation in California and 2012 as first full year of operation in Nebraska. A more consistent coding of PDMPs according to our algorithm would treat California as operational before our study period and Nebraska as operational only after our study period. We re-estimated the models underlying Tables 3 and 4 in the main paper with this alternative law coding, and found virtually identical results. Estimated associations with an operating PDMP ranged from 0.4% higher in models of nonfatal prescription opioid overdose (coefficient on PDMP was -0.002 in the paper and -0.001 using alternative dates for California and Nebraska) to 4.7% lower in models of daily MED>120mg (coefficient on PDMP was 0.269 in the paper and 0.004 using alternative dates for California and Nebraska) comparing the two approaches to coding PDMP in California and Nebraska.

Source data and definitions for control variables

From the 2006 to 2012 Medicare Provider Analysis and Review (MEDPAR), Outpatient, Carrier, and Medicare Beneficiary Summary files, we obtained outpatient and inpatient diagnoses, beneficiaries' demographic characteristics, Medicaid enrollment, Part D low-income subsidy (LIS) status, and comorbidities. We controlled for behavioral health comorbidities that could affect opioid receipt and overdose using *International Classification of Diseases - 9th Revision* codes shown in Table S1.

Calculation of total 2008 fatal overdose involving opioid pain relievers contributed by disabled Medicare beneficiaries

After coding deaths due to overdose as suggested by the Centers for Disease Control and Prevention (Table S5), we constructed death rates for our sample in 2008. By dividing the 566 deaths in 2008 out of our 1,213,680 beneficiaries in our 2007 sample cohort (alive as of 12/31/07), we obtained a death rate of 46.6/100,000. We applied this rate to the population of 7,516,000 disabled Medicare beneficiaries reported in July 2008,[11] yielding an estimated 3,505 deaths in this population. This represents 23.7% of the 14,800 deaths reported in "CDC Vital Signs: Overdoses of Prescription Opioid Pain Relievers – United States, 1999-2008."[12]

Description of models to test associations between laws and opioid receipt or overdose

To test for statistically significant associations between state laws and opioid outcomes, we fit beneficiary-year level regression models of the form:

(1) $E[Y_{ist} | Year_t, State_s, Law_{st}, Patient_{ist}] = Year_t + State_s + \beta_1 Law_{st} + \beta_2 Patient_{ist}$

where Y_{ist} is an opioid-related measure for beneficiary i living in state s in year t, as a function of the laws implemented in beneficiary i's state in year t, Law_{st} (a vector of indicators for each of the 8 types of controlled substance laws), controlling for a vector of individual covariates described above, $Patient_{ist}$. We also included 1) indicators for the state of residence, $State_s$, to account for fixed state-level differences in opioid outcomes (e.g., prescription opioid use in Nevada differs from Michigan regardless of regulation), 2) six year indicators, $Year_t$, to control for national trends in measures, and 3) an indicator for whether a state had medical marijuana laws in place. We tested controls for any medical marijuana law (MML), and alternatively, controlling for medical marijuana laws permitting dispensaries, based on differences in the association between MMLs and outcomes according to the dispensary provision in other settings.[13,14] In practice, it made no difference how MMLs were coded, as our results were identical. We estimated these models using logistic regression. To measure possible effects of legislative intensity we also estimated models substituting Law_{st} with three indicators for the number of types of laws added since the baseline year, 2006 (1, 2, 3 or more; 0 is reference), again estimating models with logistic regression. All models assume that observations are independent across, but not within states over time. For all logistic regression models described above, we adjusted standard errors using Huber-White-Sandwich variance estimators, assuming correlation of observations within but not across states.

For each logistic regression model, we report the estimated coefficients in column 1 of Appendix Tables 6-15. We also report the adjusted difference in opioid outcomes according to state laws (or legislative intensity), as shown in column 2 of Appendix Tables 6-15. These adjusted differences use the logistic regression coefficients to form predicted probabilities of each opioid outcome (i.e. long-term opioid receipt), reporting the difference in predicted probability with and without a law type (i.e. tamper resistant prescription form requirements), when other model covariates are held at their mean values.

Adjusting for Multiple Hypothesis Tests

We estimate the associations between 8 types of controlled substance laws and five opioid outcomes (40 hypothesis tests). In separate models, we estimate associations between legal intensity (adding 1, 2, or 3 or more laws since 2006) and these same opioid outcomes (3 law variables and 5 outcomes = 15 hypothesis tests). Finally, we estimate associations between the number of potentially adverse opioid outcomes (range 0 to 4) and the number of types of laws in place in a beneficiary's state in that year. When estimating these 56 parameters, one would expect about five percent of these, or three to four hypotheses, to yield significant results even if the true associations were all zero, assuming two-tailed hypothesis tests with a .05 significance level. In the main paper figures and text, we present 95% confidence intervals obtained without adjustment for multiple comparisons, but we draw inference about statistical significance after adjusting for false discovery, reporting adjusted p-values (assuming a false discovery rate of 5%), as suggested by Benjamini and Hochberg 1995.[15,16] We adjusted for multiple inference for estimated coefficients on the law categories and measures of legal intensity shown in Appendix Tables 6 through 15, adjusting for 56 tests in total. We did not adjust for multiple comparisons in secondary analyses (long-term opioid users only and fitted lines from scatter plots of state change in opioid outcomes by state change in laws). It should be noted that the Benjamini and Hochberg adjustment is less conservative than the more common Bonferroni correction. Throughout the paper and appendix, we display confidence intervals without adjustment for multiple comparisons. In practice, this adjustment mattered little since we obtained few estimates that differed from zero, even ignoring the multiple comparisons issue.

One concern with this approach is the possibility that states implement laws in response to a spike in an adverse outcome. Then, following implementation, measured differences attributed to adding a new law may simply reflect a regression to the mean. For the two laws expanding most over our study period, PDMPs and tamper-resistant prescriptions, Appendix Figures 2 and 3 show the time trend in the 3 years before implementation (-3, -2, -1) and the 3 years after implementation (+1, +2, +3), omitting any partial years, so that year zero is the linear predication between values at -1 and +1. Each of our primary opioid-related measures shows no distinct spike or trend in the years leading up to (and following) implementation of these laws, boosting our confidence in the approach we have taken.

Linear probability models accounting for individual and state error structure

The models described thus far adjust for correlation of observations within states, but did not account separately for autocorrelation of observations within beneficiaries over time. Ideally, we would like to assume an exchangeable correlation structure at the individual level and an autoregressive (e.g., AR(1)) or M-dependence structure for the observations within individuals, because we believe that observations on the same individual that are closer in time will be more highly correlated than those further apart. To overcome the lack of appropriate software available to fit these models, we developed a two-step procedure including bootstrapping techniques to evaluate whether our estimated standard errors might be too large by ignoring the within-person correlation nested within states. First, we estimated our models, and obtained residuals from these models. Second, we performed a bootstrap procedure that (1) sampled the 51 states with replacement and (2) drew a sample of individuals with replacement within a bootstrapped state and within groups that indicated the number of years in which an individual appears in our data (1 to 7 range). In this fashion, we then matched bootstrapped residuals (from our bootstrapped states) with the linear predictions from all original individuals, matching the order in which individuals were observed (e.g. the residual from the first person-year observation in the bootstrapped data was matched to the linear predication from the first person-year observation in our actual sample of beneficiaries). This preserves the error structure within states (and nested within that, the within person error structure) but it also preserved the state level covariates.

We repeated the procedure a total of 250 times and analyzed each data set, computing the standard deviation of the effect of interest as the bootstrap SE. Unfortunately, the procedure took an impractical amount of time under the logistic regression specification. Therefore, to obtain an answer in a feasible amount of time on our actual data, we compared the robust (Huber-White) standard error calculation with the above bootstrap procedure using the linear probability model (LPM). The final columns (column 3) in Tables S6-S10 show, in square brackets, the bootstrapped standard errors accounting for correlation of observations within states, and nested within states, the correlation within beneficiaries.

Comparing across columns, the estimated marginal effect from the logistic regression models are very close in magnitude to those estimated in the LPM. The Huber White adjusted standard errors from each model (logistic regression and LPM) are also very similar. Under the bootstrap procedure, compared to simply computing robust standard errors clustered by state, the standard errors are neither systematically larger or smaller compared with the Huber-White adjusted standard errors (Column 3). More importantly, in no case did the bootstrapped standard error yield an estimate that was sufficiently different that it overturned our null findings. The conclusions regarding the lack of association between state controlled substance restrictions and our five opioid outcomes do not change.

Statistical power to detect associations between legal restrictions and opioid outcomes

We had 2.2 million unique beneficiaries in our data, with 3902 in the state with the fewest beneficiaries (Wyoming). After making a conservative adjustment for design effects (51 clusters assuming 3900 beneficiaries per cluster, and allowing for no extra precision from the multiple observations per beneficiary), we estimate 88% power to detect effect sizes of .2 for all measures but long-term opioid receipt, which had a power of 74% to detect effect sizes of .2. For key measures (4 or more prescribers, daily MED >120mg, and non-fatal prescription opioid overdose), we had 99% power to detect effect sizes of .1. This precision was driven by our large sample and low intra-class correlations ranging from .017 (chronic receipt) to .0016 (non-fatal overdose).

