Original Scholarship

The Association of State Opioid Misuse Prevention Policies With Patient- and Provider-Related Outcomes: A Scoping Review

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Policy Points:

- This scoping review reveals a growing literature on the effects of certain state opioid misuse prevention policies, but persistent gaps in evidence on other prevalent state policies remain.
- Policymakers interested in reducing the volume and dosage of opioids prescribed and dispensed can consider adopting robust prescription drug monitoring programs with mandatory access provisions and drug supply management policies, such as prior authorization policies for high-risk prescription opioids.
- Further research should concentrate on potential unintended consequences of opioid misuse prevention policies, differential policy effects across populations, interventions that have not

received sufficient evaluation (eg, Good Samaritan laws, naloxone access laws), and patient-related outcomes.

Context: In the midst of an opioid crisis in the United States, an influx of state opioid misuse prevention policies has provided new opportunities to generate evidence of policy effectiveness that can inform policy decisions. We conducted a scoping review to synthesize the available evidence on the effectiveness of US state interventions to improve patient and provider outcomes related to opioid misuse and addiction.

Methods: We searched six online databases to identify evaluations of state opioid policies. Eligible studies examined legislative and administrative policy interventions that evaluated (a) prescribing and dispensing, (b) patient behavior, or (c) patient health.

Findings: Seventy-one articles met our inclusion criteria, including 41 studies published between 2016 and 2018. These articles evaluated nine types of state policies targeting opioid misuse. While prescription drug monitoring programs (PDMPs) have received considerable attention in the literature, far fewer studies addressed other types of state policy. Overall, evidence quality is very low for the majority of policies due to a small number of evaluations. Of interventions that have been the subject of considerable research, promising means of reducing the volume and dosages of opioids prescribed and dispensed include drug supply management policies and robust PDMPs. Due to low study number and quality, evidence is insufficient to draw conclusions regarding interventions targeting patient behavior and health outcomes, including naloxone access laws and Good Samaritan laws.

Conclusions: Recent research has improved the evidence base on several state interventions targeting opioid misuse. Specifically, moderate evidence suggests that drug supply management policies and robust PDMPs reduce opioid prescribing. Despite the increase in rigorous evaluations, evidence remains limited for the majority of policies, particularly those targeting patient health–related outcomes.

Keywords: opioid, state policy, scoping review, drug overdose.

The United States is in the midst of an opioid overdose crisis. In 2017 there were 70,237 drug overdose deaths in the United States, 47,600 of which were attributable to opioids.[1,2] Prescription opioid medications caused most fatal opioid overdose deaths in the first decade of the 2000s.[3] Although today most opioid overdoses involve heroin and illicit fentanyl, many who experience opioid harms were first exposed to opioids via a prescription.[1,4]

States have implemented a panoply of preventive measures in recent years to address health consequences associated with opioid misuse and addiction. These state policies target prevention at different levels, from primary prevention of initial exposure to opioids, to secondary prevention to avoid high-risk opioid exposure, to tertiary prevention to treat individuals with opioid use disorder.[5,6] Table 1 summarizes this array of approaches. While these prevention categories are not mutually exclusive, we place each state policy within a prevention group to facilitate organization of policies based on their chief intent.

Previous studies aggregated evidence from specific interventions[7,8] and integrated strategies in a single review.[9,10] Reviews published in the past two years of prescription drug monitoring program (PDMP) evaluations are inconclusive with regard to PDMP effects on overdose and other outcomes.[7,8] Reviews that synthesize evaluations of multiple interventions published prior to 2016 identified some promising state policies to decrease opioid prescribing, including PDMPs, policies

targeting insurance practices, pain clinic regulations, clinical guidelines, and naloxone access laws.[9,10] However, they also highlighted that evidence quality was low and that rigorous evaluations were needed to further investigate policy effects.[9,10] Since the publication of these reviews, state policies have evolved significantly and original empirical evaluations of state interventions have improved in study rigor,[6] suggesting that an updated review would provide additional insight into the effects of state policies targeting opioid misuse and overdose.

This scoping review aims to synthesize the available evidence on the effectiveness of prevalent state opioid policies on improving outcomes related to opioid prescribing and dispensing, patient behavior, and patient health. Given the recent increase in the adoption of state opioid policies and interest among policymakers to address the opioid crisis, we hypothesized that the evidence base evaluating these policies would have grown substantially in recent years, offering a clearer sense of policy effects on patient and prescriber outcomes. We also hypothesized that policies would demonstrate more significant effects on the outcomes most closely related to the behavior(s) they target. Specifically, we expected primary and secondary prevention policies to be most associated with changes in outcomes related to opioid prescribing and dispensing and patient behavior, and tertiary prevention strategies to have the greatest impacts on patient health. Finally, we expected that promising policies identified by previous reviews—specifically PDMPs, policies targeting insurance practices, pain clinic regulations, clinical guidelines, and naloxone access laws—would have the largest effects on provider- and patient-related outcomes compared to other state laws.

Methods

We systematically identified and synthesized findings from empirical evaluations of state opioid misuse prevention programs.

Data Sources and Searches

Following consultation with an informationist at the Taubman Health Sciences Library at the University of Michigan, we searched six online literature databases: Cumulative Index to Nursing and Allied Health Literature Complete, Criminal Justice Abstracts, the National Bureau of Economic Research (NBER), PubMed, PsychINFO, and Scopus. We conducted the initial search in PubMed; searches in other databases, with the exception of NBER, were analogous to the original search. In NBER, we searched "opioid" and reviewed all yielded articles for inclusion. We examined references from the selected materials to identify additional articles that met the inclusion criteria. To ensure that we captured all relevant studies, we compared our yielded articles with the evaluations included in the following review papers: Haegerich et al., 2014;[9] Beaudoin et al., 2016;[10] Finley et al., 2017;[8] and Fink et al., 2018.[7] We conducted the search in summer 2018 and no additional articles were added after September 1, 2018. All of the resulting citations and abstracts were exported to Mendeley 1.19.1. We did not impose a date restriction on searches. See Appendix 1 for terms and the algorithm used in the literature search.

Eligibility Criteria

Inclusion in the scoping review required that the original quantitative research article be written in English and evaluate the effect of a US state policy on a patient- or provider-related outcome (defined below). We defined state policy as a legislative or administrative action, such as a law or regulation, that directly targeted opioid misuse. For example, naloxone access laws are a legislative action in that they intend to affect naloxone access by modifying statutorily who is allowed to prescribe, dispense, and possess naloxone. We also included PDMPs because they are most often established through a formal legislative or regulatory action. We generally excluded state programs

that were not triggered by law passage or rulemaking, with the exception of drug supply management policies and opioid prescribing guidelines. While state funded and administered programs play a large part of public strategies to address opioid misuse and overdose, we focused on state initiatives with a policymaking component to inform activities directly relevant to legislative and regulatory policymakers. As a result, we determined that evaluations of state programs not triggered by a law or regulation were generally beyond the scope of this review; other studies have synthesized the evidence on the effects of these programs.[9,11,12]

We included drug supply management policies (eg, quantity and dosing limits, prior authorization restrictions) and opioid prescribing guidelines, both of which can be implemented through informal policymaking, such as bulletins, guidelines, and Medicaid protocols, for three reasons. First, these policies are an important state policy tool in promoting or restricting access to opioids and medications used in the treatment of opioid dependence. Second, state actors, depending on the state, can use their formal policymaking powers to enact these policies and guidelines. Third, it is unclear from the articles included in this section whether state actors enacted the policy through a formal or informal policymaking process.

We required that the original empirical research study assess at least one of the following outcomes: prescribing/dispensing (eg, volume of opioids prescribed or dispensed, opioid dosage prescribed or dispensed), patient behavior (eg, use of multiple providers or pharmacies, diverted opioids), and patient health (eg, fatal and nonfatal overdose, treatment visits). Outcomes classified as opioids prescribed or dispensed include total/monthly/daily opioid prescriptions, dispensed controlled substances, mean per person per month fills, and days supplied. Outcomes classified as opioid dosage prescribed include average and per-transaction morphine milligram equivalent (MME) dosage; and long-acting and short-acting opioid prescriptions.

We excluded qualitative studies, book chapters, review articles, dissertations, editorials, letters to the editor, and purely descriptive studies. We did not place restrictions on sample size or age. Eligible studies were peer-reviewed or published in *Morbidity and Mortality Weekly Report* or NBER. Two authors independently reviewed articles for inclusion, while a third author resolved outstanding conflicts regarding study inclusion.

Policies Evaluated

Included articles reviewed nine types of state policy: three primary prevention strategies (ie, continuing medical education requirements, laws related to pain management clinics, and opioid prescribing guidelines); three secondary prevention strategies (ie, anti-doctor-shopping laws, drug supply management policies, and PDMPs); and three tertiary prevention strategies (ie, naloxone access laws, Good Samaritan laws, and policies affecting opioid addiction treatment).

Continuing Medical Education Requirements. State continuing medical education requirements for pain management or controlled substances mandate that physicians receive postgraduate training in opioid prescribing, addiction, and/or related topics. As of December 2015, 23 states required at least some physicians to receive training in pain management or controlled-substance prescribing as a condition of obtaining or renewing their medical license or to specialize in pain management. Only five states required all or nearly all physicians to obtain periodic continuing medical education on topics related to pain management, controlled-substance prescribing, or substance use disorders.[13]

Laws Related to Pain Management Clinics. Pain management clinic policies regulate facilities that primarily manage and treat chronic pain by imposing operational, personnel, inspection, and other requirements on the businesses. As of June 2018, 12 states had implemented pain management clinic laws.[14,15]

Opioid Prescribing Guidelines. Opioid prescribing guidelines provide recommendations to providers on opioid prescribing practices. Guidelines vary but typically include opioid selection, dosage, duration, titration, and discontinuation; screening tools; written treatment agreements; and urine drug testing. As of July 2017, 41 states had adopted opioid prescribing guidelines for acute or emergency care.[16] This domain may include both payor policies embedded in informal regulatory actions (eg, Medicaid prescribing guidelines) and state laws or regulations requiring the development and implementation of prescribing standards. See the section on eligibility criteria inclusion parameters regarding opioid prescribing guidelines.

Anti-Doctor-Shopping Laws. Doctor shopping refers to a patient obtaining controlled substances from multiple health care prescribers without the providers' knowledge of the other prescriptions. All 50 states and the District of Columbia have a general fraud statute, which prohibits patients from obtaining drugs by fraud, deceit, misrepresentation, subterfuge, or concealment of material fact. As of 2012, 20 states also have laws that specifically prohibit patients from withholding from practitioners that they received a controlled substance or prescription order from another prescriber.[17]

Drug Supply Management Policies. Drug supply management policies limit opioid prescribing by restricting quantity or dosage that can be prescribed, or by imposing prior authorization requirements or fail-first protocols (whereby insurers require a treatment to be demonstrated as ineffective before they will approve a more expensive treatment). Such restrictions can apply to public programs and/or private plans regulated at the state level. This domain may include both payor policies embedded in informal regulatory actions (eg, Medicaid plan protocols) and state restrictions affecting private and/or public payors enacted through statute or regulation (eg, statutory prohibition of all state-regulated payors from applying concurrent review to daily buprenorphine formulations). See the section on eligibility criteria inclusion parameters regarding drug supply management policies in the analysis.

PDMPs. A PDMP is an electronic database that tracks controlled-substance prescriptions dispensed in a state. PDMPs can be used as a clinical tool to help identify patients who may be at risk for adverse consequences associated with high-risk prescription opioid receipt. Since the 1990s, PDMPs have proliferated across the country; now all states except Missouri have an operational program.[18] PDMPs vary in their features, with the most robust PDMPs requiring prescribers to register and query the database before prescribing opioids.

Naloxone Access Laws. Naloxone is an opioid antagonist designed to rapidly reverse opioid overdose. Naloxone access laws are designed to increase access to naloxone among those in a position to administer the medication in the event of overdose. Laws vary but can include the following provisions: (1) third-party prescriptions, which permit naloxone to be prescribed to third parties who might be in a position to assist others who overdose; (2) provisions that make naloxone available to

individuals without a prescription, such as standing order, collaborative practice agreements, and full prescriptive authority; (3) prescriber immunity provisions, which provide civil or criminal immunity to naloxone prescribers; and (4) lay dispensing provisions, which allow persons not otherwise permitted to dispense prescription medications to dispense naloxone. As of December 2018, all states and Washington, DC, had a naloxone access law: 48 had a third-party prescribing provision and 44 had a standing-order provision.[19,20]

Good Samaritan Laws. Good Samaritan laws provide legal protection for persons who overdose and bystanders who call emergency authorities during an overdose event. These laws vary in specific criminal protections for drug possession, drug paraphernalia, and parole or probation violation. As of December 2018, 46 states and Washington, DC, had adopted a Good Samaritan law.[20,21]

Policies Affecting Opioid Addiction Treatment. This category includes policies that influence access to treatments for opioid addiction, such as residential treatment and medication-assisted treatment. Policies vary greatly but include mandating or restricting benefit coverage for opioid use disorder, modifying public funding for treatment, or imposing provider licensing requirements. Articles included in this review assess policies related to buprenorphine access, methadone maintenance treatment, and mandated naltrexone therapy.

Data Extraction

We extracted data using a standardized article assessment form that captured the following elements: policy studied, outcome data source, study design, study years, sample, results, and limitations (Appendix 2). The limitations extracted focus on information relevant to sampling and covariate inclusion. Two authors independently reviewed ten randomly selected articles and entered relevant content into the extraction table. The same two authors reviewed the ten extractions for consistency and to resolve differences. One author then completed article extraction for the other 61 articles, while the other two authors provided feedback on the extraction.

Data Synthesis

Due to heterogeneity in the policies and outcomes evaluated, we performed a qualitative assessment and synthesis. We categorized policies as (1) primary prevention; (2) secondary prevention; and (3) tertiary prevention. Table 1 summarizes these policies but is not an exhaustive list of state strategies to address opioid misuse, overdose, and prescribing; it lists only the state policies assessed in the original empirical articles included in this review.

We categorized articles using the following three-step procedure. First, we organized studies by research design using a simplified hierarchy adopted from Haffajee (2016) (see Appendix 3).[22] Although not exhaustive of the different types of study designs used to assess public health legal interventions, the hierarchy aids policymakers in evaluating evidence quality to make policy decisions. Next, we classified studies into three categories based on outcomes evaluated: prescribing and dispensing, patient behavior, and patient health. We included studies that evaluated multiple outcomes in all relevant outcome categories. Finally, we organized studies by policy type evaluated. Similar to outcome categories, we classified studies that evaluated the independent effects of multiple policies in each relevant policy category.

We rated the quality of evidence for each policy/outcome group using a modified Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[23,24] The GRADE framework is a systematic strategy for rating the quality of a body of evidence for synthesis with the following quality grades: *high quality*—further research is very unlikely to change our confidence in the estimate of the effect; *moderate quality*—further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate; *low quality*—further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate; *very low quality*—we are very uncertain about the estimate of the effect.

Our modified GRADE approach employs the following procedure. First, we assigned all policy and outcome groups a low quality of evidence score, as the GRADE approach rates all observational studies a low score and all of our included articles used an observational design. Second, we modified the original GRADE score based on factors that can reduce or increase the quality of evidence. Factors that can reduce the quality of evidence include limitations in study design or execution, result inconsistency, indirectness of evidence, imprecision, and publication bias. Factors that can improve the quality of evidence include effect size and if unaccounted-for confounding is suspected to strengthen the findings. We automatically assigned a very low quality of evidence score for policy/outcome groups with only one evaluation. We did not assign a GRADE score to outcomes associated with multiple policies because articles within this category evaluate different combinations of policies. Since the GRADE approach rates the quality of evidence across evaluations of the same or very similar interventions, we do not believe that it is appropriate to assign a GRADE score to the synthesized findings of articles evaluating different combined interventions. The GRADE scores assigned for each policy/outcome group are available in Appendix 4.

Results

Figure 1 depicts the literature search and selection process; 71 articles met the inclusion criteria. Table 2 provides a summary of the articles included in the review: 10 assessed primary prevention interventions, 44 assessed secondary prevention interventions, and 12 assessed tertiary prevention policies. Studies most frequently evaluated PDMPs (n = 38), followed by opioid addiction treatment policies (n = 7) and laws related to pain management clinics (n = 4). The number of articles by publication year ranged from 41 in 2016-2018 to 2 between 1980 and 2000 (see Appendix 5 for a visual depiction of number of articles published annually by policy type).