FIGURES

Figure S1, panel A. Number of types of state controlled-substance laws related to opioid prescribing and dispensing, 2006

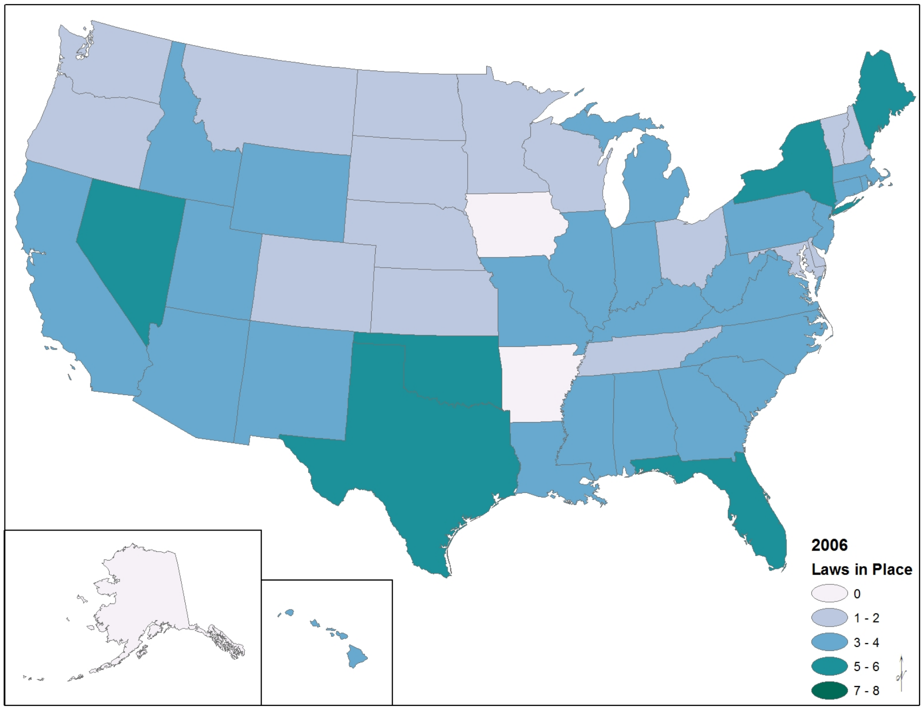


Figure S1, panel b. Number of types of controlled-substance laws related to opioid prescribing and dispensing, 2012

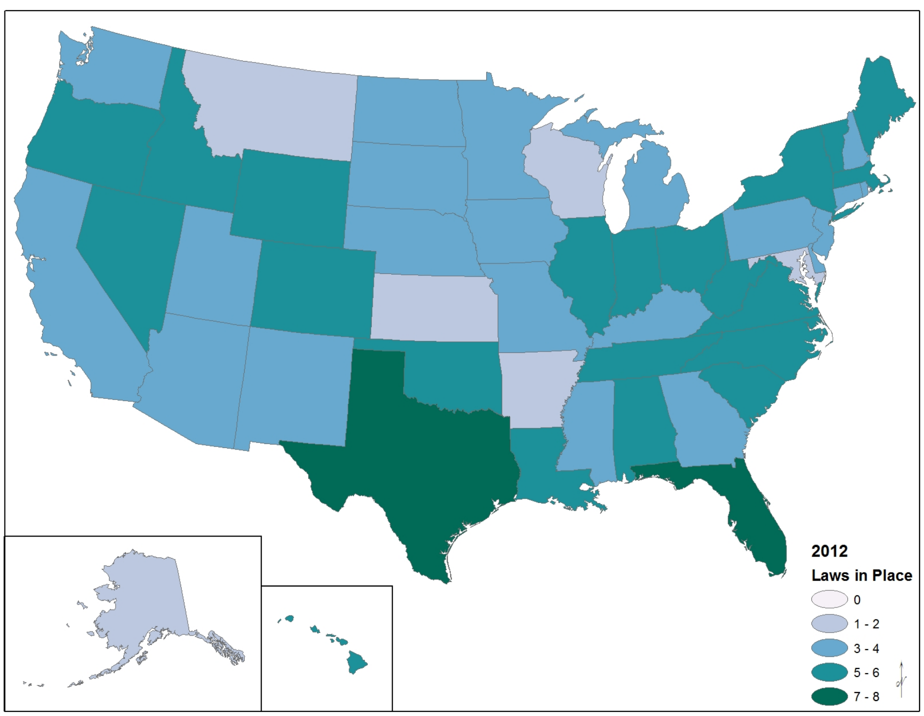
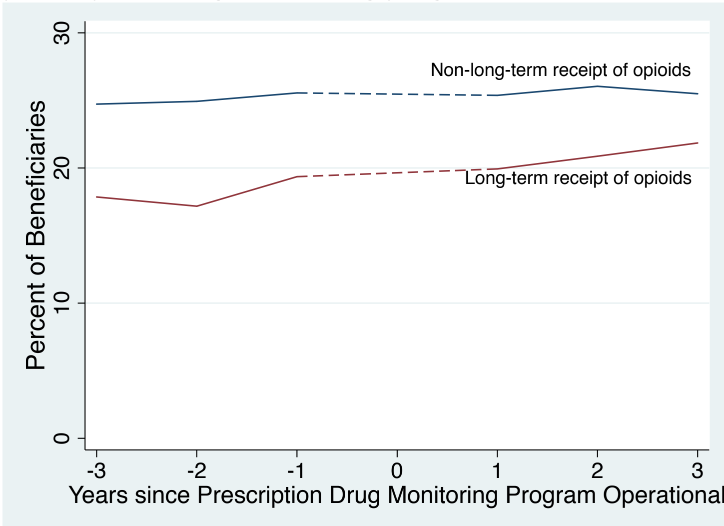
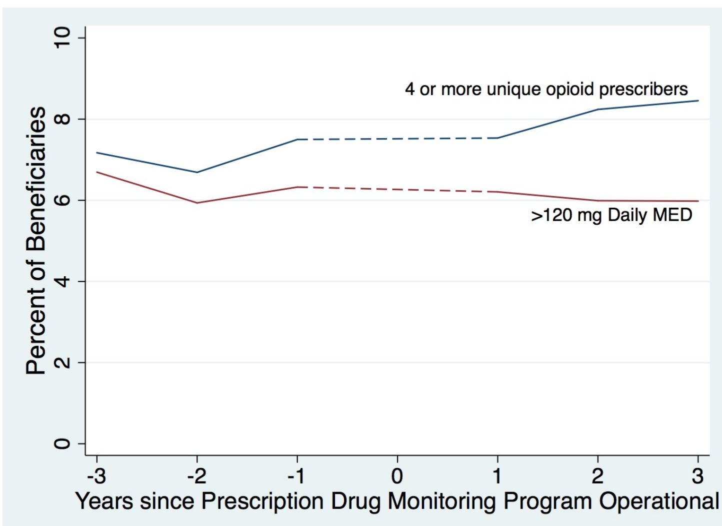


Figure S2. Prescription opioid receipt and nonfatal overdose by years from implementation of prescription drug monitoring program





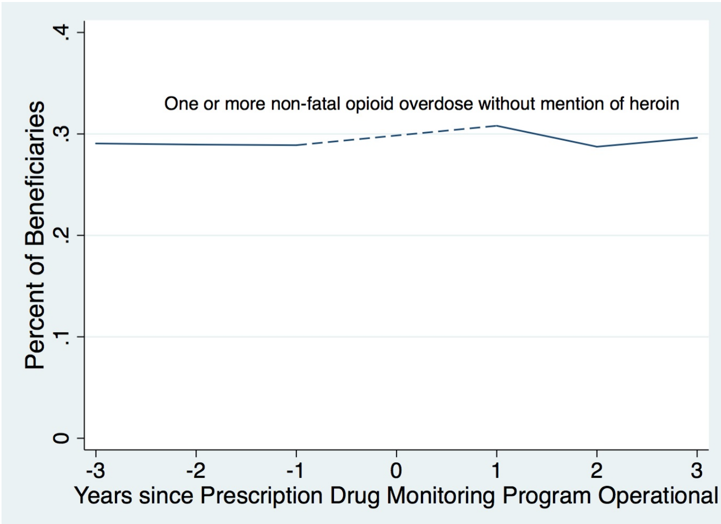


Figure S2 Legend: Long-term opioid receipt is defined as having one or more opioid prescription fill in each calendar quarter in a given year, and non-long-term opioid receipt is any annual receipt that is not chronic. MED is morphine equivalent dose. Daily MED >120mg equals 1 if daily MED exceeds 120mg in any quarter during the calendar year. Non-fatal opioid overdose excludes those with mention of heroin.