The following sections provide an overall summary of the evidence evaluating each policy. As is detailed later in the paper, contradictory rigorous evaluations on laws related to pain management clinics provide mixed findings on the effects of these policies on prescribing outcomes. Evidence suggests that drug supply management laws and robust PDMPs reduce opioid prescribing and dispensing. Specifically, drug supply management policies reduce prescribing of higher-risk opioids targeted by the policies, while increasing the frequency of lower-risk prescriptions. Robust PDMPs with mandatory access provisions were associated with reductions in a variety of opioid prescribing measures, including total prescriptions and number of opioid fills. Across interventions, the quality of evidence on patient health outcomes is insufficient to facilitate conclusions. Of the 19 policy and outcome groups, 13 (68.4%) received a very low quality of evidence score; 5 (26.3%) received a low score; and 1 (5.3%) received a moderate score.

In the subsequent policy results sections, we focus on the most rigorously designed studies, which are more appropriate for causal inference. Studies of weaker design for causal inference are described in Tables 3 to 6 and Appendices 3 and 5. All findings reported are significant at the 0.05 significance level. In other words, findings reported as “no effect” or “no change” were not significant

at the 0.05 level. See Appendix 2 for more detailed quantitative results, including effect estimates and confidence intervals.

Continuing Medical Education Requirements

Evidence on statutory or regulatory continuing medical education requirements is extremely limited due to the single evaluation that met our inclusion criteria and thus received a very low quality of evidence score. The one study in this category assessed prescribing behaviors among clinicians before and after a 2012 New Mexico Senate law, which required all health care professional licensing boards to mandate continuing medical education training for the treatment of chronic pain. The authors observed a reduction in high opioid prescription dosages (>100 MME per day) and an increase in moderate opioid prescription dosages (≤40 MME per day). They observed slight increases in the total number of opioid prescriptions filled.[30]

Laws Related to Pain Management Clinics

Based on available evidence, it is unclear whether laws related to pain management clinics exert a direct, combined, or null effect on opioid prescribing. Only one evaluation, by Lyapustina and colleagues (2016) of the 2010 Texas pain management clinic law, observed reductions in opioids prescribed, including average MME per transaction, total opioid volume (ie, total MME across all transactions), number of opioid prescriptions, and quantity of opioid pills dispensed, following policy implementation.[31] However, other studies suggest that laws related to pain management clinics have no direct effect on opioids prescribed. Dowell and colleagues (2016) did not identify an independent

association between pain management clinic laws and MMEs prescribed per state resident.[28] Evidence from Meara and colleagues (2016) further suggests that laws related to pain management clinics do not affect opioid prescribing. Using a sample of Medicare beneficiaries, the authors observed no association between pain clinic regulations and non-long-term opioid receipt and opioid dosage greater than 120 daily MME.[27] Further, other rigorous evaluations suggest that the potential effects of pain management clinic laws on opioid prescribing may occur only in combination with other policies. The evaluation conducted by Dowell and colleagues, while not identifying an independent effect of these policies, observed that states with both pain management clinic laws and mandatory provider review of the state PDMP experienced decreases in opioid MME prescribing rate.[28] In addition, several evaluations of the 2010-2011 Florida policies targeting opioid misuse observed PDMPs and pain management clinic policies together were associated with reductions in opioids prescribed. Florida introduced these policies in quick succession (see section on combined effects of multiple policy interventions).[53,86-88] Given that the initial Florida PDMP implemented on September 1, 2011, was relatively weak, since it did not contain critical provisions, such as registration or use mandates, it is challenging to attribute the entirety of the change in opioid prescribing to the PDMP, and not the combined or singular effect of the pain clinic law and other policies implemented during the same period.[94]

Two rigorous evaluations suggest that pain clinic laws alone have no effect on patient health outcomes. Dowell and colleagues did not identify an association between pain clinic laws and prescription opioid overdose deaths, heroin overdose deaths, and combined drug overdose deaths.[28] However, states with both pain clinic laws and mandatory provider review experienced decreases in prescription opioid overdose deaths and combined drug overdose deaths, but not heroin overdose deaths.[28] Meara and colleagues also observed no relationship between pain clinic laws and nonfatal prescription opioid overdose.[27]

Opioid Prescribing Guidelines

We identified only one rigorous evaluation that observed significant reductions in opioid prescribing behaviors following state opioid guideline implementation. Weiner and colleagues (2017) evaluated the Ohio 2012 emergency physician guidelines that encouraged physicians to check the Ohio PDMP before prescribing controlled medication and urged physicians to limit the quantity of opioids prescribed to no more than a three days' supply, among other provisions. The guideline was associated with a 12% decrease in the level of statewide total monthly opioid prescriptions. No included article evaluated the effect of opioid prescribing guidelines on patient behavior or patient health–related outcomes.[32]

Anti-Doctor-Shopping Laws

Evidence on anti-doctor-shopping laws is extremely limited and of very low quality. Only two studies met the inclusion criteria for this category, both of which assessed the independent effects of multiple state opioid prevention policies, including doctor-shopping restrictions.[26,27] Neither study identified an association between anti-doctor-shopping laws and opioid prescribing outcomes.

Drug Supply Management Policies

Existing evidence suggests that prior authorization laws fulfill their intended effect of limiting access to higher-risk opioids targeted by the policies. Hartung and colleagues (2018) evaluated a 2012 Oregon Medicaid prior authorization policy that required prior authorization for high-dose opioid

prescriptions; the study demonstrated a decrease in opioid prescriptions above the high-dosage threshold and an increase in the monthly probability of low-dosage opioid prescriptions following policy implementation.[37] Keast and colleagues (2018) found that a 2008 Oklahoma Medicaid prior authorization policy that required a trial of short-acting opioids prior to initiating extended release/long-acting therapy resulted in a reduction in new extended release/long-acting opioid use among opioid-naïve patients and regardless of past opioid use. The policy also was associated with an increase in short-acting opioid use.[38]

Research by Morden and colleagues (2018) suggests that prior authorization policies of varying stringency have differential effects on controlled-release oxycodone use.[39] The authors compared strict, lenient, and no prior authorization policies using outpatient fee-for-service Medicaid prescription claims in 49 states and the District of Columbia. States with prior authorization policies did not differ in controlled-release oxycodone use from states without prior authorization policies. However, in aggregate, strict Medicaid prior authorization policies were associated with a 34% reduction in controlled-release oxycodone use.[39]

Prior authorization policies may be effective at reducing outcomes related to doctor shopping. Two rigorous evaluations observed that prior authorization policies were associated with decreases in multiple pharmacy or prescriber use. Hartung and colleagues observed a small decrease in multiple pharmacy visits following policy implementation.[37] Among persons with high-risk opioid use, Keast and colleagues identified a reduction in multiple prescriber use associated with the 2008 Oklahoma Medicaid policy.[38]

The evidence on the effect of drug supply management policies on patient health outcomes is extremely limited and of very low quality. The one rigorous evaluation available suggests that a prior authorization policy for high-dosage prescriptions (>120 MME) had no effect on opioid-related emergency department visits or hospitalizations.[37]

Although studies evaluating PDMPs have mixed results across outcomes, certain PDMP features (specifically, mandatory access provisions) show more promise in reducing opioids prescribed.

PDMPs Overall. Evidence from the most rigorous evaluations suggest that PDMPs have no effect on opioid prescribing overall but may reduce higher-risk prescribing behaviors. For example, Moyo and colleagues (2017) observed that PDMP implementation is associated with decreases in schedule II and schedule III opioid prescriptions, but has no effect on mean overall MME, total schedule IV, or schedule V opioids dispensed.[42] Research by Bao and colleagues (2016) using the National Ambulatory Medical Care Survey suggests that PDMPs reduce schedule II prescriptions, but do not affect total opioid and pain medication prescriptions.[43] Other rigorous evaluations suggest that PDMPs have no effect on opioid dosage prescribed. Of the 4 evaluations that measured opioid dosage before and after PDMP implementation compared to a control group, no study identified a change in opioid dosage following policy implementation.[42,44-46]

The published evidence on the effects of PDMPs on patient health outcomes is also heavily mixed. Thirteen studies evaluated the independent effects of PDMPs on patient health. Outcomes varied greatly by study and included overdose mortality; drug use, misuse, dependence, and initiation; and health care use. Studies considered both illicit (eg, heroin and nonmedical prescription pain reliever use) and legal prescription drug use. Due to the variation in the outcomes considered, and the mixed results across studies that evaluated similar outcomes, more research is needed to clarify the effect of PDMPs on patient-health-related measures. One rigorous evaluation provides evidence on the association between PDMPs and shopping-related outcomes: using a large sample of

noninstitutionalized individuals 12 years or older, Ali and colleagues (2017) observed that PDMPs were associated with a reduction in the odds of having two or more opioid prescribers.[95]

PDMP Features. Recent studies on the adoption of robust PDMP features suggest that PDMP design influences effectiveness, helping to clarify the mixed results on PDMPs overall. Robust PDMPs with mandatory access provisions are associated with decreases in opioid prescribing and reduced doctor-shopping-related behaviors, compared to PDMPs without these provisions.

Studies most commonly evaluated mandatory access provisions, which require practitioners to check a PDMP before prescribing or dispensing an opioid. Findings from these evaluations suggest that mandatory access provisions are associated with reductions in opioid prescribing behaviors. For example, Suffoletto and colleagues' (2018) evaluation of a 2016 Pennsylvania mandatory access provision identified a reduction in the opioid prescribing rate using electronic medical record data from 15 emergency departments in a single health system.[71] Buchmueller and colleagues (2018) found that mandatory access provisions were associated with a decline in the probability of receiving opioids.[45] Wen and colleagues (2017) found that the effect of mandatory access provisions may actually be explained by the presence of a mandatory registration provision in the Medicaid population, suggesting that further research should explore interactions among features.[74]

Mandatory access provisions also appear to be associated with reductions in behaviors related to doctor shopping. Two rigorous studies, by Ali and colleagues (2017) and Buchmueller and colleagues (2018), observed that mandatory access provisions were associated with declines in new patient visits,[45] multiple prescribers,[45,52] multiple pharmacy visits,[45] and overlapping claims,[45] but had no effect on social or illegitimate opioid source use.[45] Similar to overall PDMPs, results are mixed on the effect of mandatory access provisions on patient health outcomes.

Robust PDMPs, defined as those with multiple provisions (notably, use and registration mandates and delegate access) known or hypothesized to improve the ability of prescribers to use and access PDMPs, also appear to reduce opioid prescriptions. Haffajee and colleagues (2018) used commercial claims data between 2010 and 2014 to examine the effects of four robust PDMPs on overall and high-risk opioid prescribing compared to results in four similar states without robust PDMPs. The authors observed that robust PDMP implementation was associated with declines in total opioid dosage prescribed and number of opioid fills. Robust PDMPs were less consistently associated with reduced percentage of patients prescribed opioids, with the magnitude and significance of the effects varying by state. The authors also assessed the effect of robust PDMPs on opioid prescriptions filled by three or more prescribers and pharmacists, observing a decrease only in Kentucky, compared to Mississippi, but not in the other state pairs.[96]

Good Samaritan Laws

Few studies have evaluated Good Samaritan laws and thus, while robust in design, the quality of evidence assessing the effect of these laws on patient health is low. One rigorous evaluation by Nguyen and colleagues (2018) suggests that, consistent with its goals, the 2011 New York Good Samaritan law was associated with increased heroin-related acute hospital utilization. However, the policy had no effect on nonheroin opioid-related visits, supporting the authors' hypothesis that the law would have a greater effect on heroin-related overdose than non-heroin-related events because the threat of charge and conviction is less salient for non-heroin cases.[76] Conversely, Rees and colleagues' (2017) research found no association between Good Samaritan laws and opioid-related mortality.[29]

Due to variation in the policies evaluated and outcomes considered, we are unable to draw conclusions about the effects of policies influencing opioid addiction treatment. Further, no study included in this category longitudinally evaluated changes in a treatment group compared to a control group, limiting our ability to infer causal policy effects. Of the seven less rigorous studies that met the inclusion criteria in this category, four articles assessed policies related to methadone and suggest that Medicaid coverage restrictions for methadone may be associated with decreased treatment use.[78,79,81,83,] One rigorous article evaluated policy changes related to buprenorphine access. Clark and colleagues (2014) observed that a 2008 Massachusetts Medicaid policy requiring more frequent prior authorization for higher-dose buprenorphine prescriptions was associated with a decrease in the percentage of members filling higher dosages as well as an increase in medium- and low-dosage fills.[77]

Naloxone Access Laws

Few studies have evaluated the effects of state naloxone access laws. Evidence from two rigorous evaluations, Gertner et al. (2018) and Xu et al. (2018), suggests that naloxone access laws increase prescription naloxone dispensing overall.[84,85] Xu et al. found that naloxone access laws are associated with a 79% increase in naloxone prescriptions dispensed per state-quarter. Xu et al. also found an independent effect of both standing-order provisions and third-party prescribing provisions on naloxone prescribing.[85] But Gertner et al. found that the presence of a standing-order provision was the only naloxone access law feature that independently predicted naloxone prescribing; such a

provision corresponded to an increase of 33.1 dispensed prescriptions per state-quarter, or 74% of the average number of naloxone prescriptions dispensed.[84]

Evidence from the rigorous study by Rees et al. suggests that naloxone access laws reduced overall opioid-related mortality by 9%. This effect was significant for non-heroin opioid-related mortality but not heroin-related mortality. In addition, the overall effect was limited to naloxone access laws that remove criminal liability for naloxone possession.[29]

Combined Effects of Multiple Policy Interventions

Ten articles evaluated the combined effect of multiple policies,[28,53,86-93] including seven interested in the 2010-2011 Florida law enforcement, pharmaceutical, and public health interventions.[53,86-88,91-93] Florida state activities during this period included a January 2010 requirement that pain management clinics register with the Florida Department of Health, a July 2011 law that strengthened state regulation of activities by controlled-substance dispensing entities, and the implementation of the Florida PDMP in October 2011. Overall, the evidence suggests that combined policies corresponded to reductions in opioid prescribing, lower diversion rates for some types of opioid, and potentially fewer prescription opioid overdose fatalities.

Three rigorous evaluations suggest that the combined 2010-2011 Florida interventions were associated with reductions in opioids prescribed, with effects concentrated among the highest baseline opioid users and prescribers.[86-88] Surratt and colleagues (2014) observed a decline in diversion rates following implementation of the Florida policy interventions. Using data from the Researched Abuse Diversion and Addiction-Related Surveillance System from 2009 to 2012, the authors identified a decline in average diversion rates for oxycodone, methadone, and morphine. They did not observe a

change in diversion rates for fentanyl, hydrocodone, hydromorphone, or buprenorphine.[91] One rigorous evaluation found that these policies were associated with reductions in mortality related to prescription opioids. Kennedy-Hendricks and colleagues (2016) compared drug overdose deaths from 2003 to 2012, observing a reduction in prescription opioid overdose mortality of 0.6 per 100,000 in 2010, 1.8 per 100,000 in 2011, and 3.0 per 100,000 in 2012 in Florida compared to North Carolina.[92] Moreover, increases in heroin-related mortality during this time period were smaller in Florida than in North Carolina.[92]

Two articles evaluated other state policies containing multiple opioid-relevant components; results were generally consistent with evaluations of the Florida laws. Sun and colleagues (2017) investigated a 2012 Washington state mandate that required hospitals to implement seven best practices to reduce potentially avoidable emergency department visits by Medicaid beneficiaries, including several mandates that directly or indirectly targeted opioid prescribing.[90] The authors observed that the mandates were associated with a small reduction in number of opioid prescriptions dispensed in the overall, prior risky opioid use, and chronic opioid use cohorts. However, there was no overall or subgroup change in MME per dispensed prescription.[90] Al Achkar and colleagues (2018) measured the change in total opioids dispensed in Indiana before and after a 2013 opioid prescribing emergency rule that required providers to, for certain patients, (1) evaluate opioid recipients for psychiatric conditions; (2) review patients' drug prescription history in Indiana's Prescription Electronic Collection and Tracking Program ; (3) perform regular drug screenings; and (4) obtain a signed controlled-substance agreement from the patient.[89] The emergency rules were associated with an instantaneous decrease in daily MMEs per patient for all opioids, hydrocodone, oxycodone, methadone, and hydromorphone. No change was observed for morphine, fentanyl, oxymorphone, or buprenorphine.[89]

Discussion

States can wield a variety of legal tools to address opioid misuse; these tools warrant evaluation to identify the best use of resources in tackling the opioid crisis. Recent research articles add rigor to the body of evidence assessing opioid misuse policies. In contrast with earlier reviews that identified few rigorous empirical evaluations in this area, more than half of our included studies used quasi-experimental designs helpful for causal inference (eg, interrupted time series or pre-post test designs compared to a control group).[9] Despite recent improvements in methodological rigor overall, the lack of consistent rigor within policy type and outcome groups limits our ability to confirm our second hypothesis, that policies would have the most significant effect on the outcome most closely related to their intent. Only 6 of our policy and outcome groups did not receive a very low GRADE rating, challenging our ability to synthesize the evidence within policy and outcome groups.