Figure S3. Prescription opioid receipt and nonfatal overdose by years from implementation of tamper-resistant prescription laws

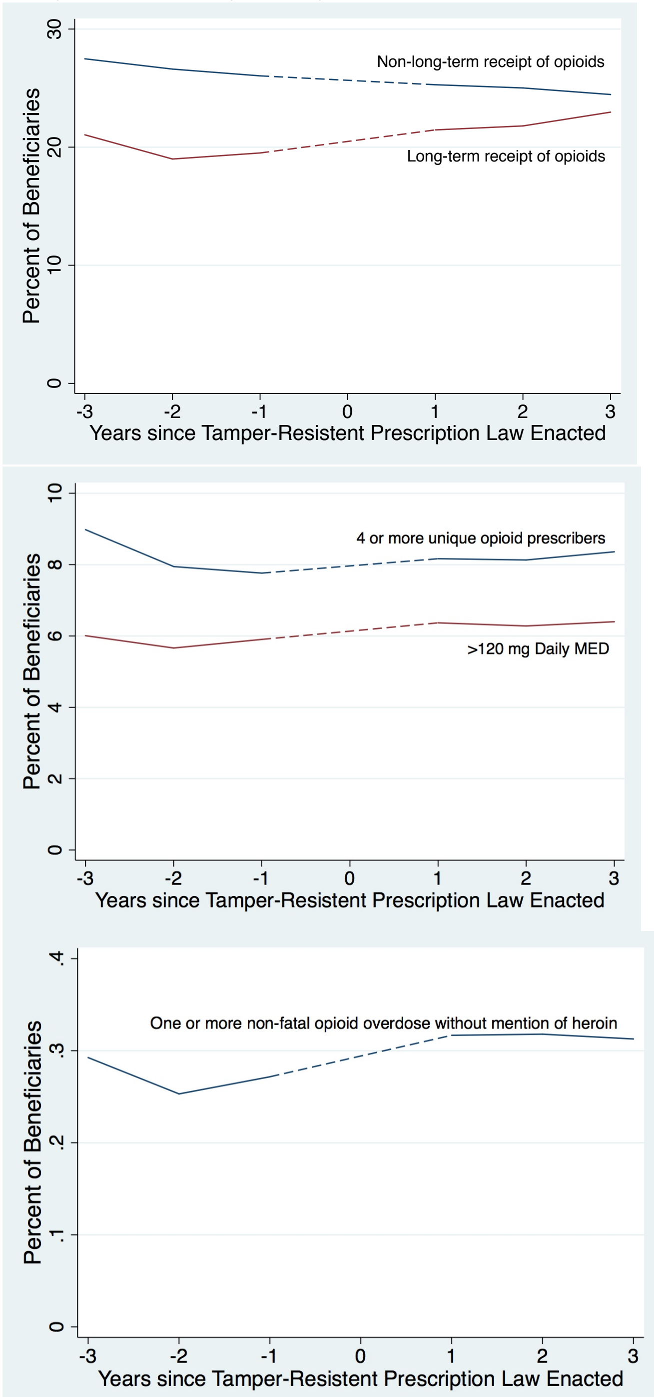


Figure S3 Legend: Long-term opioid receipt is defined as having one or more opioid prescription fill in each calendar quarter in a given year, and non-long-term opioid receipt is having one or more opioid prescription fill in 1, 2, or 3 calendar quarters. MED is morphine equivalent dose. Daily MED >120mg equals 1 if daily MED exceeds 120 mg in any quarter during the calendar year. Non-fatal opioid overdose excludes overdose with mention of heroin.

Figure S4. Estimated difference in opioid measures associated with individual controlled substance laws based on logistic regression models, beneficiaries with long-term opioid receipt

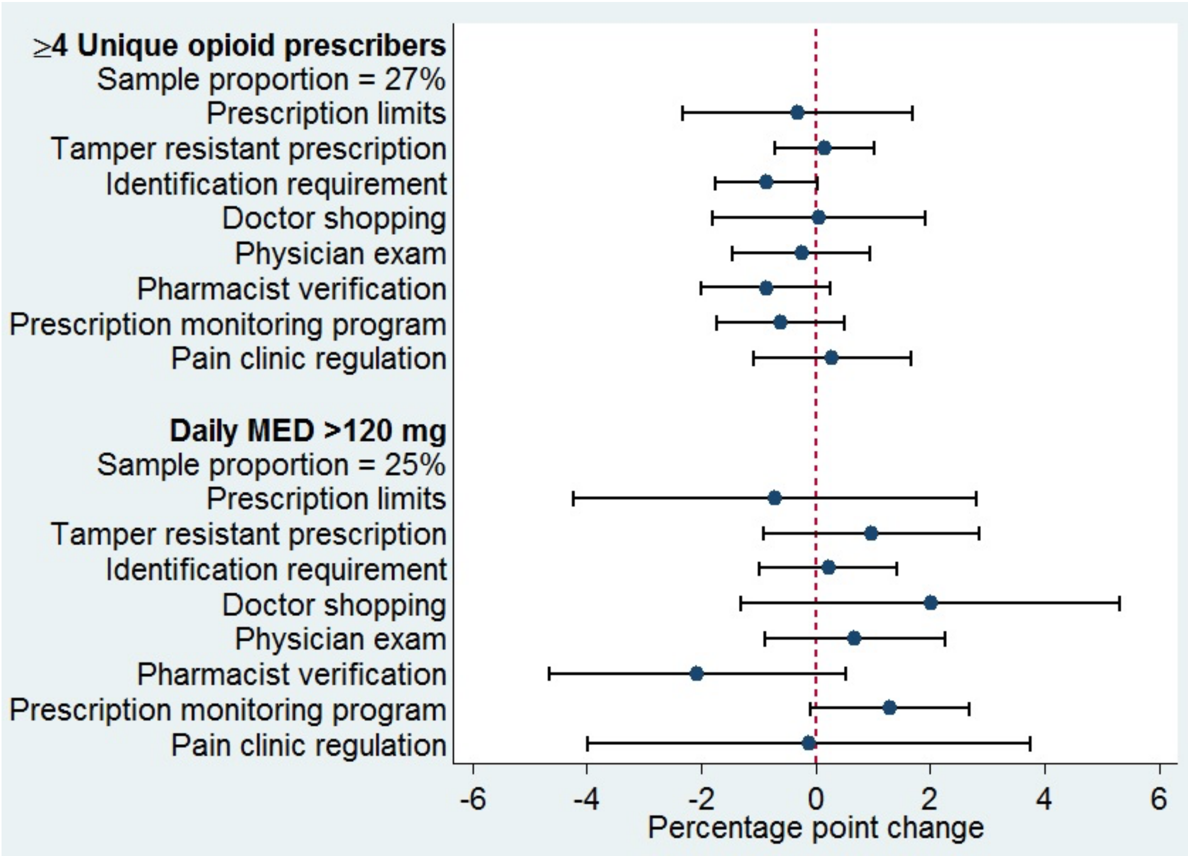


Figure S4 legend: This figure shows adjusted estimates of the association between state-level controlled substance laws and the percent of beneficiaries with long-term opioid receipt that 1) had 4 or more opioid prescribers and 2) had daily MED>120mg. The estimates reflect predicted differences in each outcome (with versus without that law type in place) based on individual-level logistic regressions of annual prescription opioid measures on time varying individual laws in place in a given state in a given year, controlling for state of residence, year indicators, age, race/ethnicity, sex, any receipt of Part D low income subsidy, Medicaid enrollment, Rx risk score (used to risk adjust payments to Medicare Part D prescription drug plans), the presence of state medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse or dependence. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. Confidence intervals around the estimates were estimated using the Delta method. Confidence intervals are not adjusted for multiple comparisons in this secondary analysis. Long-term opioid receipt is defined as having one or more opioid prescription fills in each calendar quarter in a given year. Daily MED >120mg equals 1 if daily MED exceeds 120mg in any quarter during the calendar year. In addition to estimates shown above, we estimated a negative association (-0.008, 95% CI -.035, .019) between the addition of exactly one controlled substance restriction and non-fatal overdose, and a negative association (-0.016, 95% CI -0.059, 0.027) percentage point lower non-fatal overdose for an additional law.

Figure S5. Estimated difference in composite summary of opioid outcomes and opioid index associated with number of types of state controlled-substance laws and index of laws, based on logistic regression