Despite insufficient evaluation of many policies, research has identified several state opioid misuse prevention policies that appear to influence opioid prescribing and dispensing. Evidence on drug supply management policies and robust PDMPs with mandatory access provisions suggests that these policies reduce the volume and dosages of opioids prescribed and dispensed. Specifically, drug supply management policies achieve their intended effect of reducing prescribing of higher-risk opioids (in terms of formulations, dosages, and quantity) while increasing access to less high-risk opioid prescriptions. Robust PDMPs with mandatory access provisions are associated with decreases in a variety of opioid prescribing measures, including total prescriptions, number of fills, and dosages. Research comparing robust PDMPs and mandatory access provisions to PDMPs without these provisions observed that the latter were not associated with similar reductions.[45] Evidence on the 2010-2011 Florida policy interventions suggest that a combination of law enforcement,

pharmaceutical, and public health approaches (eg, PDMPs and laws related to pain management clinics) effectively reduced opioids, especially among high-risk prescribers and users.

Two rigorous evaluations suggest that naloxone access laws increase prescription naloxone dispensing.[84,85] However, several low-rigor studies published after our article review suggest that many pharmacies fail to supply naloxone despite these laws. For example, researchers observed that only about a quarter of pharmacies dispensed naloxone two years after implementation of a 2016 California naloxone standing order.[96] An evaluation of a 2015 Texas naloxone access law with a standing-order provision observed that nearly 25% of audited pharmacies did not stock naloxone in 2018.[97] Future research should investigate barriers to pharmacist naloxone dispensing in states with standing-order provisions.

We found insufficient evidence regarding the effect of state interventions on patient health–related outcomes across policies. Two or fewer studies evaluated patient health outcomes for all primary and secondary interventions, with the exception of PDMPs. Synthesis of the patient health effects of PDMPs is complicated by the use of varied outcomes, including overdose mortality; drug use, misuse, dependence, and initiation; health care use; and consideration of both illicit (eg, heroin and nonmedical prescription pain reliever use) and licit prescription drug use. Variation in outcomes poses similar challenges for evaluation of mandatory access provision effectiveness.

Future research should concentrate on the effects of tertiary prevention policies on patient health outcomes. Studies assessing policies that influence access to opioid addiction treatment are of low rigor overall; however, initial evidence suggests that policies limiting access to methadone maintenance therapy may be associated with lower treatment use.[78,79,81,83] Future investigations should rigorously evaluate variation in state funding for medications used in the treatment of opioid dependence, state-imposed Medicaid and private payor prohibitions on utilization management applied to medication-assisted treatment formulations, and policies affecting buprenorphine waiver

requirements. Evidence from two rigorous evaluations suggests that Good Samaritan laws may increase hospitalizations, especially for heroin-related adverse health events, but do not influence opioid-related mortality.[29,76] However, a controlled pre-post evaluation by McClellan and colleagues (2018), published after our article review, observed that Good Samaritan laws were associated with reductions in opioid overdose deaths.[98] We captured only one study evaluating the effect of naloxone access laws on opioid overdose deaths, which demonstrated decreases in non-heroin opioid-related mortality but not heroin-related morality. The recent study by McClellan and colleagues also identified an association between naloxone access laws and reductions in opioid overdose deaths.[98] Unlike the prior study, McClellan and colleagues did not disaggregate opioid overdose deaths by opioid type.[98] Future research should further explore the effects of Good Samaritan and naloxone access laws on patient health.

Our review has two main limitations. First, we generally do not review evaluations of state programs not initiated by legislative or administrative actions. This limitation is particularly important when considering the small number of evaluations on naloxone access laws and anti-doctor-shopping policies. For example, previous research has identified a positive association between community-implemented naloxone distribution programs and improved patient health outcomes, such as decreased overdose and increased recovery.[99,100] Further, model-based studies provide additional evidence that increasing naloxone availability is associated with reductions in overdose mortality.[101,102] Research on anti-doctor-shopping programs suggests that these programs reduce multiple prescriber and pharmacy use but may have an unintended consequence of increasing circumvented opioids.[103] Although it is beyond the scope of this review to evaluate these programs, they add to the evidence base on what governments can do to address opioid misuse and overdose.

Second, we limited our review to evaluations implemented by US states, thereby excluding relevant evaluations of policies enacted abroad from which the United States could glean insights.

Specifically, a robust literature on syringe services programs, which provide sterile equipment to injection drug users, suggests that these policies reduce blood-borne infections.[104-106]

Beyond these limitations, our synthesis suggests a need for future research at the state policy level. First, research should examine policies included (eg, Good Samaritan and naloxone access laws) and absent (eg, opioid prescription limits and state policies affecting opioid dependence treatment among criminal justice populations) from our review that have received insufficient attention. Second, studies on opioid prescribing and dispensing policies should take a holistic perspective regarding policy effects by investigating (or highlighting as a potential limitation) unintended consequences, such as changes in illicit opioid use, underprescribing and clinically inappropriate opioid therapy tapers or discontinuation, and suicide; and differential effects of policies by socioeconomic status, race, ethnicity, and criminal justice involvement. And third, research should evaluate the effects of all policies on patient health outcomes, specifically overdose.

Conclusions

Our scoping review reveals a growing rigorous literature on the effects of state opioid misuse prevention policies on patient and provider outcomes, but persistent gaps in evidence remain. The evidence now more clearly suggests that drug supply management policies and robust PDMPs with mandatory access provisions reduce multiple opioid prescribing and dispensing measures. Despite the increase in rigorous evaluations, the literature on most state opioid misuse prevention policies remains limited, particularly as they relate to patient health outcomes. We recommend future research examine policies that have received insufficient attention, investigate unintended consequences and differential effects across socioeconomic groups, and focus on patient health outcomes.

Figure 1. Literature Search and Selection Process

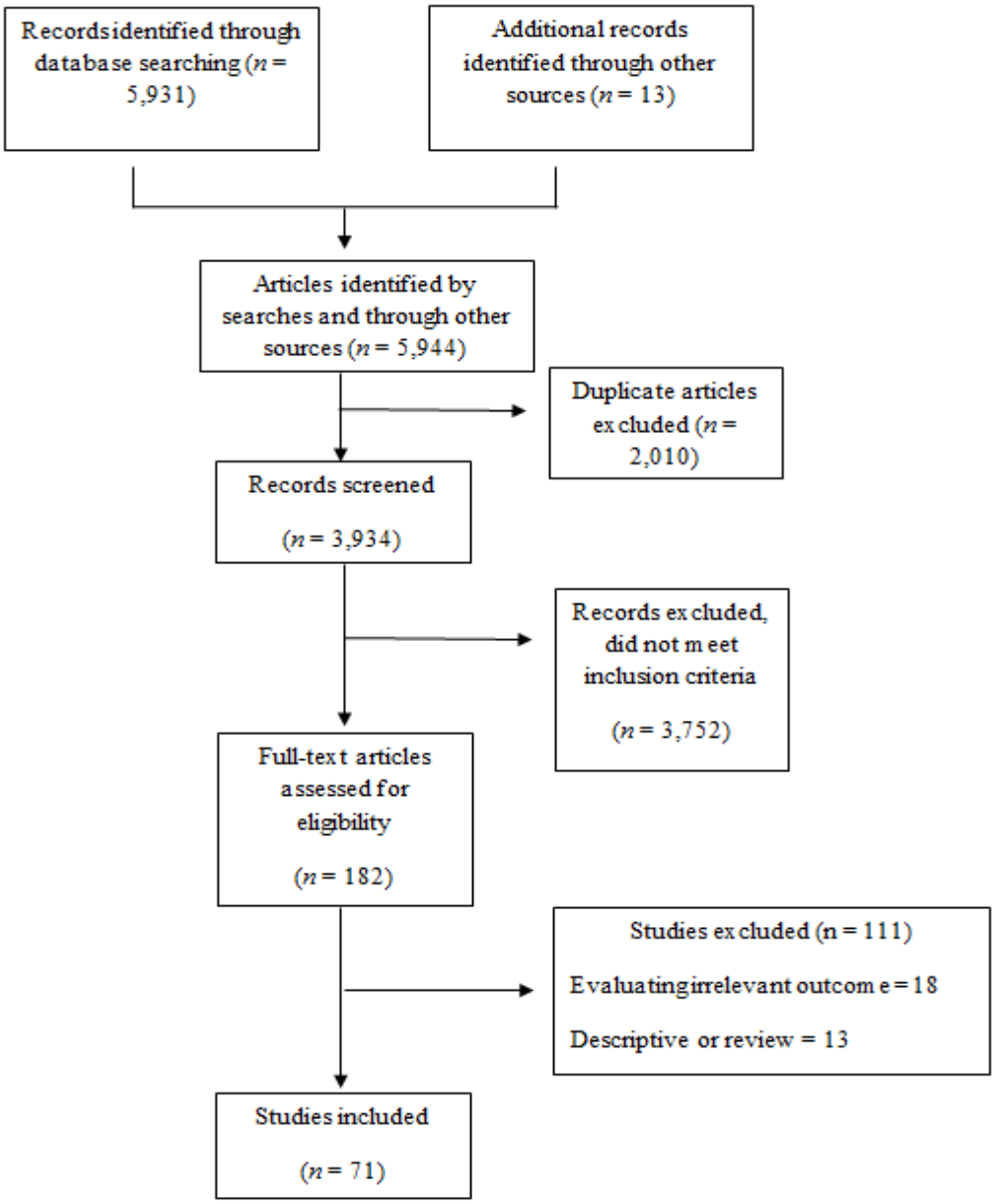

Table 1. State Policies to Curb Opioid Misuse[a]

Stage	Examples of intervention	Intervention description
Primary prevention	Continuing medical education requirements	Continuing medical education requirements on pain management or opioid prescribing. These requirements can be tied to licensure.
	Laws related to pain management clinic[b]	Policies that target inappropriate prescribing from health care facilities that primarily manage and treat chronic pain.[1]
	Opioid prescribing guidelines and prescription forms[b]	Recommendations to providers around opioid prescribing. Guidance documents vary but typically include opioid selection, dosage, duration, titration, and discontinuation; screening tools; written treatment agreements; and urine drug testing.
Secondary prevention	Anti-doctor-shopping laws	Laws and programs that restrict or prohibit patients from seeking or filling multiple opioid prescriptions from different prescribers or dispensers within a short period of time.
	Drug supply management[c]	Policies that limit opioid prescribing by restricting quantity or dosage that can be prescribed and/or requiring payer prior authorization before authorizing payment for an opioid prescription.

	Prescription drug monitoring programs (PDMPs)[c]	An electronic database that collects, monitors, and analyzes controlled-substance prescribing and dispensing. Laws vary widely but can include which providers and state officials have access to the PDMP; mandatory prescriber and dispenser querying; interstate data sharing; update frequency; schedule of controlled substance monitored; and operating agency.
Tertiary prevention	Naloxone access laws	Policies that increase lay access to naloxone. Laws vary but can include third-party prescriptions; pharmacist dispensing without a prescription; prescriber, dispenser, and layperson immunity from civil and criminal penalties; and standing-order provisions.
	Good Samaritan laws	Laws that offer legal protection to individuals who seek emergency help for a drug overdose.
	Policies affecting opioid addiction treatment	Policies that influence access to treatments for opioid addiction, such as residential treatment and medication-assisted therapy. Policies vary greatly but include mandating or restricting benefit coverage, modifying public funding for treatment, and imposing provider licensing requirements.

Data derived from Haffajee (2016).[22]

[a]This table includes interventions assessed in the research articles included in the scoping review. It is not exhaustive of all state strategies to address opioid misuse. As is identified in footnotes b and c, we acknowledge that some policies intend to influence multiple prevention categories. However, we use this categorization system to clearly communicate the chief intent of the state policies evaluated.

[b] These interventions can also be considered secondary prevention.

[c] These interventions could be considered primary, secondary, or tertiary intervention because they influence primary exposure to opioids, high-risk opioid exposure, and treatment access for individuals with an opioid dependence.

Table 2. Study Characteristics

Characteristic	**Number of Studies**
Total studies	71
Publication year	
1980-2000	2
2001-2005	0
2006-2010	6
2011-2015	22
2016-2018	41
Study design[b]	
Interrupted time series with comparison	8
Interrupted time series without comparison	8
Controlled pre-post	28
Uncontrolled pre-post	18
Uncontrolled post-only	0

Cross-sectional	10
Intervention type[c]	
Primary prevention	10
Secondary prevention	42
Tertiary prevention	12
Combined effects of multiple policies	10
Intervention[d]	
Anti-doctor-shopping laws	2
Continuing medical education requirements	1
Drug supply management	5
Good Samaritan laws	2
Naloxone access laws	3
Opioid prescribing guidelines	5
Laws related to pain management clinics	4
Policies affecting opioid addiction treatment	7
Prescription drug monitoring programs	38
Combined effects of multiple policies	10

[a] The totals from study design, intervention type, and intervention do not sum to 71 because certain studies fall into multiple categories (see footnotes b, c, and d).

[b] Haffajee et al. (2018)[25] is included in 2 study design categories: interrupted time series with comparison and controlled pre-post.

[c] Kuo et al. (2016)[26] and Meara et al. (2016)[27] analyzed policies categorized in primary prevention and secondary prevention. Dowell et al. (2016)[28] analyzed a primary prevention policy and the combined effects of multiple policies.

[d] Kuo et al. (2016)[26] and Meara et al. (2016)[27] are in 3 intervention categories: anti-doctor-shopping laws, laws related to pain management clinics, and prescription drug monitoring programs. Dowell et al. (2016)[28] is in 2 intervention categories: laws related to pain management clinics and combined effects of multiple policies. Rees et al. (2017)[29] is in 2 intervention categories: naloxone access and Good Samaritan laws.

Table 3. Primary Prevention

Outcome Type ***GRADE Quality of Evidence Score**[a]	**Study Design**	**Number of Studies**	**Summarized Findings**
Continuing medical education requirements			
Prescribing/dispensing **Very low due to 1 evaluation and limitations in study design*	Uncontrolled pre-post	1	Decline in high-dosage opioids dispensed (Katzman et al., 2014)[30] Increase in low-dosage opioids dispensed (Katzman et al., 2014)[30] No change in opioid prescriptions filled (Katzman et al., 2014)[30]
Laws related to pain management clinics			
Prescribing/dispensing [c]	ITS without	1	Decline in opioids prescribed (Lyapustina et al.,

* *Very low due to inconsistency in results*	comparison		2016)[31] Decline in opioid dosage prescribed (Lyapustina et al., 2016)[31] Effects concentrated among highest baseline opioid prescribers and highest baseline opioid users (Lyapustina et al., 2016)[31]
	Controlled pre-post	3	
Patient behavior **Very low due to 1 evaluation*	Controlled pre-post	1	Decline in long-term opioid receipt (Meara et al., 2016)[27] No change in receipt of high-dosage or non-long-term opioid receipt (Meara et al., 2016)[27] No change in prescription opioid dosage dispensed associated with pain clinic law alone (Dowell et al., 2016)[28] Decline in schedule II opioids prescribed (Kuo et al., 2016)[26]
	Controlled pre-post	2	No change in schedule III opioids prescribed (Kuo et al., 2016)[26]
Patient health **Low*			No change in 4 or more opioid prescribers (Meara et al., 2016)[27] No change in nonfatal prescription opioid overdose (Meara et al., 2016)[27]

			No change in prescription opioid overdose death rates associated with pain clinic laws alone (Dowell et al., 2016)[28] No change in heroin-related mortality (Dowell et al., 2016)[28]
Opioid prescribing guidelines			
Prescribing/dispensing **Low*	ITS with comparison	1	Decline in total opioid prescriptions and total MME per month (Weiner et al., 2017)[32] Decline in total prescriptions greater than 3-day supply and total MME per month per prescription greater than a 3-day supply (Weiner et al., 2017)[32]
	Uncontrolled pre-post	3	Decline in opioids prescribed (Franklin, 2012)[33] Decline in high-dose opioid prescriptions (Garg 2013; Sullivan 2016)[34,35] No change in median opioid dose (Sullivan 2016)[35]
Patient health **Very low due to 1 evaluation*	Uncontrolled pre-post	1	Increase in methadone poisonings (Fulton-Kehoe, 2015)[36] No change in other prescription opioid poisonings (Fulton-Kehoe, 2015)[36]

Abbreviations: ITS, Interrupted time series; MME, morphine milligram equivalent.