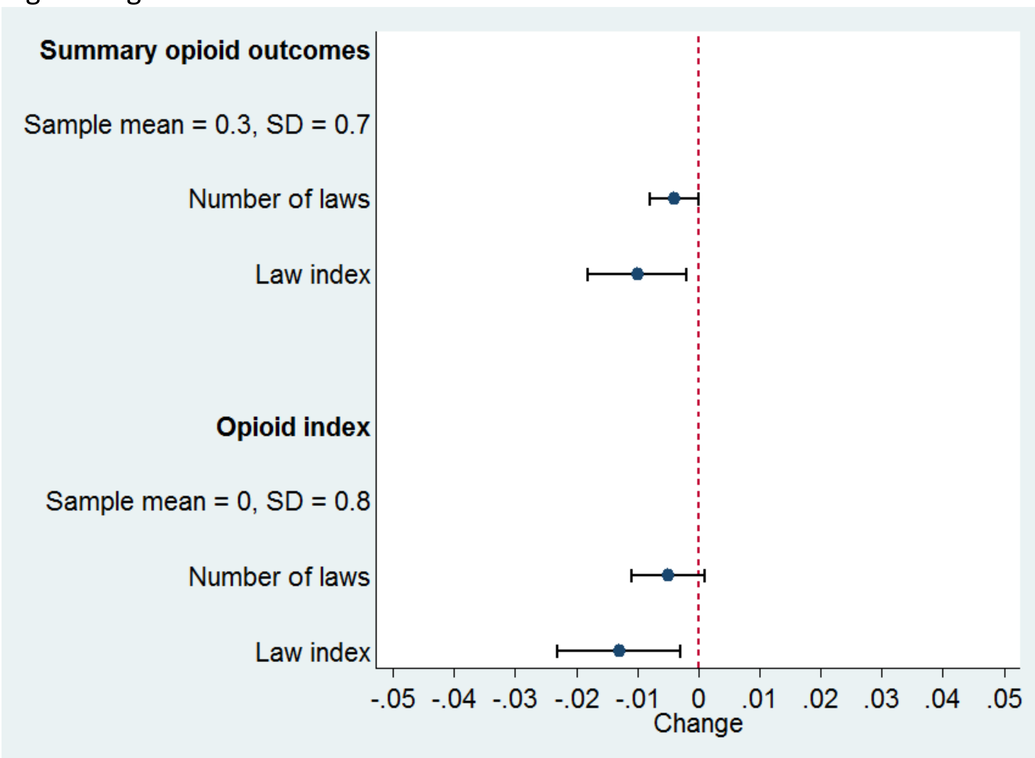
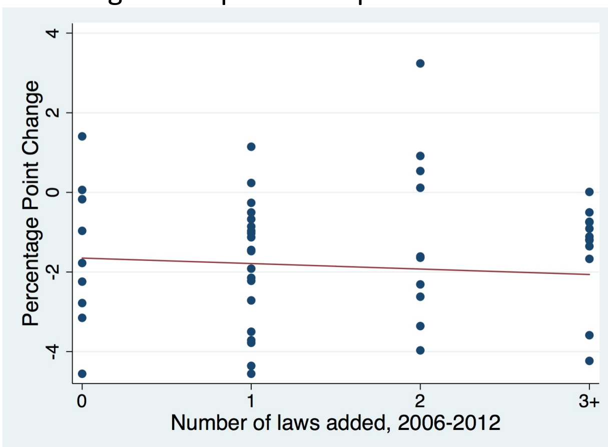


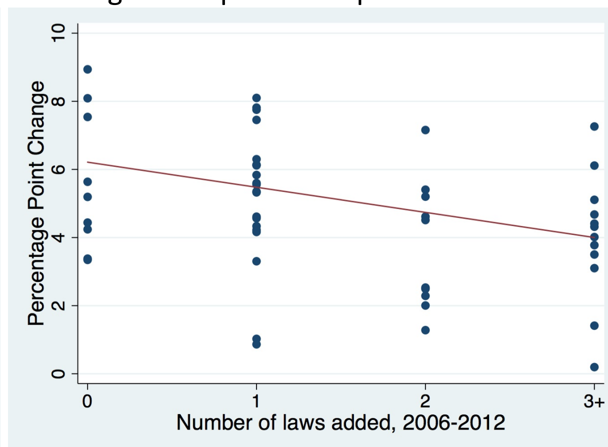
Figure S5 legend: This figure shows adjusted estimates of the association between state-level controlled substance laws and opioid measures. The coefficient estimates are marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on individual-level logistic regressions of annual prescription opioid measures on time varying measures of laws in place in a given state in a given year, controlling for year indicators, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score (used to risk adjust payments to Medicare Part D prescription drug plans), state medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse or dependence. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. Confidence intervals around marginal effects are estimated using the Delta method. Confidence intervals are not adjusted for multiple comparisons. Summary opioid outcomes is the sum of the following opioid measures: long-term opioid receipt, 4 or more unique opioid prescribers, daily MED >120 mg, and nonfatal opioid overdose without mention of heroin. Long-term opioid receipt is defined as having one or more opioid prescription fills in each calendar quarter in a given year. Daily MED >120mg equals 1 if daily MED exceeds 120mg in any quarter during the calendar year. Opioid index is the primary factor score from an iterated primary factor analysis of the four outcomes in summary of opioid outcomes. Number of laws is a count of the number of types of controlled-substance laws (0 to 8) in place in a given state and year. Law index is the primary factor score from an iterated primary factor analysis of the eight law types in the variable, Number of laws.

Figure S6. State-level changes in annual measures of prescription opioid receipt and overdose by the number of controlled substance prescribing and dispensing laws added, 2006 to 2012

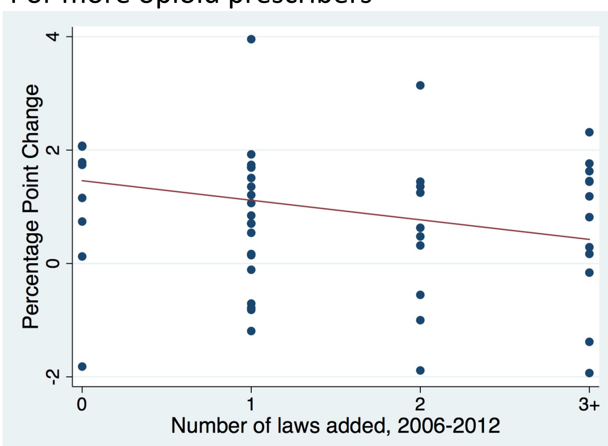
Non-long-term opioid receipt



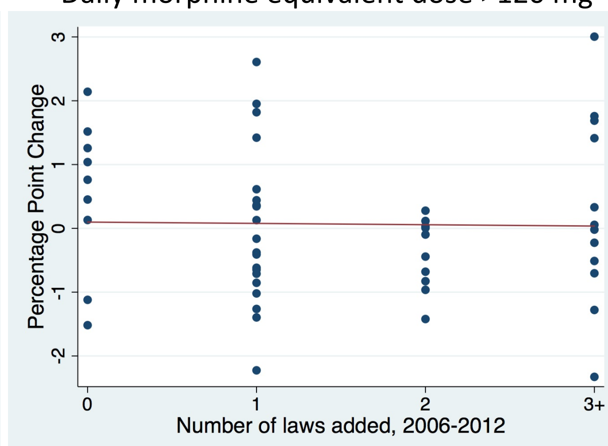
Long-term opioid receipt



4 or more opioid prescribers



Daily morphine equivalent dose >120 mg



One or more non-fatal opioid overdose events without mention of heroin

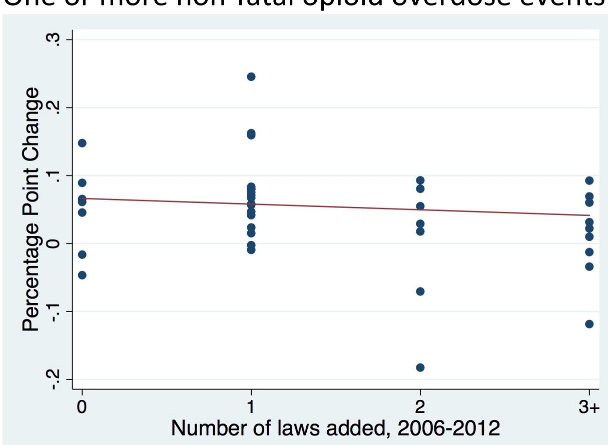


Figure S6 Legend: Chronic receipt is defined as having one or more opioid prescription fill in each calendar quarter in a given year, and non-chronic is any annual receipt that is not chronic. MED is morphine equivalent dose. Daily MED >120mg equals 1 if daily MED exceeds 120mg in

any quarter during the calendar year. Non-fatal opioid overdose excludes those with mention of heroin. Each dot represents a value for one state or the District of Columbia.
Linear fit model weights state observations by the number of beneficiaries in sample in 2012. Non-long-term opioid receipt: regression coefficient = -.14, p-value=.53; long-term opioid receipt: regression coefficient = -.74; p-value=.004; four or more opioid prescribers: regression coefficient = -.35; p-value=.01; mean daily MED >120mg: regression coefficient = -.02; p-value=.92; non-fatal opioid overdose without mention of heroin: regression coefficient = -.008; p-value=.283.

TABLES

Table S1. Codes used for exclusion criteria and select behavioral health diagnoses

Description	ICD-9 codes or other codes used
Exclusion	
Cancer exclusion (n= 498,217 person years)	140-171.9, 174-195.9, 200-208.9, 273.0, 273.3, V10.46
End Stage Renal Disease exclusion (n= 289,848 person years)	Basis of eligibility for Medicare was end stage renal disease
Hospice exclusion (n=17,615 person years)	Any claim in Medicare's Hospice file
Behavioral health diagnosis	
Depression	293.83, 296.2, 296.3, 296.90, 296.99, 298.0, 300.4, 301.12, 309.0, 309.1, 311
Serious Mental Illness	Schizophrenia and schizoaffective disorder: 295.0, 295.1, 295.2, 295.3, 295.4, 295.6, 295.7, 295.8, 295.9 Bipolar disorder: 296.0,296.1,296.4,296.5,296.6,296.7, 296.8, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9 Other nonorganic psychoses: 298.0, 298.1,298.2, 298.3, 298.4, 298.8, 298.9
Alcohol Abuse	V113.x, V791.x, 291.0-291.9, 303.0-303.9

Starting with 9,498,892 person years for beneficiaries age 21 to 64 with 12 months fee-for-service parts A, B, and D

Table S2. Morphine Equivalents Conversion Table

Oral Opioid Prescription Products Examined	**Morphine equivalents per milligram**
Codeine	0.15
Hydrocodone	1
Hydromorphone	4
Lovorphanol	12
Meperidine	0.1
Methadone	4
Morphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.3
Propoxyphene	0.6
Tapentadol	0.367

Source: Opioid Dosage Calculator Washington State Agency Medical Directors Group (accessed November 7, 2015 at http://agencymeddirectors.wa.gov/mobile.html) and Narcotic Equivalence Converter (Accessed July 4, 2013 at http://www.medcalc.com/narcotics.html). This table identifies opioid conversion factors used in analyses. One daily MED equals ~5mg oxycodone weekly.