[a] See Appendix 4 for the modified GRADE Summary of Findings. The GRADE approach automatically rates observational studies a low quality of evidence score. Since all of our included articles use an observational approach, compared to a randomized trial, all policy/outcome pairs are initially given a low quality of evidence score. Policy/outcome groups can then be rated up or down. If the quality of evidence score is moved up or down from the low rating, we provide an explanation following the score.

Table 4. Secondary Prevention

Outcome Type ***GRADE Quality of Evidence Score**[a]	**Study Design**	**Number of Studies**	**Specific Findings**
Anti-doctor-shopping laws			
Prescribing/dispensing **Very low due to limitations in study design*	Controlled pre-post	2	No change in schedule II or III opioid prescriptions (Kuo et al., 2016)[26] No change in receipt of high-dosage opioids and non-long-term opioid receipt (Meara et al., 2016)[27]
Patient behavior **Very low due to one evaluation*	Controlled pre-post	1	No change in four or more opioid prescribers (Meara et al., 2016)[27]
Patient health **Very low due to one evaluation*	Controlled pre-post	1	No change in nonfatal prescription opioid overdose (Meara et al., 2016)[27]

Drug supply management policies			
Prescribing/dispensing **Moderate due to magnitude and consistency of effect* Patient behavior **Very low due to one evaluation* Patient health	Controlled pre-post Uncontrolled pre-post Controlled pre-post Controlled pre-post Cross-	3 1 2 1	Decline in high-dose opioid prescriptions (Hartung et al, 2018; Keast et al., 2018)[37,38] Increase in low-dose opioids (Hartung et al, 2018; Keast et al., 2018)[37,38] No change in total opioids or opioid dosage between 61 and 120 MED (Hartung et al, 2018)[37] Stringent prior authorization policy associated with a reduction in controlled-release oxycodone use compared to lenient prior authorization policy (Morden et al., 2008)[39] No change in high-dose opioids (Riggs et al., 2017)[40] Minimal decrease in total daily opioids dispensed (Riggs et al., 2017)[40] Decline in multiple pharmacy visits (Hartung et al., 2018)[37] Decline in multiple prescriber use among high-risk opioid users (Keast 2018)[38]

**Very low due to limitations in study design*	sectional	1	No change in opioid-related emergency department visit or hospitalization (Hartung et al., 2018)[37] Lower rates of opioid misuse in high and low prior authorization policies compared to no prior authorization policy (Cochran et al., 2017)[41] Lower rates of opioid overdose in low prior authorization policy compared to absence of prior authorization policy (Cochran et al., 2017)[41]
Prescription drug monitoring programs[b]			
Prescribing/dispensing **Low*	ITS with comparison	1	Decline in schedule II and III opioids prescribed (Moyo et al., 2017)[42] No change in total opioids and schedule IV-V opioids prescribed (Moyo et al., 2017)[42]
	Controlled pre-post	6	Decline in schedule II opioids prescribed (Bao et al., 2016)[43] and overall opioid dosage (Brady et al. 2014)[44] Decline in oxycodone shipments

	Uncontrolled pre-post	4	(Reisman et al. 2009)[57] No change in high-dosage opioids prescribed (Buchmueller et al. 2018),[45] total opioids prescribed (Bao et al. 2016; Buchmueller et al. 2018),[43,45] overall opioid dosage dispensed (Brady et al. 2014; Paulozzi et al. 2017),[44,46] long-term opioid receipt (Meara et al., 2016)[27]
	Cross-sectional	3	Decline in opioids dispensed (Deyo et al. 2018)[38] No change in opioids prescribed (Baehren et al., 2010;[47] Landau et al., 2018[48]), controlled substances nor uncontrolled substances (McAllister et al., 2015)[49]
Patient behavior **Very low due to inconsistency in results*	Controlled pre-post	2	Higher odds of any analgesic prescription (Simoni-Wastila et al., 2018)[42] Lower opioid and controlled-release oxycodone prescriptions (Curtis et al., 2006)[50] No change in prescription of pain

Patient health ** Very low due to inconsistency in results*	ITS with comparison	2	medication or opioids (Lin et al., 2018)[51] Decline in frequency of 2+ opioid prescribers and 4+ new patient visits (Ali et al., 2017;[52] Buchmueller et al., 2018[45]) No change in illegitimate opioid source (Ali et al., 2017)[52]
	ITS without comparison	1	
	Controlled pre-post	10	No change in overlapping claims, 5+ prescribers, out-of-state prescribers and pharmacies (Buchmueller et al. 2018)[45] Decline in oxycodone-related mortality (Delcher et al., 2015)[53] and overall opioid-related mortality (Patrick 2016)[54] No change in non-oxycodone- or heroin-related mortality (Delcher et al., 2015)[53] Increase in prescription opioid and heroin treatment admissions (Branham et al. 2017)[55]

			Increase in drug overdose morality (Li, 2014)[56] Decline in past-year days used of NMPR[c] and heroin (Ali et al., 2017)[52] Decline in inpatient drug rehabilitation admissions (Reisman et al. 2009)[57] No change in overall drug overdose mortality or opioid-related overdose mortality (Nam et al., 2017;[58] Paulozzi et al. 2011)[46] No change in heroin or prescription opioid overdose mortality (Nam et al., 2017)[58] No change in opioid-related poisonings (Buchmueller et al., 2018)[45] No change in prescription-drug- or heroin-related treatment admissions (Dave et al., 2017),[59] emergency department visits involving an opioid (Maughan et al., 2015)[60] No change in past-year NMPR[c] or past-year heroin use, abuse/dependence, or initiation (Ali et al., 2017)[52] Smaller increase in intentional exposures and opioid treatment

			admissions (Reifler, 2012)[61]; and prescription opioid-related overdose (Pauly, 2018)[62]

Abbreviations: ITS, interrupted time series; NMPR: Nonmedical prescription pain reliever.

[a] See Appendix 4 for the modified GRADE Summary of Findings. The GRADE approach automatically rates observational studies a low quality of evidence score. Since all of our included articles use an observational approach, compared to a randomized trial, all policy/outcome pairs are initially given a low quality of evidence score. Policy/outcome groups can then be rated up or down. If the quality of evidence score is moved up or down from the low rating, we provide an explanation following the score.

[b] We excluded the following studies from Table 4 because they evaluated PDMP provisions, not overall PDMPs, or compared robust to nonrobust PDMPs: Brown et al, 2017;[63] Gilson et al., 2011;[64] Green et al., 2012;[65] Haffajee et al., 2018;[25] Kuo et al., 2016;[26] Pardo et al., 2016;[66] Phillips et al., 2017;[67] Rasubala et al., 2015;[68] Ringwalt et al., 2015;[69] Sigler et al., 1984;[70] Suffoletto et al., 2018;[71] Sun et al., 2017;[72] Wastila et al., 1996;[73] Wen et al., 2017;[74] and Yarbrough et al., 2018.[75] See Appendix 2 for a detailed summary of these evaluations.

[c] Low-dose opioids are prescriptions <61 morphine equivalent dose or short-acting opioids. High-dose opioids are prescriptions >120 morphine equivalent dose or long-acting opioids.

Table 5. Tertiary Prevention

Outcome Type **GRADE Quality of Evidence Score*[a]	**Study Design**	**Number of Studies**	**Specific Findings**
Good Samaritan laws			
Patient health **Low*	Controlled pre-post	2	Increase in emergency department and inpatient hospital admissions for opioids and heroin (Nguyen et al., 2018)[76] No change in opioid-related, non-heroin-related, or heroin-related mortality (Rees et al., 2017)[29] No change in nonprescription use of prescription pain killers (Rees et al., 2017) [29]
Policies affecting opioid addiction treatment			
Patient health * *Very low due to inconsistency in results*	ITS without comparison	1	Decline in high-dose buprenorphine fills following buprenorphine prior authorization policy (Clark et al., 2014)[77] Increase in medium- and low-dose fills following buprenorphine prior authorization policy (Clark et al.,

			2014)[77]
	Uncontrolled pre-post	2	Decrease in methadone maintenance enrollment after removal of methadone from Medicaid benefit (Deck et al., 2006)[78]
	Cross-sectional	4	Patients who paid out of pocket for methadone treatment more likely to leave care than patients with benefit coverage (Fuller et al., 2006)[79]
			Increase in buprenorphine use associated with state funds to subsidize buprenorphine and state special prescribing requirements (Andrews et al., 2014)[80]
			No change in buprenorphine use associated with state regulating buprenorphine beyond federal standards (Andrews et al., 2014)[80]
			Greater use of opioid addiction treatment in states with Medicaid methadone coverage (Bachhuber et al., 2017)[81]
			Lower relapse rate associated with

			mandated naltrexone treatment (Merlo et al., 2011)[82] Opioid addiction treatment use higher in states with Medicaid coverage than in states with block-grant coverage or no public coverage (Saloner et al., 2016)[83]
Naloxone access laws			
Prescribing/dispensing **Low*	Controlled pre-post	2	Increase in naloxone prescriptions associated with naloxone access law, lay dispensing, provider immunity (Gertner et al., 2018)[84] Increase in naloxone prescriptions associated with standing-order provision (Gertner et al., 2018; Xu et al., 2018)[84,85] Increase in naloxone prescriptions associated with third-party provisions (Xu et al., 2018)[85] Decrease in naloxone prescriptions associated with third-party provisions (Gertner et al., 2018)[84]
Patient health **Very low due to one evaluation*	Controlled pre-post	1	Decrease in opioid-related and non-heroin opioid-related mortality associated with naloxone access laws

			(Rees et al., 2017)[29] Decrease in opioid-related and non-heroin opioid-related mortality associated with naloxone access laws that remove criminal liability for naloxone possession (Rees et al., 201)[29] No change in opioid-related mortality, non-heroin opioid-related mortality, and heroin-related mortality associated with standing order provision (Rees et al., 201)[29] No change in heroin-related mortality associated with naloxone access law, standing order, or removing criminal liability for naloxone possession (Rees et al., 201)[29]

[a] See Appendix 4 for the modified GRADE Summary of Findings. The GRADE approach automatically rates observational studies a low quality of evidence score. Since all of our included articles use an observational approach, compared to a randomized trial, all policy/outcome pairs are initially given a low quality of evidence score. Policy/outcome groups can then be rated up or down. If the quality of evidence score is moved up or down from the low rating, we provide an explanation following the score.

Table 6. Multiple Policies

Outcome Type[a]	Study Design	Number of Studies	Significant Findings
Prescribing/dispensing	ITS with comparison	3	Decline in opioids prescribed (Rutkow et al., 2015[b])[86] Decline in opioids prescribed by high-risk providers (Rutkow et al., 2015[b];[86] Chang et al., 2016[b])[87] Decline in percentage of high-risk patients prescribed opioids (Chang et al., 2018[b])[88] Decline in opioid dosage dispensed (Rutkow et al., 2015[b]) [86] Decline in opioid dosages prescribed by high-risk prescribers (Chang et al., 2016[b];[87] Rutkow et al., 2015[b]) [86] Decline in opioid dosage prescribed to high-risk patients (Chang et al., 2018[b];[88] Rutkow et al., 2015[b])[86]
	ITS without comparison	2	No change in opioid dosages prescribed by low-risk prescribers (Chang et al.,

			2016[b])[87] No change in opioid dosage prescribed to low-risk patients (Chang et al., 2018[b])[88]
Patient behavior	Controlled pre-post	1	Decline in daily MEDs per patient for opioid, hydrocodone, oxycodone, methadone, and hydromorphone dispensed (Al Achkar et al., 2018)[89]
	Uncontrolled pre-post	1	Decline in opioids dispensed in the overall cohort, prior risk ,of opioid use cohort, and opioid chronic opioid use cohort (Sun 2017)[90]
Patient health	ITS with comparison	1	No change in daily MEDs per patient for morphine, fentanyl, oxymorphone, and buprenorphine (Al Achkar et al., 2018)[89]
	Controlled pre-post	2	Decline in opioids prescribed (Dowell, 2016)[28]
	Uncontrolled pre-post	1	Decline in diversion rates for oxycodone, methadone, and morphine (Surratt et al., 2014[b])[91]

			No decline in diversion rates for fentanyl, hydromorphone, and buprenorphine (Surratt et al., 2014[b])[91] Decline in oxycodone-related mortality (Delcher et al., 2015[b])[53] Decline in prescription-opioid-related mortality (Kennedy-Hendricks et al., 2016[b];[92] Dowell, 2016) [28] Smaller heroin-related mortality increase than comparison state (Kennedy-Hendricks et al., 2016[b])92 Decline in overdose mortality due to oxycodone, methadone, hydrocodone, and other opioid analgesics (Johnson et al., 2014[b])[93] Increase in overdose mortality due to morphine, hydromorphone, and heroin (Johnson et al., 2014[b])[93]

Abbreviations: ITS, interrupted time series; MED, morphine equivalent dose.

[a] We do not provide a GRADE quality of evidence score for multiple policies because each article evaluates different components of the same group of policies or a different combination of policies entirely.

[b] Articles evaluating some components or the entire combined effects of the 2010-2011 Florida interventions.

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Appendix 1: Search strategy

PubMed Scoping Review Search Strategy (https://www-ncbi-nlm-nih-gov.proxy.lib.umich.edu/pubmed?otool=umichlib)

Date Searched: 05/30/2018

Final number of results: 1546

(patient education as topic[MeSH Terms] OR education, continuing[MeSH Terms] OR patient education[text word] OR provider education[text word] OR continuing education[text word] OR clinical practice guideline[MeSH Terms] OR overdose education [text word] OR provider guideline[text word] OR prescribing practices[text word] OR pain management clinic[text word] OR pain clinic [text word] OR pill mill[text word] OR drug approval[text word] OR drug approval[MeSH Terms] OR abuse deterrent drug formulation[text word] OR take back[text word] OR take-back[text word] OR guideline[text word] OR (overdose prevention[text word] AND education[text word]) OR prescription drug monitoring program[text word] OR drug monitoring[MeSH Terms] OR prescription monitoring program[text word] OR PDMP[text word] OR urine testing[text word] OR drug

supply[text word] OR formulary[text word] OR quantity limit* [text word] OR reimbursement[text word] OR "Reimbursement Mechanisms"[Mesh:NoExp] OR doctor shopping[text word] OR doctor-shopping[text word] OR pharmacy shopping[text word] OR pharmacy-shopping[text word] OR prescription drug monitoring[text word] OR naloxone[MeSH Terms] OR naloxone[text word] OR medication assisted treatment[text word] OR (reversal[text word] and agent*[text word]) OR buprenorphine[text word] OR syringe exchange program[text word] or syringe-exchange program[text word] OR needle exchange program[text word] OR needle exchange program[MeSH Terms] OR needle-exchange program[text word] OR good Samaritan[text word] OR marijuana [text word] OR cannabis [text word] OR prior authorization[text word] OR lock in[text word] OR lock-in[text word] OR insurance[Title/Abstract] OR Medicaid[Title/Abstract]) AND ((analgesics, opioid[MeSH Terms] OR opioid related disorders[MeSH Terms] OR analgesics/therapeutic use[MeSH Terms] OR ((opioid*[text word] OR opiate*[text word] OR heroin[text word] OR morphine[text word]) OR oxycodone[text word] AND (addict*[text word] OR disorder*[text word] OR dependen*[text word] OR abuse*[text word] OR overdose [text word] OR mortality[text word])))) AND ((state government[MeSH term] OR health policy[MeSH term] OR state health plans[MeSH Terms] OR (policy[text word] OR policies[text word] OR program[text word] OR programs[text words] OR rules[text word] OR regulation[text word] OR legislation[text word]) AND (state[text word] OR states[text word] OR state's[text word] OR states'[text word] OR Alabama[text word] OR Alaska[text word] OR Arizona[text word] OR Arkansas[text word] OR California[text word] OR Colorado[text word] OR Connecticut[text word] OR Delaware[text word] OR Florida[text word] OR Georgia[text word] OR Hawaii[text word] OR Idaho[text word] OR Illinois[text word] OR Indiana[text word] OR Iowa[text word] OR Kansas[text word] OR Kentucky[text word] OR Louisiana[text word] OR Maine[text word] OR Maryland[text word] OR Massachusetts[text word] OR Michigan[text word] OR Minnesota[text word] OR Mississippi[text word] OR Missouri[text word] OR Montana[text word] OR Nebraska[text word] OR Nevada[text word] OR New Hampshire[text word] OR New Jersey[text word] OR New Mexico[text word] OR New York[text word] OR North Carolina[text word] OR North Dakota[text word] OR Ohio[text word] OR Oklahoma[text word] OR Oregon[text word] OR Pennsylvania[text word] OR Rhode Island[text word] OR South Carolina[text word] OR South Dakota[text word] OR Tennessee[text word] OR Texas[text word] OR Utah[text word] OR Vermont[text word] OR Virginia[text word] OR Washington[text word] OR West Virginia[text word] OR Wisconsin[text word] OR Wyoming[text word] OR Alabama's[text word] OR Alaska's[text word] OR Arizona's[text word] OR Arkansas'[text word] OR California's[text word] OR Colorado's[text word] OR Connecticut's[text word] OR Delaware's[text word] OR Florida's[text word] OR Georgia's[text word] OR Hawaii's[text word] OR Idaho's[text word] OR Illinois'[text word] OR Indiana's[text word] OR Iowa's[text word] OR Kansas'[text word] OR Kentucky's[text word] OR Louisiana's[text word] OR Maine's[text word] OR Maryland's[text word] OR Massachusetts'[text word] OR Michigan's[text word] OR Minnesota's[text word] OR Mississippi's[text word] OR Missouri's[text word] OR Montana's[text word] OR Nebraska's[text word] OR Nevada's[text word] OR New Hampshire's[text word] OR New Jersey's[text word] OR New Mexico's[text word] OR New York's[text word] OR North Carolina's[text word] OR North Dakota's[text word] OR Ohio's[text word] OR Oklahoma's[text word] OR Oregon's[text word] OR Pennsylvania's[text word] OR Rhode Island's[text word] OR South Carolina's[text word] OR South Dakota's[text word] OR Tennessee's[text word] OR Texas'[text word] OR Utah's[text word] OR Vermont's[text word] OR Virginia's[text word] OR

Washington's[text word] OR West Virginia's[text word] OR Wisconsin's[text word] OR Wyoming's[text word]))

PsychInfo Scoping Review Search Strategy
(http://web.b.ebscohost.com.proxy.lib.umich.edu/ehost/search/advanced?vid=0&sid=5db759a6-7619-4446-80d1-b342d5bb848b%40sessionmgr120)

Date Searched: 05/30/2018

Final number of results: 1887

CINAHL Complete Scoping Review Search Strategy
(http://web.b.ebscohost.com.proxy.lib.umich.edu/ehost/search/advanced?vid=0&sid=099187ca-b46e-4e9f-b4fb-38a21d4d8770%40pdc-v-sessmgr06)

Date Searched: 05/31/2018

Final number of results: 381

Criminal Justice Abstracts Scoping Review Search Strategy
(http://web.b.ebscohost.com.proxy.lib.umich.edu/ehost/search/advanced?vid=0&sid=9fb4893b-baa3-4bd3-b194-e0360e34ac8c%40pdc-v-sessmgr05)

Date Searched: 06/05/2018

Final number of results: 139

Scopus Scoping Review Search Strategy (https://www-scopus-com.proxy.lib.umich.edu/search/form.uri?display=basic)

Date Searched: 06/05/2018

Final number of results: 1978

Appendix 2: Articles included in scoping review

Abbreviations

(A)OR: (Adjusted) odds ratio

ARCOS: Automated Reports and Consolidated Orders System

CDC Wonder: CDC Wide-ranging Online Data for Epidemiological Research data

CI: Confidence interval

ED: Emergency department

EM: Emergency medicine

ER: Extended release

FFS: Fee for service

GSL: Good Samaritan Law

HMO: Health maintenance organization

IRR: Incident rate ratio

LIP: Lock-in program

LA(O): Long acting opioid

MAT: Medication assisted treatment

MCPP: Multiple Copy Prescription Program

MED: Morphine equivalent dosage

MME: Morphine milligram equivalent

NAL: Naloxone Access Law

NCHS: National Center for Health Statistics

NDATSS: National Drug Abuse Treatment System Survey

NMPR: Non-medical prescription pain reliever

NSDUH: National Survey on Drug Use and Health

OAT: Opioid agonist therapy

PA: Prior authorization

PDMP: Prescription drug monitoring program

PRRP: Patient review and restriction program

RADARS: Researched, Abuse, Diversion, and Addiction-Related Surveillance System

RR: Relative risk

SA(O): Short-acting (opioid)

SE: Standard error

TEDS: The Treatment Episodes Data Set

*We define statistically significant as $p < 0.05$. Statistical significant at lower levels is reported.

Article	Intervention description	Years	Sample	Design	Outcome data source	Finding(s)	Strengths and limitations
Primary prevention							
Continuing medical education requirement							
Katzman 2014	2012 New Mexico Senate Bill 215 requirement that all health care professional licensing boards mandate continuing medical education training in the treatment for chronic pain	2008-2013	1090 participants in 6 courses	Uncontrolled pre-post	New Mexico Board of Pharmacy PDMP	Total MME of opioids dispensed increased from January-June 2008 (835,798, 584) to July-December 2011 (1,039,292,508) and declined from January-June 2012 (998,153,444) to January-June 2013 (926,180,808). Opioid prescriptions filled, no. increased from January-June 2008 (748518) to July-December 2011 (880838) and remained largely constant from January-June 2012 (863768) to	Limitations: No controls for patient medical conditions, provider characteristics, nor other opioid relevant policies

						January-June 2013 (896925) . Opioid MME per prescription, No. declined from 1117 in January-June 2008 to 1033 in January-June 2013 The proportion of opioid prescriptions with dosage >100 MME per day declined from 14.3% in 2010 to 12.1% in 2013. The proportion of opioid analgesics up to 40 MME per day increased from 49.5% in 2010 to 56.9% in 2013.	
Laws related to pain management clinics							
Dowell 2016	Opioid prescribing policies, pain clinic laws and mandated provider review of PDMP before prescribing opioids	2006-2013	38 states and DC	Controlled pre-post	IMS Health National Prescription Audit; National Vital Statistics System Multiple Cause of Death mortality files	Combined policies (pain clinic law and PDMP mandatory access requirement) reduced prescribing rates by 80.1 ($p < 0.01$) MMEs prescribed per state residents per year and prescription opioid overdose deaths per 100,000 state residents by -1.198 ($p < 0.01$). Implementation of pain clinic laws alone did not significantly reduce opioid prescribing or prescription opioid overdose death rates. Neither the combined nor pain clinic laws were associated with a statistically significant reduction in heroin	Strengths: State and year fixed effects, intervention dose Limitations: IMS Health data does not capture direct opioid dispensing

						death rate.	
Kuo 2016	Multiple state laws: (1) physical examination before prescribing, (2) requiring tamper-resistant prescriptions forms, (3) mandating pain clinic regulation; (4) setting prescription drug limits; (5) prohibiting doctor shopping or fraud; (6) requiring patient identification before dispensing; (7) immunity from prosecution for individual seeking assistance during an overdose	2006-2012	5 % national sample of Medicare beneficiaries with Parts A, B, and D coverage and not in an HMO and with no cancer diagnosis in the year before or the year of study	Controlled pre-post	Medicare claims from Medicare summary files, Medicare Provider Analysis and Review Files, and Outpatient Standard Analytic Files, Medicare Carrier Files, and Prescription Drug Event Files	Only state laws regulating pain clinics were associated with a significant reduction in schedule II opioid prescriptions (0.64 95% CI: 0.47, 0.89). No law was associated with a change in schedule III prescribing.	Strengths: Indicators for patient characteristics Limitations: Blunt policy definitions
Lyapustina 2016	Texas 2010 pain management clinic law	2009-2011	Patients with any prescription claim activity throughout observation period	Interrupted time series analysis without compariso n	IMS Health LRx LifeLink Anonymized Longitudinal Prescription database	Texas's pain management clinic law associated with decline in average MME per transaction (−0.57 mg/month, 95% CI: -1.09, -0.06), opioid volume (kg) (-9.99, 95% CI: -12.9, -7.11), no. of opioid prescriptions (thousands) (-12.2, 95% CI: -15.3, -9.15), and quantity of opioid pills dispensed (-714, 95% CI: -877, -550). The effects of the policy were greatest among prescribers with the highest	Strengths: Sensitivity analyses conducted by varying period and converting closed to open cohort Limitations: No indicator for patient or provider characteristics, opioid mortality, and other opioid relevant policies

						baseline opioid prescribing volume and patients with the highest baseline opioid utilization.	
Meara 2016	Legal restrictions of controlled substances: (1) prescription limits, (2) PDMP, (3) physician examination or pharmacist verification, (4) tamper-resistant prescription, (5) patient identification, (6) pharmacist verification, (7) doctor-shopping restrictions, & (8) pain-clinic regulation	2006-2012	Random 40% sample of all Medicare beneficiaries who were 21 – 64 years of age and enrolled in fee for service Medicare Parts A, B, and D, excluding patients with cancer diagnoses or end stage renal disease or receiving hospice care	Controlled pre-post	Medicare administrative claims. National Death Index	Minimal association between individual state policies and opioid-related outcomes. No policy associated with change in four or more opioid prescribers, proportion of beneficiaries with daily morphine equivalent dose >120 mg, and non-fatal prescription opioid overdose without mention of heroin. Tamper-resistant prescription (-0.49, $p<0.05$) and pain clinic regulation (-0.71, $p<0.5$) associated with reduction in long-term opioid receipt. Other policies not associated.	Strengths: Covariates for beneficiary's demographic characteristics, behavioral health diagnoses, and patient risk scores Limitations: Limited external validity due to sample, aggregate policy measure
Opioid prescribing guidelines							
Franklin 2012	WA 2007 State Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain	2003-2010 (data for 1996-2002 borrowed from previous paper)	WA worker's compensation population	Uncontrolled pre-post	Medical Information Payment System	Mean daily MED was relatively stable between 2002-2006, declined in 2008 to 129.7 mg/day MED, in 2009 to 113 mg/day MED, and in 2010 to 105 mg/day MED Opioid related overdose deaths increased from 2007 to 2009 and declined sharply in 2009.	Limitations: No demographic controls
Fulton-Kehoe 2015	WA 2007 State Interagency Guideline on	2006-2010	Individuals ages 18-64 enrolled in WA Medicaid who had at least	Uncontrolled pre-post	WA Medicaid	Increase in enrollees with methadone or other opioid	Strengths Covariates for demographic characteristics

	Opioid Dosing for Chronic Non-Cancer Pain		1 paid claim for an opioid prescription in Medicaid FFS. Excluded individuals if medical claims with a cancer diagnosis and dual eligible.			prescription, any opioid poising, and total opioid poisonings per 100,000 during study period. Methadone poisonings occurred at 10 times the rate of other prescription opioid poisonings and increased between 2006 and 2010. Rates of other prescription opioid poisonings appeared to level off after implementation of the WA opioid guideline in 2007.	Limitations: Minimal pre-period
Garg 2013	WA 2007 State Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain	2004-2010	Individuals enrolled in WA workers' compensation program aged 18 to 64 with ≥ 1 opioid prescriptions	Uncontrolled pre-post	Medical Information Payment System	Decline in mean monthly prevalence of opioid use by 25.6% between 2004 (14.4%) and 2010 (10.7%). Decline in incident users who went on to chronic opioid therapy between pre-guideline period (6.3%, 95% CI: 6.1–6.6%) and post-guideline period (4.7%, 95% CI: 4.5–5.0%) Decline in high dose prescriptions (OR: 0.65, 95% CI: 0.59-0.71)	Limitations: Limited controls included
Sullivan 2016	WA 2007 State Interagency Guideline on Opioid Dosing for Chronic Non-Cancer Pain	2006-2010	Individuals ages 18-64 enrolled in WA Medicaid who had at least 1 paid claim for an opioid prescription in Medicaid FFS. Excluded individuals if medical claims with a cancer	Uncontrolled pre-post	WA Medicaid enrollment and outpatient pharmacy claims	Median opioid dose was unchanged at 37.6 mg MED from 2006 to 2010. Significant decreases in opioid doses corresponding to the (-.44, 95% CI: -.50, -.37); the 90th	Limitations: Minimal pre-period, no demographic controls

			diagnosis and dual eligible.			(-1.82, 95% CI: -2.14, -1.50); the 95th (-4.29, 95% CI: -5.37, -3.22); and 99th percentiles (-25.40, 95% CI: -31.39, -19.41).	
Weiner 2017	Ohio 2012 emergency physician guidelines	2010-2014	Statewide total of opioid prescriptions per month by emergency physicians	Interrupted time series analysis with compariso n	Ohio PDMP	Guidelines associated with a 12.0% (95% CI: -17.7, -6.3) reduction in the level of total opioid prescriptions per month and a 0.9% (95% CI: –1.1, –0.7) decline in trend compared to pre-guideline trend. Guidelines associated with a 17.4% (95% CI: -27.4, -7.3) reduction in the level of total MME per month and a –0.9% (95% CI: –1.3, –0.6) decline in trend compared to pre-guideline trend. Guidelines associated with an 11.2% (95% CI: -18.8, -3.6) reduction in the level of total monthly opioid prescriptions greater than a 3-day supply and a 0.9% (95% CI: –1.3, –0.5) decline in trend. Guidelines associated with a 24.8% (95% CI: -43.5, -6.1) reduction in total MME per month for prescriptions greater than a 3-day supply, and a –.9% (95% CI: –1.8, –0.1) decline	Strengths: Introduced orthopedic surgery as a control group in a 2-group interrupted time series model, controlled for number of emergency physicians

						in trend Significant reduction in the level of prescribing for hydromorphone (29.6%, 95% CI: –46.9%, –12.3%), oxycodone (20.8%, 95% CI: –31.7%, –10.1%), codeine (16.3%, 95% CI: –25.1%, –7.5%), and hydrocodone (11.3%, 95% CI: –15.6%, –6.9%), as well as small declines in trend. Guidelines were associated with a decrease in orthopedic surgery prescribing, the comparison, but the effect was larger for emergency medicine prescribing.	
Secondary prevention							
Anti-doctor shopping laws							
Kuo 2016	Multiple state laws: (1) physical examination before prescribing, (2) requiring tamper-resistant prescriptions forms, (3) mandating pain clinic regulation; (4) setting prescription drug limits; (5) prohibiting doctor shopping or fraud; (6) requiring patient identification before	2006-2012	5 % national sample of Medicare beneficiaries with Parts A, B, and D coverage and not in an HMO and with no cancer diagnosis in the year before or the year of study	Controlled pre-post	Medicare claims from Medicare summary files, Medicare Provider Analysis and Review Files, and Outpatient Standard Analytic Files, Medicare Carrier Files, and Prescription Drug Event Files	Only state laws regulating pain clinics were associated with a significant reduction in schedule II opioid prescriptions (0.64 95% CI: 0.47, 0.89). No law was associated with a change in schedule III prescribing.	Strengths: Indicators for patient characteristics Limitations: Blunt policy definitions