Table S3. Codes used to identify non-fatal opioid-related overdoses

ICD-9 Code	Description	Frequency	% of overdoses with ICD-9 code
965.0*	Poisoning by opiates and related narcotics	0	0%
965.00	Poisoning by opium (alkaloids), unspecified	10,917	41.2%
965.02	Poisoning by methadone	4,964	18.7%
965.09	Poisoning by other opiates and related narcotics	20,644	77.9%
E850.1	Accidental poisoning by methadone	511	1.9%
E850.2	Accidental poisoning by other opiates and related narcotics	3,448	13.0%
E950.0	Suicide & self-inflicted poisoning by analgesics	3,833	14.5%
E980.0	Undetermined poisoning by analgesics, antipyretics, and antirheumatics	2,380	9.0%
965.01	Poisoning by heroin	3,620	13.7%
E850.0	Accidental poisoning by heroin	351	1.3%

*No records with four-digit ICD-9 code 965.0 were observed
Records could contain more than one ICD-9 code. We distinguished overdose events that did and did not mention heroin.
Non-fatal prescription opioid overdose, was based on primary or secondary diagnosis codes in emergency department and inpatient claims, excluding discharge status of “died.
Codes were based on Dunn et al., 2010 (accessed July 3, 2015 at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3000551/#APP1) and Larochelle, 2015, (accessed July 8, 2015 at http://www.ncbi.nlm.nih.gov/pubmed/25895077).

Table S4. State controlled substance prescribing and dispensing restrictions

Legal restriction	Description
Prescription Limit	Prescribing or dispensing regulations that limit: • Number of days after issuance when prescription can be filled • Days supply dispensed • Quantity prescribed and/or dispensed • Quantity/days supply when prescribed orally • Quantity/ days supply prescribed by non-physicians
Doctor Shopping	Makes it unlawful for patients to withhold from health care practitioner that they have received or been prescribed a controlled substance by another practitioner. Also prohibits patients from obtaining drugs via: fraud, deceit, subterfuge, misrepresentation, or concealment of material fact.
Identification Requirement	Requires or permits pharmacists to require identification prior to dispensing controlled substances.
Physician Exam/Relationship	Physician must examine patient, obtain history and perform patient evaluation, or requires a patient-physician relationship that includes physical examination before prescribing controlled substance.
Pharmacist Verification	If a pharmacist suspects there is not a patient-provider relationship, the pharmacist may not dispense prescription.
Tamper-resistant Prescription Forms	Special tamper-resistant prescription forms, or their digital equivalent, are required for controlled substances.
Pain Clinic Regulations	Pain clinic regulations are designed to prevent indiscriminant or inappropriate prescription of controlled substances by clinics. Pain clinic regulations can include specific registration, licensure, or ownership requirements or other state oversight of pain management clinics.
Operational Prescription Drug Monitoring Program (PDMP)	PDMPs collect, monitor, and analyze prescribing and dispensing records submitted by pharmacies and dispensing physicians. In some states, PDMPs were established by statute but not immediately operational. Our PDMP determination is based on when the program became operational.

Table S5. Codes used to identify fatal opioid-related overdoses

ICD-10 Code	Description
Cause of Death	
X40-X44	Accidental poisoning by and exposure to drugs and other biological substances
X60-X64	Intentional self-poisoning, suicide, by and exposure to drugs and other biological substances
Y10-Y14	Poisoning by and exposure to drugs and biological substances, undetermined intent
Type of Drug	
T40.2-T40.4	Prescription opioid pain reliever

Source: CDC Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999-2008. Accessed November 2, 2015 at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm
This excludes homicides with a cause of death of drug poisoning involving opioid pain relievers, X85.

Table S6. Model estimates for proportion of beneficiaries with non-long-term opioid receipt (sample proportion = 25%)

VARIABLES	(1) Logistic coefficients	(2) Marginal Effects (x100)	(3) Linear probability (x100)
Prescription limits	0.032***	0.597***	0.583***
	(0.010)	(0.186)	(0.192)
			[1.210]
Tamper resistant prescription	-0.011	-0.208	-0.206
	(0.013)	(0.235)	(0.240)
			[0.255]
Identification requirement	0.030**	0.564**	0.552*
	(0.015)	(0.279)	(0.281)
			[0.299]
Doctor shopping	-0.036	-0.664	-0.757
	(0.029)	(0.528)	(0.554)
			[0.927]
Physician exam	0.011	0.199	0.191
	(0.020)	(0.366)	(0.371)
			[0.392]
Pharmacist verification	0.007	0.138	0.144
	(0.010)	(0.183)	(0.191)
			[0.261]
Prescription monitoring program	-0.007	-0.139	-0.112
	(0.009)	(0.171)	(0.175)
			[0.223]
Pain clinic regulation	-0.023*	-0.422*	-0.416*
	(0.012)	(0.230)	(0.222)
			[0.304]
Age			
25-29	0.095***	1.810***	1.713***
	(0.010)	(0.188)	(0.176)
30-34	0.119***	2.272***	2.178***
	(0.011)	(0.220)	(0.200)
35-39	0.037***	0.701***	0.637***
	(0.013)	(0.254)	(0.231)
40-44	-0.016	-0.304	-0.376
	(0.017)	(0.311)	(0.293)
45-49	-0.077***	-1.410***	-1.506***
	(0.022)	(0.404)	(0.399)
50-54	-0.113***	-2.075***	-2.191***
	(0.025)	(0.441)	(0.445)

55-59	-0.098***	-1.796***	-1.910***
	(0.027)	(0.483)	(0.483)
60-64	-0.065**	-1.197**	-1.304**
	(0.030)	(0.546)	(0.542)
Year			
2007	0.008	0.147	0.142
	(0.006)	(0.108)	(0.110)
2008	-0.044***	-0.810***	-0.819***
	(0.007)	(0.121)	(0.126)
2009	-0.060***	-1.102***	-1.117***
	(0.009)	(0.161)	(0.176)
2010	-0.074***	-1.365***	-1.382***
	(0.011)	(0.198)	(0.218)
2011	-0.111***	-2.030***	-2.047***
	(0.014)	(0.243)	(0.276)
2012	-0.122***	-2.236***	-2.251***
	(0.015)	(0.262)	(0.300)
Female	0.294***	5.487***	5.392***
	(0.008)	(0.154)	(0.132)
Black	0.116***	2.191***	2.182***
	(0.012)	(0.225)	(0.237)
Other Non-white Race	0.084***	1.596***	1.545***
	(0.018)	(0.341)	(0.334)
Low income Subsidy	-0.118***	-2.249***	-2.169***
	(0.009)	(0.182)	(0.170)
Medicaid	0.037***	0.690***	0.675***
	(0.012)	(0.223)	(0.216)
Rx HCC	0.282***	5.265***	5.496***
	(0.009)	(0.164)	(0.183)
Depression Diagnosis	0.252***	4.858***	4.969***
	(0.013)	(0.259)	(0.231)
Serious Mental Illness Diagnosis	-0.091***	-1.663***	-1.786***
	(0.017)	(0.313)	(0.326)
Alcohol Use Diagnosis	0.405***	8.252***	8.264***
	(0.008)	(0.185)	(0.183)
Medical Marijuana Law	0.002	0.041	0.077
	(0.019)	(0.348)	(0.356)
Constant	-1.268***		22.101***
	(0.039)		(0.707)
Observations	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.592		
R-squared			0.019

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, any Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, presence of state medical marijuana laws, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Column 1 reports coefficients from logistic regression, Column 2 reports the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Column 3 reports results from a linear probability model. Coefficients and standard errors were multiplied by 100 for ease of presentation across outcomes in tables S6 to S10. Variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimate for Column 2 is based on the delta method. Non-long-term opioid receipt is defined as having one or more opioid prescription fill in, one, two, or three, but fewer than four calendar quarters in a given year. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S7. Model estimates for proportion of beneficiaries with long-term opioid receipt (sample proportion = 20%)

VARIABLES	(1) Logistic coefficients	(2) Marginal effects (x100)	(3) Linear probability (x100)
Prescription limits	-0.036	-0.524	-0.982
	(0.060)	(0.891)	(0.652)
			[0.810]
Tamper resistant prescription	-0.033**	-0.486**	-0.472*
	(0.017)	(0.245)	(0.307)
			[0.253]
Identification requirement	-0.037*	-0.543*	-0.875**
	(0.020)	(0.292)	(0.364)
			[0.269]
Doctor shopping	0.002	0.023	0.573
	(0.021)	(0.310)	(0.368)
			[0.551]
Physician exam	-0.028	-0.414	-0.487
	(0.033)	(0.484)	(0.631)
			[0.352]
Pharmacist verification	0.026	0.375	0.374
	(0.017)	(0.243)	(0.295)
			[0.356]
Prescription monitoring program	-0.010	-0.140	-0.176
	(0.015)	(0.219)	(0.235)
			[0.332]
Pain clinic regulation	-0.049**	-0.708**	-0.704**
	(0.021)	(0.293)	(0.301)
			[0.378]
Age			
25-29	0.589***	10.092***	2.240***
	(0.024)	(0.488)	(0.130)
30-34	1.061***	20.035***	5.171***
	(0.028)	(0.645)	(0.278)
35-39	1.332***	26.098***	7.489***
	(0.032)	(0.764)	(0.422)
40-44	1.556***	30.840***	10.336***
	(0.032)	(0.754)	(0.550)
45-49	1.743***	34.366***	13.163***
	(0.032)	(0.742)	(0.608)
50-54	1.831***	35.770***	14.659***
	(0.032)	(0.734)	(0.629)

55-59	1.796***	34.852***	14.070***
	(0.034)	(0.767)	(0.639)
60-64	1.646***	31.632***	11.609***
	(0.035)	(0.779)	(0.592)
Year			
2007	0.104***	1.547***	1.400***
	(0.008)	(0.118)	(0.113)
2008	0.121***	1.808***	1.602***
	(0.009)	(0.131)	(0.121)
2009	0.194***	2.957***	2.720***
	(0.010)	(0.162)	(0.182)
2010	0.247***	3.801***	3.517***
	(0.013)	(0.203)	(0.221)
2011	0.288***	4.472***	4.139***
	(0.016)	(0.264)	(0.300)
2012	0.306***	4.765***	4.427***
	(0.017)	(0.278)	(0.331)
Female	0.293***	4.273***	4.263***
	(0.017)	(0.251)	(0.221)
Black	-0.462***	-6.148***	-6.606***
	(0.086)	(1.037)	(1.233)
Other Non-white Race	-0.517***	-6.619***	-6.847***
	(0.065)	(0.722)	(0.859)
Low income Subsidy	0.010	0.152	0.127
	(0.019)	(0.271)	(0.314)
Medicaid	-0.053***	-0.782***	-0.773***
	(0.018)	(0.264)	(0.253)
Rx HCC	0.467***	6.803***	7.746***
	(0.024)	(0.350)	(0.556)
Depression Diagnosis	0.558***	8.912***	9.528***
	(0.016)	(0.278)	(0.352)
Serious Mental Illness Diagnosis	-0.634***	-7.708***	-9.543***
	(0.018)	(0.177)	(0.387)
Alcohol Use Diagnosis	-0.115***	-1.617***	-2.166***
	(0.032)	(0.431)	(0.496)
Medical Marijuana Law	0.045***	0.660***	0.556
	(0.012)	(0.176)	(0.478)
Constant	-3.756***		-2.333
	(0.048)		(1.459)
Observations	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.692		
R-squared			0.072

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, any Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, presence of state medical marijuana laws, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Column 1 reports coefficients from logistic regression, Column 2 reports the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Column 3 reports results from a linear probability model. Coefficients and standard errors were multiplied by 100 for ease of presentation across outcomes in tables S6 to S10. Variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimate for Column 2 is based on the delta method. Bootstrapped standard errors to account for the autocorrelation of observations within states over time, and nested within states, within individuals over time are denoted with [] in Column 3. Long-term opioid receipt is defined as having one or more opioid prescription fill in all four calendar quarters in a given year. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S8. Model estimates for proportion of beneficiaries with 4 or more opioid prescribers (sample proportion = 8%)

VARIABLES	(1) Logistic coefficients	(2) Marginal Effects (x100)	(3) Linear probability (x100)
Prescription limits	-0.040	-0.227	-0.311
	(0.073)	(0.423)	(0.373)
			[0.949]
Tamper resistant prescription	-0.026	-0.147	-0.160
	(0.024)	(0.133)	(0.161)
			[0.182]
Identification requirement	-0.034	-0.188	-0.260*
	(0.021)	(0.117)	(0.149)
			[0.175]
Doctor shopping	-0.005	-0.030	0.046
	(0.038)	(0.213)	(0.348)
			[0.614]
Physician exam	-0.033	-0.189	-0.229
	(0.029)	(0.163)	(0.167)
			[0.208]
Pharmacist verification	-0.006	-0.034	-0.103
	(0.034)	(0.189)	(0.186)
			[0.245]
Prescription monitoring program	-0.024	-0.136	-0.134
	(0.025)	(0.143)	(0.146)
			[0.168]
Pain clinic regulation	-0.019	-0.107	-0.156
	(0.043)	(0.236)	(0.248)
			[0.367]
Age			
25-29	0.381***	2.500***	1.490***
	(0.022)	(0.165)	(0.107)
30-34	0.566***	3.975***	2.507***
	(0.023)	(0.198)	(0.154)
35-39	0.534***	3.670***	2.175***
	(0.025)	(0.209)	(0.131)
40-44	0.526***	3.553***	2.099***
	(0.028)	(0.223)	(0.146)
45-49	0.485***	3.175***	1.748***
	(0.031)	(0.234)	(0.127)
50-54	0.385***	2.417***	0.944***
	(0.035)	(0.249)	(0.164)

55-59	0.216***	1.289***	-0.204
	(0.042)	(0.264)	(0.213)
60-64	-0.028	-0.154	-1.469***
	(0.041)	(0.228)	(0.218)
Year			
2007	0.095***	0.551***	0.660***
	(0.009)	(0.053)	(0.054)
2008	0.084***	0.484***	0.536***
	(0.015)	(0.090)	(0.082)
2009	0.099***	0.573***	0.629***
	(0.018)	(0.110)	(0.105)
2010	0.122***	0.714***	0.802***
	(0.023)	(0.140)	(0.132)
2011	0.122***	0.708***	0.889***
	(0.023)	(0.141)	(0.126)
2012	0.124***	0.723***	0.903***
	(0.027)	(0.165)	(0.148)
Female	0.403***	2.276***	2.332***
	(0.016)	(0.091)	(0.085)
Black	-0.060	-0.330	-0.307
	(0.080)	(0.436)	(0.536)
Other Non-white Race	-0.281***	-1.441***	-1.524***
	(0.063)	(0.295)	(0.295)
Low income Subsidy	0.116***	0.627***	0.348***
	(0.017)	(0.090)	(0.107)
Medicaid	0.144***	0.783***	0.876***
	(0.020)	(0.106)	(0.130)
Rx HCC	0.656***	3.685***	5.708***
	(0.028)	(0.149)	(0.439)
Depression Diagnosis	0.809***	5.554***	6.695***
	(0.017)	(0.138)	(0.220)
Serious Mental Illness Diagnosis	-0.200***	-1.043***	-1.787***
	(0.015)	(0.074)	(0.154)
Alcohol Use Diagnosis	0.466***	3.177***	4.488***
	(0.027)	(0.221)	(0.275)
Medical Marijuana Law	0.065***	0.373***	0.487***
	(0.017)	(0.095)	(0.148)
Constant	-3.978***		-0.241
	(0.049)		(0.647)
Observations	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.718		
R-squared			0.048

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, any Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, presence of state medical marijuana laws, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Column 1 reports coefficients from logistic regression, Column 2 reports the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Column 3 reports results from a linear probability model. Coefficients and standard errors were multiplied by 100 for ease of presentation across outcomes in tables S6 to S10. Variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimate for Column 2 is based on the delta method. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S9. Model estimates for proportion of beneficiaries with daily morphine equivalent dose >120 mg (sample proportion = 6%)

VARIABLES	(1) Logistic coefficients	(2) Marginal effects (x100)	(3) Linear probability (x100)
Prescription limits	-0.007	-0.032	-0.156
	(0.056)	(0.249)	(0.212)
			[0.740]
Tamper resistant prescription	0.030	0.131	0.200
	(0.040)	(0.175)	(0.244)
			[0.265]
Identification requirement	-0.006	-0.026	-0.089
	(0.028)	(0.123)	(0.143)
			[0.158]
Doctor shopping	0.075	0.333	0.445
	(0.072)	(0.327)	(0.504)
			[0.656]
Physician exam	0.009	0.041	-0.011
	(0.040)	(0.177)	(0.195)
			[0.244]
Pharmacist verification	-0.084	-0.364	-0.294
	(0.064)	(0.277)	(0.218)
			[0.278]
Prescription monitoring program	0.062	0.269	0.298
	(0.038)	(0.165)	(0.200)
			[0.231]
Pain clinic regulation	-0.047	-0.203	-0.309
	(0.090)	(0.380)	(0.388)
			[0.482]
Age			
25-29	0.659***	3.830***	0.621***
	(0.036)	(0.269)	(0.056)
30-34	1.193***	8.600***	1.672***
	(0.038)	(0.423)	(0.099)
35-39	1.484***	11.811***	2.550***
	(0.046)	(0.588)	(0.169)
40-44	1.656***	13.521***	3.350***
	(0.047)	(0.627)	(0.207)
45-49	1.804***	14.678***	4.217***
	(0.046)	(0.619)	(0.258)
50-54	1.823***	14.390***	4.358***
	(0.045)	(0.579)	(0.269)