	dispensing; (7) immunity from prosecution for individual seeking assistance during an overdose						
Meara 2016	Legal restrictions of controlled substances: (1) prescription limits, (2) PDMP, (3) physician examination or pharmacist verification, (4) tamper-resistant prescription, (5) patient identification, (6) pharmacist verification, (7) doctor-shopping restrictions, & (8) pain-clinic regulation	2006-2012	Random 40% sample of all Medicare beneficiaries who were 21 – 64 years of age and enrolled in fee for service Medicare Parts A, B, and D, excluding patients with cancer diagnoses or end stage renal disease or receiving hospice care	Controlled pre-post	Medicare administrative claims. National Death Index	Minimal association between individual state policies and opioid-related outcomes. No policy associated with change in four or more opioid prescribers, proportion of beneficiaries with daily morphine equivalent dose >120 mg, and non-fatal prescription opioid overdose without mention of heroin. Tamper-resistant prescription (-0.49, $p<0.05$) and pain clinic regulation (-0.71, $p<0.5$) associated with reduction in long-term opioid receipt. Other policies not associated.	Strengths: Covariates for beneficiary's demographic characteristics, behavioral health diagnoses, and patient risk scores Limitations: Limited external validity due to sample, aggregate policy measure
Drug supply management							
Cochran 2017	"High PA" (i.e., required PA for 17 to 74 opioids,)with "Low PA" (i.e., required PA for 1 opioid), and no PA (i.e., no PA for any opioid medication)	2010-2012	Medicaid enrollees who initiated a new opioid medication not used for addiction treatment aged 18 to 64, not dually eligible for Medicare, without previous cancer treatment, not in long term care for 90 or more days, and not receiving	Cross-sectional	PA Medicaid	Lower rates of opioid abuse among High PA (ARR: 0.89 (95% CI: 0.85-0.93) and Low PA (ARR: 0.93, 95% CI: 087-1.00), compared to no PA.	Strengths: Variety of demographic and health characteristics controls included Limitations: Other covariates explaining placement in plans with varying PA

			hospice services				
Hartung 2018	2012 Oregon Medicaid PA policy for opioid prescriptions above 120 mg per day	2011-2013	Individuals enrolled in either the Oregon or Colorado fee-for-service Medicaid program between 01/2011 and 12/2013 who had at least 1 opioid prescription fill during study period and were not dual eligible	Controlled pre-post	Medicaid administrative claims	Policy implementation associated with a reduction in the estimated monthly probability of an opioid prescription > 120 mg per day MED by 1.7% (95% CI: -2.0, -1.4). Policy implementation associated with an increase in estimated monthly probability of an opioid prescription < 61 mg per day MED by 1.0% (95%CI: 0.4, 1.7). Policy implementation associated with a decrease in multiple pharmacy visits by 0.1% (95%CI: -0.02, -0.001) No statistically significant difference between Oregon and Colorado in total opioid prescription or opioid prescriptions 61-120 MED. No change in opioid related emergency department or hospitalization in both states	Strengths: Propensity score matching to weight Colorado populations for similarity to OR Limitations: Significant variation between Oregon and Colorado Medicaid programs, no indicator for other opioid relevant policies
Keast 2018	2008 Oklahoma Medicaid PA policy requiring a trial of short-acting opioids prior to initiating extended-release/long-acting opioid	2007-2009	Oklahoma (OK) and Oregon (OR) Medicaid fee for service beneficiaries aged 18 – 64 that were not dual eligible and were enrolled for a minimum of 75 % of the study period	Controlled pre-post	Medicaid administrative claims	Policy associated with statistically significant change in new ER/LA opioid in opioid-naïve patients (-0.0074), new ER/LA opioid among all sample (-0.0140), ER/LA opioid count (-0.1630), short-	Strengths: Propensity scoring to weight OR populations for similarity to OK Limitations: No controls for other opioid relevant

	therapy					acting opioid count (0.3633), total opioid count (0.3088), and non-opioid pain medication count (-0.3674). No statistically significant reduction was observed for ER/LA opioid as a proportion of total opioid prescriptions. Among high-risk opioid users, policy associated with statistically significant change in long-term opioid use (0.0333), opioid-opioid overlap claims (-0.0305), opioid-benzodiazepine overlap (0.0110), multiple pharmacy use (-0.0050), and multiple prescriber use (-0.0704). No significant change in high dosage opioid use or opioid-related hospitalization or ED visits.	policies
Morden 2008	PA policy: (1) binary PA indicator for controlled-release oxycodone; (2) strict or lenient policy	1996-2005	Outpatient FFS Medicaid prescription claims in 49 states and DC	Controlled pre-post	Outpatient FFS Medicaid prescription drug dispensing records	PA resulted in a non-significant 0.19 reduction in controlled-release oxycodone use (95% CI: -36%, 2%). State-specific use changes for controlled-release oxycodone ranged from -0.76 to 0.09. A strict PA policy associated with a 0.34 reduction in controlled-release oxycodone use (95% CI: 0.47, 0.92) and a lenient PA policy	Limitation: Potential confounding associated with other differences between states with and without PA policies

						associated with a 0.06 reduction (95% CI: 0.884, 1.33)	
Riggs 2017	2014 Colorado Medicaid SA opioid quantity limit	2014	Patients aged 18 years or older who purchased at least 1 SAO prescription at a KP pharmacy using the Medicaid benefit during either the pre-implementation or post-implementation period and were continuously enrolled in a KPCO insurance plan from 05/03/2014-03/31/2015	Uncontrolled pre-post	KPCO electronic medical and pharmacy records	Primary study population: Median total daily oral morphine equivalents (OME) decreased from 6.8 mg pre to 6.6 mg post (p = 0.027). No statistically significant change in: mean total daily dose of long acting opioids, proportion of patients purchasing any long-acting opioid, and proportion of patients purchasing >120 mg MME per day. Secondary study population of individuals who exceeded the SAO limit at baseline: Median total daily oral morphine equivalents (OME) decreased from 42.2 pre to 32.2 post (p<0.001). Decrease in nonadjuvanted pain medication from 65.9% pre to 55.0% post (p<0.001). No statistically significant change in mean total daily dose of long acting opioids in OME, proportion of patients purchasing any long acting opioid, and proportion of patients purchasing >120 mg MME per day.	Limitations: No indicators for patient or provider characteristics, no comparison group
Prescription drug monitoring programs							
Ali 2017	PDMP:	2004-2014	67,000 randomly	Controlled	NSDUH	No association	Strengths:

	PDMP, PDMP without enhancements, PDMP with mandatory access, PDMP with mandatory enrollment, and PDMP with both mandatory access and enrollment		selected noninstitutionalized individuals 12 years or older in the United States	pre-post		between PDMP implementation and past-year non-medical prescription pain (NMPR) reliever use, abuse/dependence, nor initiation. PDMP implementation associated with an approximately ten-day reduction in days of NMPR use in past year ($p<0.05$). Mandatory access provision associated with an approximately 20-day reduction in days of past-year NMPR use ($p<0.01$). No association between PDMP implementation and past-year heroin use, abuse/dependence, or initiation. PDMP without mandatory access and enrollment associated with significant reduction in past-year days of heroin use. PDMPs without mandatory access or enrollment provisions associated with a 56% reduction in the odds of having two or more prescribers as a source for of opioid prescriptions used nonmedically ($p <0.05$). PDMPs with a mandatory access provision were	Controlled for pain management clinic regulation and demographic characteristics of respondents, state and quarter fixed effects, state-specific linear time trends

						associated with an 80% reduction in the odds of having two or more prescribers as a source for non-medical opioid prescriptions ($p < 0.05$). PDMPs without access or enrollment provision associated with a 56% change in having two or more prescribers as a source for opioid prescriptions used nonmedically. Other provisions not statistically significantly associated with two or more prescribers. PDMP not statistically significantly associated with social sources and illegitimate sources for NMPR acquisition.	
Baehren 2010	2006 Ohio PDMP (OARRS)	June-July 2008	Emergency department patients age 18 or older with painful conditions, including dental, neck, back, head, joint, or abdominal paint.	Un-controlled pre-post	Survey of University of Toledo Medical Center Emergency Department Physicians	Opioid prescribing altered for 41% of patients In cases of altered prescribing, 61% resulted in fewer or no opioid medications prescribed compared with pre-OARRS. 39% resulted in patients prescribed more painkillers than originally planned.	Limitations: Single institution, lead physician treated nearly one third of patients in data set, no blinding of providers and research assistants, self-reported documentation of prescriptions, no covariates for patient or provider characteristics
Bao 2016	PDMP	2001-2010	Patients age 18 or older who reported pain as a reason for a visit to an office-based physician	Controlled pre-post	National Ambulatory Medical Care Survey	The implementation of a PDMP associated with a 3.7-5.5% reduction in the probability of prescribing a	Strengths: State and year fixed effects; Covariates for patient, provider and visit characteristics

						Schedule II opioid ($p < 0.01$) PDMPs associated with a nonsignificant decrease in prescribing of opioid of any kind and pain medication overall Reduction in schedule II opioids was significant in the first six months of implementation. No subsequent reductions were significant. Significant 4.3 percentage point reduction in overall pain medication in third year.	
Brady 2014	PDMP: (1) binary indicator for PDMP implementation; (2) governing agency; (3) statutory requirements for committee oversight; (4) explicit laws that impose no expectation on practitioners	1998-2008	Opioids dispensed in each state	Controlled pre-post	ARCOS	Binary PDMP associated with a reduction in MMEs per capita (-0.033, $p = 0.69$). The impact of PDMPs varied by state. MMEs dispensed per capita was 434.39 (SE: 22.99) in state quarters with PDMPs governed by health departments, 678.27 (SE: 17.51) governed by board of pharmacies, and 478.01 (SE: 29.56) governed by other. No value is statistically significant. MMEs dispensed per capita was 551.02 (SE: 25.66) in states with statutory requirement for committee	Strengths: Calendar year, demographic characteristics, and geographic region Limitations: No indicator accounting for cross-state trade and other relevant policies

						oversight and 494.27 (SE: 14.80) in states without requirement. No value is statistically significant. MMEs dispensed per capita was 531.25 (SE: 23.80) in states with laws that impose no expectation on practitioners and 504.72 (SE: 15.26) without requirement. No value is statistically significant. Effects varied significantly by state.	
Branham 2017	PDMP	1992-2012	Change in prescription opioid and heroin admissions	Interrupted time series without compariso n group	TEDS	PDMP implementation was associated with a 0.41 relationship between heroin and prescription opioid admissions overall ($p \leq 0.01$). PDMP implementation was associated with a 0.50 relationship between heroin and prescription opioid admissions 5 years after implementation ($p = 0.036$) Less than daily data collection associated with a -154.9 relationship between heroin and prescription opioid admissions compared to daily data collection ($p = 0.01$)	Strengths: Covariates for region and data collection frequency Limitations: No indicators for other relevant policies, only three time points for pre and post interventions
Brown 2017	New York PDMP ("I-STOP") mandatory	2010-2015	Six prescription opioids (fentanyl base, hydrocodone,	Interrupted time series without compariso	ARCOS, NYSDOH Bureau of Narcotics	Change in the sign of the slope for the distribution of MMEs before (b =	Strengths: Covariates for patient characteristics,

	access		hydromorphone, oxycodone, codeine, and morphine) dispensed and opioid and heroin overdose in New York	n group	Enforcement data, Statewide Planning and Research Cooperative System (SPARCS)	-3.31, $p < 0.001$) and after ($b = 2.73$, $p < 0.001$) I-STOP. Increase in the rate of heroin overdose morbidity from before ($b = 30$, $p < 0.001$) to after ($b = 101.9$, $p < 0.001$) I-STOP Increase in the rate of heroin overdose plus prescription overdose morbidity before ($b = 38.3$, $p = 0.001$) and after ($b = 98.8$, $p < 0.001$) I-STOP Evidence suggestive that prescriptions fills decreased after I-STOP. No statistically significant change in the rate of overdose morbidity due to prescription opioids before and after I-STOP.	diagnoses and treatment services Limitations: SPARCS does not include substance abuse centers not co-located in hospitals, no indicators for other relevant policies
Buchmueller 2018	PDMP with and without "must access" provisions	2007-2013	Random 5% sample of Medicare beneficiaries enrolled in Part D and fee-for-service Medicare	Controlled pre-post	Medicare Part D claims	PDMPs without mandatory access provision associated with a statistically significant increase in filling at 5 or more pharmacies (0.001) and in proportion of patients with 4 or more new patient visits (0.004). No statistically significant difference in probability of taking opioids, for 211+ days supply, 120+ daily MED, overlapping claims, 5+ prescribers, out of	Strengths: Sensitivity analysis conducted to assess influence of other opioid-relevant policies, fixed effects for states and half-years Limitations: Outcome data does not include opioid purchases not reimbursed through Medicare

						state prescribers, out of state pharmacies, and opioid poisonings PDMPs with mandatory access provisions were associated with a decline in probability of taking opioids (-0.007, 95% CI: -0.0133, -0.0004), overlapping claims (-0.006, 95% CI: -0.0095, -0.0016), 5+ prescribers (-0.002, 95% C: -0.0035, -0.001), 5+ pharmacies (-0.001, 95% CI: -0.0015, -0.003), and 4+ new patient visits (-0.002, 95% CI: -0.0031, -0.004). Must-access provisions were not statistically significantly associated with a change in 211+ days supply, 120+ daily MED, out of state prescribers, out of state pharmacies, and opioid poisonings Stronger mandatory access provisions were associated with the greatest reductions.	
Curtis 2006	PDMP	2000	Individuals whose health insurance required AdvancePCS to track claims, were enrolled continuously during calendar year 2000, and filled at least one prescription drug claim for any drug during study period	Cross-sectional	AdvancePCS (now Caremark Rx, INC)	Counties with PDMP had 36.5 fewer opioid analgesic claims per 1,000 total prescription claims compared to counties without a PDMP ($p < 0.01$). Counties with PDMP had 2.0 fewer controlled-release oxycodone claims per 1,000 total prescription	Strengths: Demographic and drug use prevalence covariates Limited: No controls for geographic variation in medical conditions, insurance coverage, or other opioid

						claims compared to counties without a PDMP ($p < 0.01$).	relevant policies
Dave 2017	PDMP: 1) binary indicator for operational PDMP; (2) binary measures for mandatory access provision	2003-2014	Treatment admissions to federally funded facilities	Controlled pre-post	TEDS	PDMP did not statistically significantly affect treatment admissions for prescription drugs across age groups. Mandatory access provision significantly associated with 5.8 ($p <0.05$) fewer treatment admissions for prescription drugs per 10,000 individuals ages 18-24, 3.2 ($p < 0.1$) admissions among individuals aged 25-44, and 0.35 ($p < 0.01$) fewer admission among individuals aged 45+. Effect not statistically significant for ages 12-17. No reduction in heroin related treatment admissions associated with PDMP or mandatory access provision observed in any age group.	Strengths: Specific PDMP feature; state and year fixed effects; differential policy response across relevant age groups; urbanity, different abuse substances; and referral source for treatment admission; demographic covariates; time period selected attempts to address confounding due to physical examination requirement policies
Deyo 2018	Oregon prescriber PDMP, PDMP, registration, and query rate	2011-2014	Oregon clinicians who prescribed an opioid. Clinicians who registered for the PDMP prior to December 1, 2011 were excluded.	Uncontrolled pre-post	Food and Drug Administration National Drug Codes, Oregon vital records	Decrease in opioids dispensed from 16.9 to 15.0 per capita per quarter during the first three years of PDMP operation. Gradual downward statistically insignificant decrease in total number of daily MME dispensed per capita (2.80 to 2.41)	Strengths: Propensity score matching Limitations: No indicators for prescriber demographics, patient diagnosis