55-59	1.660***	12.343***	3.368***
	(0.049)	(0.561)	(0.221)
60-64	1.380***	9.431***	1.936***
	(0.048)	(0.483)	(0.148)
Year			
2007	0.000	0.002	0.007
	(0.013)	(0.059)	(0.066)
2008	0.012	0.051	0.059
	(0.021)	(0.092)	(0.099)
2009	0.039	0.175	0.209
	(0.026)	(0.116)	(0.125)
2010	0.042	0.188	0.244
	(0.035)	(0.156)	(0.170)
2011	-0.080*	-0.345*	-0.400*
	(0.048)	(0.200)	(0.234)
2012	-0.104**	-0.443**	-0.497**
	(0.047)	(0.192)	(0.229)
Female	0.084***	0.369***	0.386***
	(0.020)	(0.088)	(0.095)
Black	-0.745***	-2.720***	-3.238***
	(0.119)	(0.344)	(0.451)
Other Non-white Race	-0.669***	-2.364***	-2.994***
	(0.090)	(0.247)	(0.405)
Low income Subsidy	-0.055**	-0.247**	-0.422***
	(0.024)	(0.107)	(0.144)
Medicaid	-0.245***	-1.140***	-1.318***
	(0.017)	(0.084)	(0.104)
Rx HCC	0.340***	1.494***	2.021***
	(0.018)	(0.084)	(0.120)
Depression Diagnosis	0.551***	2.785***	3.399***
	(0.023)	(0.131)	(0.188)
Serious Mental Illness Diagnosis	-0.494***	-1.801***	-2.708***
	(0.020)	(0.060)	(0.119)
Alcohol Use Diagnosis	-0.149***	-0.616***	-0.923***
	(0.028)	(0.106)	(0.155)
Medical Marijuana Law	0.150***	0.683***	0.834***
	(0.028)	(0.132)	(0.147)
Constant	-4.351***		3.211***
	(0.054)		(0.322)
Observations	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.684		
R-squared			0.022

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, any Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, presence of state medical marijuana laws, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Column 1 reports coefficients from logistic regression, Column 2 reports the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Column 3 reports results from a linear probability model. Estimates and standard errors in columns 2 and 3 were multiplied by 100 for ease of presentation across outcomes in tables S6 to S10. Variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimate for Column 2 is based on the delta method. Long-term opioid receipt is defined as having one or more opioid prescription fill in all four calendar quarters in a given year. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S10. Model estimates for proportion of beneficiaries with non-fatal prescription opioid overdose without mention of heroin (sample proportion = 0.28%)

VARIABLES	(1) Logistic coefficients	(2) Marginal effects (x100)	(3) Linear probability (x100)
Prescription limits	-0.132	-0.017	-0.040
	(0.219)	(0.031)	(0.058)
			[0.050]
Tamper resistant prescription	0.009	0.001	0.006
	(0.035)	(0.004)	(0.009)
			[0.016]
Identification requirement	-0.026	-0.003	-0.010
	(0.047)	(0.006)	(0.013)
			[0.019]
Doctor shopping	-0.128	-0.015	-0.040*
	(0.081)	(0.009)	(0.023)
			[0.030]
Physician exam	0.003	0.0004	-0.004
	(0.055)	(0.007)	(0.013)
			[0.025]
Pharmacist verification	-0.068	-0.008	-0.021
	(0.056)	(0.007)	(0.013)
			[0.025]
Prescription monitoring program	-0.018	-0.002	-0.001
	(0.021)	(0.003)	(0.006)
			[0.017]
Pain clinic regulation	-0.002	0.0002	0.002
	(0.032)	(0.004)	(0.011)
			[0.023]
Age			
25-29	0.163**	0.022*	0.011
	(0.079)	(0.011)	(0.015)
30-34	0.169**	0.023**	-0.002
	(0.080)	(0.011)	(0.016)
35-39	0.116*	0.015*	-0.032***
	(0.066)	(0.009)	(0.012)
40-44	0.101	0.013	-0.043***
	(0.072)	(0.010)	(0.013)
45-49	0.108	0.014	-0.050***
	(0.070)	(0.009)	(0.011)
50-54	0.087	0.011	-0.061***
	(0.063)	(0.008)	(0.009)

55-59	-0.012	-0.002	-0.090***
	(0.069)	(0.008)	(0.011)
60-64	-0.253***	-0.029***	-0.133***
	(0.081)	(0.009)	(0.012)
Year			
2007	0.131***	0.017***	0.037***
	(0.019)	(0.003)	(0.005)
2008	-0.009	-0.001	0.002
	(0.025)	(0.003)	(0.006)
2009	0.181***	0.024***	0.053***
	(0.028)	(0.004)	(0.008)
2010	0.140***	0.018***	0.042***
	(0.024)	(0.003)	(0.006)
2011	0.120***	0.016***	0.046***
	(0.026)	(0.003)	(0.008)
2012	0.095***	0.012***	0.038***
	(0.032)	(0.004)	(0.008)
Female	0.275***	0.034***	0.048***
	(0.030)	(0.004)	(0.008)
Black	-0.915***	-0.090***	-0.177***
	(0.086)	(0.006)	(0.014)
Other Non-white Race	-0.535***	-0.055***	-0.130***
	(0.073)	(0.007)	(0.018)
Low income Subsidy	0.066	0.008	0.008
	(0.044)	(0.005)	(0.010)
Medicaid	-0.068**	-0.009*	-0.021**
	(0.034)	(0.004)	(0.008)
Rx HCC	0.681***	0.085***	0.288***
	(0.027)	(0.003)	(0.016)
Depression Diagnosis	1.533***	0.314***	0.508***
	(0.026)	(0.008)	(0.022)
Serious Mental Illness Diagnosis	0.939***	0.181***	0.702***
	(0.021)	(0.006)	(0.035)
Alcohol Use Diagnosis	1.040***	0.220***	0.971***
	(0.028)	(0.010)	(0.046)
Medical Marijuana Law	-0.037	-0.005	-0.011
	(0.029)	(0.004)	(0.007)
Constant	-7.802***		-0.153***
	(0.096)		(0.027)
Observations	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.847		
R-squared			0.008

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, any Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, presence of state medical marijuana laws, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Column 1 reports coefficients from logistic regression, Column 2 reports the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Column 3 reports results from a linear probability model. Coefficients and standard errors were multiplied by 100 for ease of presentation across outcomes in tables S6 to S10. Variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimate for Column 2 is based on the delta method. Bootstrapped standard errors to account for the autocorrelation of observations within states over time, and nested within states, within individuals over time are denoted with [] in Column 3. Long-term opioid receipt is defined as having one or more opioid prescription fill in all four calendar quarters in a given year. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S11. Model estimates for proportion of beneficiaries with non-long-term opioid receipt, number of types of laws (sample proportion = 25%)

	Number of Types of Laws					
	(1)	(2)	(3)	(4)	(5)	(6)
VARIABLES	Logistic coefficients	Marginal effects (x100)	Linear probablity (x100)	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)
Number of Types of Laws Added Since 2006						
1 Law Added	-0.001	-0.027	-0.024			
	(0.008)	(0.157)	(0.164)			
			[0.176]			
2 Laws Added	-0.001	-0.024	-0.021			
	(0.017)	(0.308)	(0.319)			
			[0.318]			
3 Laws Added	-0.015	-0.287	-0.293			
	(0.026)	(0.473)	(0.490)			
			[0.504]			
Number of Types of Laws				-0.004	-0.066	-0.067
				(0.007)	(0.139)	(0.144)
Observations	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.592			0.592		
R-squared			0.019			0.019

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Columns 1 and 4 report results from logistic regression, Columns 2 and 5 report the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Columns 3 and 6 report results from a linear probability model. Estimates and standard errors in Columns 2, 3, 5 and 6 were multiplied by 100 for ease of presentation. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimates for Columns 2 and 5 are based on the delta method. After adjustment for multiple comparisons, none of the estimates above are statistically significant. Chronic receipt is defined as having one or more opioid prescription fill in each calendar quarter in a given year, non-chronic is any annual receipt that is not chronic. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S12. Model estimates for proportion of beneficiaries with long-term opioid receipt, number of types of laws (sample proportion = 20%)

	Number of Types of Laws					
	(1)	(2)	(3)	(4)	(5)	(6)
VARIABLES	Logistic coefficients	Marginal effects (x100)	Linear probability	Logistic coefficients	Marginal effects (x100)	Linear probability
Number of Types of Laws Added Since 2006						
1 Law Added	-0.016*	-0.238*	-0.301*			
	(0.009)	(0.133)	(0.172)			
			[0.176]			
2 Laws Added	-0.041*	-0.588*	-0.713*			
	(0.023)	(0.333)	(0.416)			
			[0.412]			
3 Laws Added	-0.071***	-1.009***	-1.029**			
	(0.026)	(0.368)	(0.471)			
			[0.512]			
Number of Types of Laws				-0.021***	-0.310***	-0.319**
				(0.008)	(0.115)	(0.140)
Observations	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.692			0.692		
R-squared			0.072			0.072