						No significant difference between PDMP registrants and nonregistrants in change in prescriptions, multiple prescribers, or inappropriate prescriptions. Registered prescribers had more (6.04) opioid patients with an average daily MME >/= 90 than nonregistered prescribers (p = 0.012) Registered prescribers had greater percentage (12.2%) of opioid prescriptions that overlap a sedative-hypnotic prescription within 30 days than nonregistered prescribers (11.0%) (p=0.043). Registered prescribers had lower opioid-related hospitalizations (199) than nonregistered prescribers (158) (p=.034)	
Gilson 2011	California Senate Bill 151 requiring use of tamper-resistant security prescription form, rather than triplicate forms, for all medications in Schedule II-V	2000-2006	Opioid prescriptions	Interrupted time series without comparison	Controlled Substance Utilization Review and Evaluation System	Requiring a security form was associated with a sustained prescribing increase for SA hydromorphone (5.215, p < .001), meperidine (10.256, p < .001), and SA oxycodone (5.504, p < .001). No prescribing changes were found for SA fentanyl,	Limitations: No covariates for prescriber characteristics or other opioid relevant policies

						methadone, SA morphine, or long-acting opioids.	
Green 2012	PDMP pharmacist accessibility: Connecticut prescribers and dispensers of controlled substances registered with PDMP can actively query system; Rhode Island: PDMP can not be directly access or queried by health professionals	2011	Connecticut Pharmacists registered with the Connecticut PDMP at the time of the survey, Connecticut Pharmacists Association's membership listserv, and Connecticut pharmacists registered with the Department of Consumer Protection's communication listserv Rhode Island: All Rhode Island pharmacists licensed to dispense medications	Cross-sectional	Primary data collection	7.8 % of Rhode Island pharmacist had used the PDMP compared to 67.9 % of Connecticut pharmacist ($p < 0.01$)	Limitations: Small sample ($n = 210$), response bias, no indicator for other opioid relevant policies or prescriber characteristics
Haffajee 2018	PDMP: Robust PDMP defined as exhibiting at least eight of ten features that facilitate prescribers' access to comprehensive, timely data or have been established by prior literature on PDMP evaluation as important for improving prescribers' use and data utility. Robust states = Kentucky, New Mexico, Tennessee, and New York. Neighboring comparison states without	2010-2014	Commercially insured adults aged 18-64 Controlled pre-post: Commercially insured adults aged 18-64 with opioid fills at any time during study period	Interrupted time series with comparison, controlled pre-post	Optum commercial claims	Relative percent difference in mean opioid fills per enrollee: -16.15 in Kentucky vs. Mississippi ($p < 0.001$), -6.79 in New Mexico vs. Texas ($p < 0.001$), -5.23 in Tennessee vs. Georgia ($p < 0.001$), and -2.93 in New York vs. New Jersey ($p < 0.10$). Relative percent difference in mean MED dispensed per enrollee equaled -18.33 in Kentucky vs. Mississippi ($p < 0.001$), -10.72 in New Mexico vs. Texas ($p < 0.01$), -10.43 in Tennessee vs. Georgia ($p <$	Strengths: Four pairs of comparison and intervention states, sensitivity analyses to check for bias associated with changing study population Limitations: No indicator for other opioid relevant policies

	robust PDMP = Missouri, Texas, Georgia, New Jersey					0.01), and -10.54 in New York vs. New Jersey ($p < 0.05$). Relative percent difference in percent of enrollees with daily MED ≥100mg: -20.42 in Kentucky vs. Mississippi ($p < 0.01$). Not statistically significant for other states. Relative percent difference in mean quarters with opioid Rx filled by ≥3 doctors per enrollee: -40.44 in Kentucky vs. Mississippi ($p < 0.001$). Not statistically significant for other states. Relative percent difference in mean quarters with opioid Rx filled by ≥3 pharmacies per enrollee: -38.06 in Kentucky vs. Mississippi ($p < 0.001$). Not statistically significant for other states	
Kuo 2016	Multiple state laws: (1) physical examination before prescribing, (2) requiring tamper-resistant prescriptions forms, (3) mandating pain clinic regulation; (4) setting prescription drug limits; (5) prohibiting	2006-2012	5 % national sample of Medicare beneficiaries with Parts A, B, and D coverage and not in an HMO and with no cancer diagnosis in the year before or the year of study	Controlled pre-post	Medicare claims from Medicare summary files, Medicare Provider Analysis and Review Files, and Outpatient Standard Analytic Files, Medicare Carrier Files, and Prescription	Only state laws regulating pain clinics were associated with a significant reduction in schedule II opioid prescriptions (0.64 95% CI: 0.47, 0.89). No law was associated with a change in schedule III prescribing.	Strengths: Indicators for patient characteristics Limitations: Blunt policy definitions

	doctor shopping or fraud; (6) requiring patient identification before dispensing; (7) immunity from prosecution for individual seeking assistance during an overdose				Drug Event Files		
Landau 2018	PDMP	2017	Random sample of patients reporting with pain-related complaints to the Emergency Department at UPMC Mercy Hospital	Uncontrolled pre-post	Primary data collection	Pre-PDMP, EM providers indicated they planned to prescribe an opioid analgesic in 63.1% of encounters. Post-PDMP, EM providers reported that they planned on prescribing an opioid analgesic in 66.0 % of encounters. 89.3% of encounters resulted in no change in opioid prescribing planned	Limitations: Convenience sample of providers and patients
Li 2014	PDMP: (1) binary indicator for PDMP implementation; (2) governing agency: (3) statutory requirements for committee oversight; (4) explicit laws that impose no expectation on practitioners; (5) statutory authority to monitor non-controlled substances	1999-2008	All drug overdose deaths in the United States	Controlled pre-post	Multi-cause-of-death files of the National Center for Health Statistics	PDMPs were associated with increased risk in drug overdose mortality compared to non-PDMP states (aRR 1.11; 95% CI: 1.02, 1.21). Board of pharmacy governing agency associated with increased risk of drug overdose mortality compared to non-PDMP state (aRR 1.14, 95% CI: 1.00, 1.30). No statistically significant	Strengths: Time trend, demographic characteristics, geographic region, macroeconomic condition, and drug overdose death reporting accuracy included as indicators in model Limitations: Aggregate drug overdose death dependent variable, limited covariates included in

						difference for department of health and other governing agencies. No statutory requirement for committee oversight requirement associated with increased risk of drug overdose mortality compared to non-PDMP state (aRR: 1.13, 95% CI: 1.02, 1.26). No statistically significant difference for statutory requirements for committee oversight and other governing agencies. Explicit laws that impose no expectation on practitioner associated with increased risk of drug overdose mortality compared to non-PDMP state (aRR: 1.17, 95% CI: 1.02, 1.34). No statistically significant difference for no explicit law. No statutory authority to monitor non-controlled substances associated with increased risk of drug overdose mortality compared to non-PDMP state (aRR: 1.13, 95% CI: 1.02, 1.24). No statistically significant	model

						difference for statutory requirement Significant state variation in drug overdose mortality	
Lin 2018	PDMP: (1) binary indicator for PDMP implementation; (2) mandatory enrollment; (3) mandatory access	2012	Ambulatory visits to non-federally employed office-based physicians in 39 states	Cross-sectional	NAMCS survey	The binary and characteristic PDMP indicators were not statistically significantly associated with pain medication or opioid prescriptions.	Strengths: Covariates for prescriber characteristics, practice setting, practice region, electronic medical record adoption, and new patient status Limitations: No model indicators for other opioid relevant policies, reporting bias
Maughan 2015	Prescriber-accessible PDMP	2004-2011	ED visits involving opioid analgesics per quarter, per 100,000 in 11 metropolitan area residents	Controlled pre-post	Drug Abuse Warning Network public use files	PDMP was not associated with a difference in the rate of emergency department visits involving opioid analgesics	Strengths: Covariates for unemployment rate Limitations: Aggregate PDMP indicator, no indicators for other opioid relevant policies and opioid mortality
McAllister 2015	2009 Florida PDMP called Electronic Florida Online Reporting of Controlled Substances Evaluation program (E-FORCSE)	2013, 2014	Patients aged 18 or older treated in the immediate care areas of the emergency departments. Patients excluded if they were not directly discharged from the ED, had incomplete medical record, if E-FORCE data was not provided to the provider	Un-controlled pre-post	Primary data collection	There was no change in the average number of controlled substance prescriptions nor uncontrolled substance prescriptions per patient when E-FORCSE data was provided to prescribers in emergency department	Strengths: Indicator for patient medical complaint and sex Limitations: No covariates for provider characteristics
Meara 2016	Legal restrictions of controlled substances: (1)	2006-2012	Random 40 % sample of all Medicare beneficiaries	Controlled pre-post	Medicare administrative claims. National	Minimal association between individual state policies and	Strengths: Covariates for beneficiary's demographic

	prescription limits, (2) PDMP, (3) physician examination or pharmacist verification, (4) tamper-resistant prescription, (5) patient identification, (6) pharmacist verification, (7) doctor-shopping restrictions, & (8) pain-clinic regulation		who were 21 – 64 years of age and enrolled in fee for service Medicare Parts A, B, and D, excluding patients with cancer diagnoses or end stage renal disease or receiving hospice care		Death Index	opioid-related outcomes. No policy associated with change in four or more opioid prescribers, proportion of beneficiaries with daily morphine equivalent dose >120 mg, and non-fatal prescription opioid overdose without mention of heroin. Tamper-resistant prescription (-0.49, $p<0.05$) and pain clinic regulation (-0.71, $p<0.5$) associated with reduction in long-term opioid receipt. Other policies not associated.	characteristics, behavioral health diagnoses, and patient risk scores Limitations: Aggregate policy measure
Moyo 2017	PDMP	2007-2012	5% national sample of Medicare beneficiaries in 10 states	Interrupted time series with comparison group	Medicare Part D Prescription Drug Event claims	PDMP implementation was associated with reduced opioid volume compared to non-PDMP states: - Overall: -2.36 kg/ month, 95% CI: -3.44, -1.28 - Schedule II: -1.89 kg/month, 95% CI: -3.38, -0.40 - Schedule III: -0.38 kg/month, 95% CI: -0.54, -0.03 PDMP implementation was not associated with a change in: total opioid volume of Schedule IV or V opioids; mean MMEs overall; or number of	Strengths: Propensity score matching to identify comparison state, five pairs of comparison and intervention states Limitations: No indicators for other opioid-relevant policies, binary PDMP indicator

						prescriptions dispensed. In stratified analyses, MME declined by 3.73 mg/ prescription (95% CI: 6.22, 1.24) among disabled beneficiaries and by 3.02 mg/prescription (95% CI: 3.86, 2.18) among Medicare Advantage Drug Plan beneficiaries. There were no changes in older adults and PDMP beneficiaries.	
Nam 2017	PDMP	All drug categories: 1999-2014; Each drug category: 1999-2010	All death certificates filed in all jurisdictions in the US	Controlled pre-post	CDC WONDER, NCHS mortality data, US Census Bureau and NCHS estimated population data	PDMP implementation not associated with reductions in mortality due to overall drug overdose or to overdose related to prescription opioids, heroin, methadone, or synthetic opioids. PDMPs in operation ≥ than 5 years associated with higher rates of overall drug overdose mortality using both the underlying cause of death data (1.39, p = 0.02) and multiple cause of death data (1.36, p = 0.01). PDMPs in operation ≥ 5 years also associated with higher mortality rates due to legal narcotics (0.90 p = 0.04) legal narcotics and benzodiazepines (0.94, p = 0.04), illicit drugs (0.82, p = 0.01), and	Strengths: State-specific linear time trends, covariates for percentage of state population that is male, white, high school educated or better (age 25 or older), uninsured, enrolled in the Medicaid program, and median household income Limitations: Binary PDMP indicator

						other drugs (1.16, p = 0.02). Not statistically significant for all PDMPs.	
Pardo 2016	PDMP: (1) Binary indicator for PDMP operationalized and (2) PDMP assigned weights based on program characteristics	1999-2014	Age-adjusted opioid overdose death in all 50 states and DC	Controlled pre-post	CDC WONDER	PDMP states did not have a statistically significant different opioid overdose rate than no PDMP states (p = 0.18) Every 1-point increase in PDMP strength was associated with a 0.01 (significant at p = 0.01) reduction in overdose deaths related to opioid pain relievers in model 1. Every 1-point increase in PDMP strength was associated with a 0.015 (significant at p = 0.05) reduction in overdose deaths related to opioid pain relievers in model 2. PMPs in the third quartile were associated with an approximately 0.18 (95% CI: -0.34, -0.016) reduction in opioid overdose death rates compared with states without a PMP. PMPs in the 1st, 2nd, and 4th quartiles did not have a statistically significant different effect than no PMP. Effects of NAL, GSL, and pain clinic laws were non-significant.	Strengths: Covariates for GSL, pain clinic management laws, access to medical marijuana dispensaries, demographic measures, policy precision addressed Limitations: Absence of some PDMP characteristics (e.g. prescriber participation as obligatory or voluntary)
Patrick 2016	PDMP: (1) Binary indicator for	1999-2013	Age-adjusted opioid overdose death in 35	Interrupted time series with	CDC WONDER	PDMP implementation associated with a	Strengths: Covariates for demographic

	PDMP implementation, (2) four or more drug schedules monitored, (3) data updated at least weekly, & (4) mandatory use or registration		states	comparison		decrease in opioid-related overdose death rates (AOR: -1.12, $p < 0.001$). Four or more drug schedules monitored associated with a decrease in opioid-related overdose death rates (AOR: -0.55, $p < 0.05$) Data updated at least weekly associated with a decrease in opioid-related overdose death rates (AOR: -0.82, $p < 0.001$) Mandatory use or registration associated not statistically significantly associated with opioid-related overdose death rates	characteristics, state fixed effects, and PDMP enactment Limitations: No covariates for other opioid related policies
Paulozzi 2011	PDMP: (1) binary indicator for PDMP implementation and (2) binary proactive indicator (i.e. PDMP generating reports for prescribers, dispensers, or law enforcement authorities without being solicited)	1999-2005	Unintentional drug overdose deaths, opioid overdose mortality, and opioid consumption in 50 states and DC	Controlled pre-post	Multiple cause of death mortality files from National Center for Health Statistics, ARCOS	PDMP states and proactive states did not have a statistically significant difference, in drug overdose deaths, opioid-related mortality rate, nor mean MME rates than non PDMP states and non-proactive states.	Strengths: Covariates for population median age, median household income, ethnicity distributions, education level, and urbanity Limitations: Limited policy precision, no covariates for other opioid relevant policies
Pauly 2018	PDMP: (1) PDMP enactment, (2) PDMP operational (2) CS Schedules monitored by the PDMP (II only or II-III, II-IV, II-V),	2004-2014	All provider, facility, and pharmaceutical claims for eligible privately insured adults	Controlled pre-post	Truven Health Marketscan administrative claims data	States with PDMPs experienced significantly less increase in prescription opioid-related overdose rates (aRR=1.003, 95% CI: 1.001, 1.004)	Strengths: Covariates include demographics and diagnosed substance use disorders Limitations: Lacking

	(3) frequency of data reporting from dispense to the PDMP central server, (4) requirement for unsolicited reporting of patient's prescription history to in-state prescribers or licensure boards (5) mandated prescriber query of PDMP data prior to prescribing in certain circumstances					than states without PDMPs (aRR=1.008, 95% CI: 1.005, 1.01). Several features of PDMPs were associated with protective effects on prescription opioid-related overdose—such that there was no change in poisoning in states with such PDMP features, while there were increases in poisoning rates in states without such features. This included PDMPs requiring daily or weekly upload of dispensing data, those requiring prescribers to query the PDMP data in certain situations, those with schedule II-IV or schedule II-V monitoring, and those requiring unsolicited reports.	important demographic covariates (e.g. race and ethnicity) and indicators for other opioid relevant policies
Phillips 2017	PDMP with mandatory access provision: (1) binary indicator (2) time since enactment	2011-2014	Residents of 50 states and DC	Controlled pre-post	CDC WONDER	Mandatory access provision associated with an 0.11 increase in mean annual age-adjusted opioid related mortality rate per 100,000 people (p = 0.005) For every additional year since mandatory access provision enactment, mean opioid-related mortality rate increased by 0.056 compared with states without provision (p = 0.0048)	Strengths: Covariates for state urbanity, population on, education, and unemployment Limitations: Severely limited covariates, significant heterogeneity within PDMP program not accounted for, newly adopted laws restrict follow-up period
Rasubala 20	2013 New York PDMP	2013	Every patient who visited the	Un-controlled	Primary data collection	A majority of patients received	Limitations: Potential