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and long-term opioid receipt, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Columns 1 and 4 report results from logistic regression, Columns 2 and 5 report the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Columns 3 and 6 report results from a linear probability model. Estimates and standard errors in Columns 2, 3, 5 and 6 were multiplied by 100 for ease of presentation. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimates for marginal effects in columns 2 and 5 are based on the delta method. Block bootstrapped standard errors to account for the autocorrelation of observations within states over time and within individuals over time are denoted with [] in Columns 3 and 6. Chronic receipt is defined as having one or more opioid prescription fill in each calendar quarter in a given year, non-chronic is any annual receipt that is not chronic. Area under the ROC curve was calculated after unweighted logistic regression. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S13. Model estimates for proportion of beneficiaries with 4 or more opioid prescribers, number of types of laws (sample proportion = 8%)

	Number of Types of Laws					
	(1)	(2)	(3)	(4)	(5)	(6)
VARIABLES	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)
Number of Types of Laws Added Since 2006						
1 Law Added	-0.010	-0.054	-0.089			
	(0.016)	(0.087)	(0.101)			
			[0.113]			
2 Laws Added	-0.049*	-0.269*	-0.335*			
	(0.027)	(0.147)	(0.173)			
			[0.186]			
3 Laws Added	-0.077**	-0.419**	-0.523**			
	(0.038)	(0.203)	(0.253)			
			[0.272]			
Number of Types of Laws				-0.023**	-0.127**	-0.154**
				(0.011)	(0.062)	(0.073)
Observations	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.718			0.718		
R-squared			0.048			0.048

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and 4 or more unique opioid prescribers, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Columns 1 and 4 report results from logistic regression, Columns 2 and 5 report the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Columns 3 and 6 report results from a linear probability model. Estimates and standard errors in Columns 2, 3, 5 and 6 were multiplied by 100 for ease of presentation. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimates for Columns 2 and 5 are based on the delta method. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S14. Model estimates for proportion of beneficiaries with daily morphine equivalent dose >120 mg, number of types of laws (sample proportion = 6%)

	Number of Types of Laws					
	(1)	(2)	(3)	(4)	(5)	(6)
VARIABLES	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)
Number of Types of Laws Added Since 2006						
1 Law Added	0.006	0.027	0.033			
	(0.032)	(0.141)	(0.163)			
			[0.161]			
2 Laws Added	-0.003	-0.011	0.008			
	(0.049)	(0.214)	(0.223)			
			[0.232]			
3 Laws Added	0.043	0.193	0.210			
	(0.052)	(0.236)	(0.300)			
			[0.280]			
Number of Types of Laws				0.014	0.062	0.069
				(0.018)	(0.077)	(0.093)
Observations	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.684			0.684		
R-squared			0.022			0.022

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and daily MED>120 mg, based on regression models controlling for year, state of residence, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Columns 1 and 4 report results from logistic regression, Columns 2 and 5 report the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and Columns 3 and 6 report results from a linear probability model. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimates for Columns 2 and 5 are based on the delta method. Daily MED >120mg equals 1 if daily MED exceeds 120mg in any quarter during the calendar year. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

Table S15. Model estimates for proportion of beneficiaries with non-fatal prescription opioid overdose without mention of heroin, number of types of laws (sample proportion = 0.28%)

	Number of Types of Laws					
	(1)	(2)	(3)	(4)	(5)	(6)
VARIABLES	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)	Logistic coefficients	Marginal effects (x100)	Linear probability (x100)
Number of Types of Laws Added Since 2006						
1 Law Added	0.001	0.0002	0.002			
	(0.023)	(0.003)	(0.006)			
			[0.010]			
2 Laws Added	-0.019	-0.002	-0.004			
	(0.040)	(0.005)	(0.012)			
			[0.017]			
3 Laws Added	-0.070	-0.008	-0.019			
	(0.048)	(0.006)	(0.015)			
			[0.021]			
Number of Types of Laws				-0.026**	-0.003**	-0.007*
				(0.013)	(0.002)	(0.004)
Observations	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212	8,693,212
Area under ROC curve	0.847			0.847		
R-squared			0.008			0.008

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and non-fatal opioid overdose without mention of heroin, based on regression models Column 3controlling for year, state of residence, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Columns 1 and 4 report results from logistic regression, Columns 2 and 5 report the marginal effects, or the predicted difference in the dependent variable associated with that independent variable, based on the logistic regression, and

Columns 3 and 6 report results from a linear probability model. Coefficients and standard errors in Columns 2 and 5 were multiplied by 100 for ease of comparison with Columns 3 and 6. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. The variance estimates for Columns 2 and 5 are based on the delta method. Area under the ROC curve was calculated after unweighted logistic regression. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, only the estimate of association between 1 law added since 2006 and non-fatal opioid overdose without mention of heroin is statistically significant.

Table S16. Model estimates for number of potentially adverse opioid measures

	(1)
Outcome:	Number of adverse opioid measures (mean=.33, SD=.69)
Number of Types of Laws	-0.004*
	(0.002)
Age	
25-29	0.044***
	(0.003)
30-34	0.093***
	(0.005)
35-39	0.122***
	(0.007)
40-44	0.157***
	(0.008)
45-49	0.191***
	(0.009)
50-54	0.199***
	(0.009)
55-59	0.171***
	(0.009)
60-64	0.119***
	(0.007)
Year	
2007	0.021***
	(0.002)
2008	0.022***
	(0.002)
2009	0.036***
	(0.003)
2010	0.046***
	(0.004)
2011	0.046***
	(0.005)
2012	0.048***
	(0.005)
Female	0.070***
	(0.004)
Black	-0.103***
	(0.022)

Other Non-white Race	-0.115***
	(0.015)
Low income Subsidy	0.001
	(0.005)
Medicaid	-0.012***
	(0.004)
Rx HCC	0.158***
	(0.011)
Depression Diagnosis	0.201***
	(0.007)
Serious Mental Illness Diagnosis	-0.133***
	(0.005)
Alcohol Use Diagnosis	0.024***
	(0.009)
Medical Marijuana Law	0.019***
	(0.006)
Constant	0.005
	(0.023)
Observations	8,693,212
R-squared	0.073

*** p<0.01, ** p<0.05, * p<0.1 This table shows adjusted estimates of the association between state-level controlled substance laws and measures of opioid receipt based on regression models controlling for year, state of residence, age, race/ethnicity, sex, Part D low income subsidy, Medicaid enrollment, Rx risk score used to risk adjust payments to Medicare part D prescription drug plans, medical marijuana legislation, and diagnoses of depression, serious mental illness and alcohol abuse/dependence. Number of potentially adverse opioid measures ranges from 0 to 4. It is a beneficiary-specific count of opioid outcomes: long-term opioid receipt, 4 or more unique opioid prescribers, daily morphine equivalent dose >120 mg, and non-fatal opioid overdose. All variance estimates account for the autocorrelation of observations within states over time using Huber-White Sandwich estimators. Daily MED >120mg equals 1 if daily MED exceeds 120mg in any quarter during the calendar year. P-values for estimates above do not adjust for multiple comparisons. With this adjustment, estimates of associations between outcomes and laws are not statistically significant.

REFERENCES

1. Opioid Dose Calculator. (Accessed May 14, 2015, at http://agencymeddirectors.wa.gov/mobile.html.)
2. Narcotic equivalence converter. 2001. (Accessed May 14, 2015, at http://www.medcalc.com/narcotics.html.)
3. Larochelle MR, Zhang F, Ross-Degnan D, Wharam J. Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene. JAMA Intern Med 2015;175:978-87.
4. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med 2010;152:85-92.
5. 2014 NASCSA Survey of Controlled Substance Authorities. 2014. (Accessed February 3, 2016, at http://www.nascsa.org/surveys/2014csauthoritiessurvey.pdf.)
6. National Alliance for Model State Drug Laws. States that Require Prescribers and/or Dispensers to Access PMP Database in Certain Circumstances. 2014.
7. Prescription Drug Monitoring Program Center of Excellence. Mandating PDMP Participation by Medical Providers: Current Status and Experience in Selected States. 2014.
8. Davis C, Chang S. Legal interventions to reduce overdose mortality: Naloxone access and overdose good Samaritan laws. The Network for Public Health Law 2015.
9. Naloxone Overdose Prevention Laws Map. 2016. (Accessed Feb 3, 2016, at http://lawatlas.org/query?dataset=laws-regulating-administration-of-naloxone.)
10. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention. Prescription Drug Overdose: State Laws. Selected State Legislative Strategies Governing Prescription Drug Abuse and Diversion in the US: Center for Disease Control; 2012.
11. Centers for Medicare & Medicaid Services. Medicare & Medicaid Statistical Supplement: 2009 Edition 2009.
12. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morbidity and mortality weekly report 2011;60:1487.
13. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med 2014;174:1668-73.
14. Powell D, Pacula RL, Jacobson M. Do Medical Marijuana Laws Reduce Addictions and Deaths Related to Pain Killers? NBER Working Paper 21345. Cambridge, MA: NBER.2015.
15. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B (Methodological) 1995:289-300.
16. McDonald JH. Multiple comparisons. Handbook of Biological Statistics 3rd ed. Baltimore, Maryland: Sparkey House Publishing; 2015:254-60.
17. Bertrand M, Duflo E, Mullainathan S. How Much Should We Trust Differences-In-Differences Estimates? The Quarterly Journal of Economics 2004;119:249-75.