15	mandatory access provision		dental urgent care center	pre-post		pain medications in 3-month periods: pre I-STOP 76.8%, post-1 (67.0%), post-2 (64.1%). Among patients who received pain medications, there was a decrease in the percentage prescribed opioids during study period: pre I-STOP (30.6%), post-1 (14.1%), post-2 (9.6%) ($p < 0.05$). The odds of a patient needing opioid analgesic decreased over study period. Decrease in patients who received opioid analgesics pre (452) and post-1 (190) and post-2 (140) I-STOP ($p < 0.0001$). No change in non-opioid analgesics	confounding associated with lack of model covariates and other potential explanations
Reifler 2012	PDMP	2003-2009	74 opioid treatment centers from 33 states	Controlled pre-post	RADARS	Poison Center intentional exposures increased, on average, per quarter by 1.019 without PDMP (95% CI: 1.008, 1.030) and 1.002 with PDMP (95% CI: 0.992, 1.012). Opioid treatment admissions increased, on average, per quarter by 1.049 without PDMP (95% CI: 1.036, 1.063) and 1.026 (95% CI: 1.009, 1.044) with PDMP.	Limitations: Self report and selection bias inherent within RADARS, PDMP variation not captured, no indicators for other opioid relevant policies and state demographic features
Reisman 2009	PDMP	1997-2003	(1) State shipments of prescription	Controlled pre-post	ARCOS, TEDS	Significant reduction in the rise of oxycodone	Strengths: Nine socioeconomic variables,

			opioids and (2) drug admissions into publicly funded drug rehabilitation facilities in 14 states with PDMP, 26 states without PDMP			shipments for PDMP compared to non-PDMP (-370.9, p = 0.019). Odds of patient entering an inpatient drug rehabilitation program for prescription opioid abuse in PDMP was significantly lower than non-PDMP (OR: 0.775, 95% CI: 0.764, 0.785).	population density, and housing density included as covariates
Ringwalt 2015	North Carolina (NC) PDMP query rate: (1) total number of providers who used or queried the PDMP and (2) the mean number of days on which those providers queried the system	2009-2011	Number of prescriptions for controlled substances in NC	Un-controlled post only	Health Information Designs	No association between either explanatory variables and controlled substance prescriptions or controlled substance fills	Limitations: Large 6-month blocks for mean and total queries, no indicator for prescriber or patient characteristics included in model
Sigler 1984	1982 Texas' triplicate prescription law	1981-1982	All prescriptions for schedule II drugs dispensed to ambulatory patients at a 1200-bed teaching hospital	Uncontrolled pre-post	Primary data collection	Decrease in schedule II prescriptions as a percentage of total prescriptions from 1.57 in 1981, 0.55 in 1982, and 0.57 in 1983 60.4% decrease in schedule II drugs from 1981 to 1982.	Limitations: No controls for prescriber characteristics (except prescriber category), patient characteristic, other hospital or public policies
Simoni-Wastila (2018)	PDMP: (1) no PDMP, (2) electronic-only PDMP (ePDMP), and (3) electronic and paper PDMP (e+pPDMP)	2007	Medicare-eligible retirees and their dependents	Cross-sectional	MarketScan Coordination of Benefits administrative claims data	Compared to non-PDMP, PDMP had increased odds of any analgesic prescription (aOR ePDMP=1.19, 99% CI: 1.19, 1.20; aOR e+pPDMP = 1.04, 99%CI: 1.03, 1.05). Among analgesic	Strengths: Covariates include basic sociodemographic, specific comorbidities related to analgesic use and psychiatric conditions, and annual number of physician office visits

						users, the odds of receiving potent schedule II analgesics relative to schedule V analgesics were lowest for individuals residing in e+pPDMP states (aOR e+pPDMP = 0.54, 99%CI: 0.53, 0.55), followed by ePDMP states (aOR ePDMP = 0.76, 99%CI: 0.75, 0.77) relative to non-PDMP states. The odds of receiving schedule III-V OAs were highest for individuals in PDMP compared to non-PDMP states.	Limitations: Other variations in PDMP policy may explain change
Suffoletto 2017	2016 Pennsylvania PDMP mandatory access provision	2015-2017	All patients aged 18 or older discharged with an opioid prescription each month from 15 emergency departments in the University of Pittsburgh Medical Center system	Interrupted times series without comparison	Primary data collection	Decline in opioid prescribing rate by -12.4 % (95% CI: 10.8, 14.1) over study period	Strengths: Sensitivity analysis conducted with varied pre-implementation periods Limitations: No indicator for other opioid relevant policies and prescriber or patient characteristics
Sun 2018	2014 Washington automated PDMP	2013-2015	Washington state Medicaid beneficiaries aged 16 or older enrolled between 01/01/2013 – 09/30/2015, excluding members with a cancer history, dual eligible, received hospice or nursing care, and enrolled for less than 3 months	Un-controlled pre-post	Medicaid claims from the Washington State Health Care Authority	PDMP not significantly associated with reduction in the proportion of visits with opioid prescribing (5.8/1, 000 encounters, 95% CI: –0.11, 11.8) or total dispensed MME (2.66, 95% CI: -0.15, 5.48). No evidence that effect was concentrated in high-risk opioid	Strengths: Hospital and year fixed effects, interaction term between binary PDMP indicator and query rate and 6 individual high-risk factors, covariates for patient demographics and health characteristics Limitations:

						users.	Blunt policy definition
Wastila 1996	MCPP	1989	38,384 patient office visits	Cross-sectional	1989 Ambulatory Medical Care Survey	MCPPs had a negative influence (-1.11, $p \leq 0.001$) on schedule II opioid use and a positive influence (0.59 $p \leq 0.001$) on schedule III opioid use. There was no statistically significant association between MCPP and schedule IV opioid use.	Limitations: No controls for other opioid-relevant policies and patient or provider characteristics, dosage and quantity not considered
Wen 2017	PDMP: (1) registration and access mandate, (2) registration mandate, (3) access mandates	2011-2014	Number of prescription fills in 46 states	Controlled pre-post	2011-14 Medicaid State Drug Utilization	Average number of Schedule II opioid prescriptions per quarter was 15.3 in states without any mandate and 13.9 in state with a mandate ($p < 0.05$). Registration mandate alone associated with a -1.49 reduction in number of opioid prescriptions per 100 Medicaid enrollees compared to no registration mandate ($p <0.05$) Registration and access mandate associated with a -1.90 reduction in number of opioid prescriptions per 100 Medicaid enrollees compared to no registration mandate ($p <0.05$) Access mandate associated with a minimal and non significant reduction.	Strengths: Covariates for opioid-relevant state policies and economic conditions, state and year fixed effects
Yarbrough 20	PDMP with real-time	2010-2013	Total days supply of	Controlled pre-post	Medicare Part D	PDMPs associated with a reduction in	Strengths: Physician and

18	access to patient information defined as (1) prescriber and dispenser access, (2) online access, and (3) required reporting of all prescriptions dispensed by a pharmacy. Control defined as states with explicit language in PDMP statute not requiring physicians to utilize the program		analgesics in states that implemented a new online PDMP during 2011-2013			days supply prescribed per physician for: - Opioids overall: 2%, $p < 0.01$ - Oxycodone: 5.2%, $p < 0.01$ - Hydrocodone: 2.8%, $p < 0.01$ PDMPs associated with a 1.4% increase in days supply prescribed per physician of schedule IV opioids ($p< 0.05$). PDMPs were not associated with changes in days supply in states without mandatory access requirements. PDMPs not associated with difference in prescribing of non-opioid analgesics, schedule II, or schedule III drugs.	year fixed effects, covariates for county-level economic and demographic effects Limitations: No data on dose strength
Tertiary prevention							
Good Samaritan Laws							
Nguyen 2018	New York 2011 GSL	2010-2012	270 hospitals in NY and NJ	Controlled pre-post	State Emergency Department Databases and State Inpatient Databases	Good Samaritan laws associated with increases in emergency department visits and inpatient hospital admissions related to opioids (IRR: 1.21, 95% CI: 1.00, 1.48) and heroin (IRR: 1.34, 95% CI: 1.00, 1.86). The results were inconclusive for non-heroin opioid overdose (IRR: 0.98, 95% CI: 0.86, 1.13)	Strength: Hospital and time fixed effects
Rees 2017	Naloxone	1999-2014	Opioid-related,	Controlled	National	Adoption of	Strength: State

	access laws and Good Samaritan laws		heroin-related, and non-heroin opioid related deaths in the United States per 100,000 population by year	pre-post	Vital Statistics System	naloxone access laws associated with a 0.043 reduction in all opioid-related mortality, a 0.045 reduction in non-heroin opioid-related mortality, and no change in heroin related mortality (all values were not statistically significant at p = 0.0048) Adoption of naloxone access laws standing order provision associated with a 0.015 reduction in all opioid-related mortality, a 0.015 reduction in non-heroin opioid-related mortality, and a 0.091increase in heroin-related mortality (all values were not statistically significant at p = 0.05). Removing criminal liability for naloxone possession associated with 0.134 decrease in the number of opioid-related deaths (p < 0.01), a 0.134 decrease in the number of deaths involving opioids other than heroin (p < 0.05), and a 0.169 decrease in heroin-related deaths (not statistically significant at p = 0.05) Adoption of Good Samaritan laws was associated	and year fixed effects, population, PDMP implemented, police officers per capita, medical marijuana legalization, beer tax, cigarette tax, and unemployment rate covariates

						with a 0.101 reduction in all opioid-related mortality, 0.098 reduction in non-heroin opioid-related mortality, and a 0.070 increase in heroin-related mortality (all values were not statistically significant at p = 0.05). Neither naloxone access laws nor Good Samaritan laws were associated with a change in non-prescription use of prescription painkillers.	
Opioid addiction treatment policies							
Andrews 2014	Three types of state policies that affect clinician prescribing of buprenorphine: (1) policies that regulate buprenorphine beyond federal standards; (2) states with funds available to subsidize buprenorphine use; (3) policies that impose special requirements for prescribing buprenorphine	2005, 2011	2005: 170 opioid treatment programs 2011: OTPs that participated in 2005 plus a subsample of replacement OTPs	Cross-sectional	NDATSS 2011 follow-up survey to NDATSS conducted by Cornell University's Survey Research Institute	States that regulate buprenorphine beyond federal standards had 1.23 higher odds of any use of buprenorphine, 0.69 lower odds of use for detoxification, and 1.06 higher odds for maintenance. None of these values were statistically significant at p < 0.05. States with funds available to subsidize buprenorphine had 2.06 higher odds of any use of buprenorphine, 2.51 higher odds for detoxification, and 1.81 higher odds for maintenance. All of these values were statistically significant at the p < 0.05. States that	Limitations: No physician license to prescribe buprenorphine, client characteristic, or other relevant state policy indicators

						imposed special requirements for prescribing buprenorphine had 1.94 higher odds for any use of buprenorphine, 4.55 higher odds for detoxification, and 2.88 higher odds for maintenance. Only the use of buprenorphine for maintenance was statistically significant at $p < 0.05$.	
Bachhuber 2017	State Medicaid coverage of methadone maintenance	2013, 2014	Pregnant women age 18-44 who reported using either heroin or opioid analgesics, were admitted to residential or outpatient treatment, and had Medicaid insurance	Cross-sectional	TEDS	Admissions in states with coverage of methadone maintenance were more likely to receive OAT in all settings (32.9%, 95% CI: 19.2, 46.7), residential settings (14.3%, 95%CI: -0.7, 29.2), intensive outpatient (40.2%, 15.5, -64.8), and non-intensive outpatient (37.9%, 15.5, 64.8) than admissions in states without coverage.	Strengths: Covariates for sociodemographic, substance use and treatment characteristics Limitations: TEDS does not include data from privately treated facilities, no indicators for other opioid misuse policies nor opioid misuse incidence or prevalence
Clark 2014	2008 Massachusetts Medicaid PA policy focused on buprenorphine dose levels with higher dosages requiring more frequent PA	2007-2008	Primary Care Clinician plan and fee-for service members with a diagnosis of opioid dependence who filled at least one prescription for buprenorphine + naloxone during study period	Interrupted time series without comparison group	MassHealth claims	The percentage of members filling doses greater than 24 mg/day decreased from 16.5% to 4.1%. 0.81% monthly decrease in high-dose group. Increase from 34.1% - 37.5% in medium dose (> 16 and ≤ 24 mg) and from 44.3% - 54.3% low dose (≤ 16 mg) groups after policy. Relapse events increased sharply	Strengths: Measured variation among different dose levels of buprenorphine users Limitations: No controls for other opioid-relevant policies

						after policy implementation but returned to pre-policy trends by the end of 2008	
Deck 2006	Removal of substance abuse and mental health treatment, including methadone treatment, from Oregon Medicaid benefit for expansion population	2002, 2003	Single childless adults aged 18 to 64 addicted to opiates eligible for the Oregon Health Plan	Uncontrolled pre-post	Oregon's Client Process Monitoring System , Medicaid Management Information System	Opiate users presenting for publicly funded treatment after policy changed had 60% lower odds of being placed in a methadone maintenance program compared to the prior year ($p < 0.001$).	Strengths: Demographic and medical history covariates Limitations: No covariates for other opioid relevant policy, cohort variation between 2002 and 2003
Fuller 2006	Removal of substance abuse and mental health treatment, including methadone treatment, from Oregon Medicaid benefit for expansion population	2003-2004	149 clients at a methadone program	Uncontrolled pre-post	Primary data collection	Of the 68 individuals who self-paid, 23 left treatment. Of the 48 individuals who did not lose the benefit, 9 left care.	Limitations: Small sample, large dropout rate (33% at time 4), potential sampling bias associated with voluntary participation
Merlo 2011	2005 Florida policy that required anesthesiologists referred for opiate use disorder treatment only return to practice following treatment if they agreed to pharmacotherapy with naltrexone for a minimum of 2 years	Not provided. Treatment group selected from providers that signed contract after policy implementation; control group selected from providers that signed contract immediately before implementation	18 anesthesiologist and 4 anesthesiology residents	Cross-sectional	Primary data collection	72.7% of the no naltrexone group experienced a relapse and 9.1% of the naltrexone group experienced a relapse ($p < 0.01$).	Limitations: Small sample, no covariates included
Saloner 2016	Varying state public funding for methadone: (1) Medicaid coverage, (2) block grant funding only, & (3) no public	2012	Medicaid enrollees admitted to treatment for opioid use disorder, excluding detoxification admissions in 36 states	Cross-sectional	TEDS	45.0% of Medicaid-enrolled individuals used OAT in states with Medicaid coverage for methadone maintenance, 30.1% in states with block grant coverage only and	Strengths: Models adjusted for individual-level demographic and substance use characteristics, sensitivity analysis to

	coverage					17.0% in states with no coverage (p = < 0.01).	account for if difference were not exclusive to Medicaid populations Limitations: Limited to methadone treatment
Naloxone access laws							
Gertner 2018	Naloxone access law: (1) any naloxone access laws provision, (2) prescriber immunity, (3) third party prescription, (4) standing order, & (5) lay dispensing	2007- 2016	Total number of outpatient prescriptions dispensed and reimbursed through Medicaid in all 50 states	Controlled pre-post	Medicaid State Drug Utilization Data	Any naloxone provision in place associated with an 18.0 increase in dispensed naloxone prescriptions per state-quarter (p -= 0.002). Standing order provisions associated with an average increase of 33.1 naloxone prescriptions per state-quarter (p – 0.001). Lay dispensing associated with an average increase in 1.24 naloxone prescriptions per state-quarter (p = 0.912). Third party immunity associated with an average decrease in naloxone prescriptions per state-quarter by 20.5 (p = 0.013). Prescriber immunity associated with an average increase of 23.8 naloxone prescriptions per state-quarter (p = 0.011).	Strengths: State level covariates, including state unemployment, Medicaid enrollment, federal Medicaid assistance percentages , percent of state expenditures on Medicaid, lagged crude opioid overdose death rates, state unemployment measures, and Medicaid enrollment; state fixed effects Limitations: No indicator for other opioid relevant policies
Rees 2017	Naloxone access laws and Good Samaritan laws	1999-2014	Opioid-related, heroin-related, and non-heroin opioid related deaths in the United States per 100,000 population by year	Controlled pre-post	National Vital Statistics System	Adoption of naloxone access laws associated with a 0.043 reduction in all opioid-related mortality, a 0.045 reduction in non-heroin opioid-related mortality, and 0.006 increase in heroin related	Strength: State and year fixed effects, population, PDMP implemented, police officers per capita, medical marijuana legalization, beer tax,

						mortality (all values were not statistically significant) Adoption of naloxone access laws standing order provision associated with a 0.015 increase in all opioid-related mortality, a 0.015 reduction in non-heroin opioid-related mortality, and a 0.091 increase in heroin-related mortality (all values were not statistically significant). Removing criminal liability for naloxone possession associated with 0.134 decrease in all opioid-related deaths ($p < 0.01$), a 0.134 decrease in all non-heroin opioid-related mortality ($p < 0.05$), and a 0.169 decrease in heroin-related mortality (not statistically significant) Adoption of Good Samaritan laws was associated with a 0.101 reduction in all opioid-related mortality, 0.098 reduction in non-heroin opioid-related mortality, and a 0.070 increase in heroin-related mortality (all values were not statistically significant)	cigarette tax, and unemployment rate covariates
Xu 2018	Naloxone access laws: (1) standing order or third	2007-2016 - Symphony Health's PHAST	Annual number of retail naloxone prescriptions	Controlled pre-post	Symphony Health's PHAST Prescription	NAL with standing order or third party prescribing	Strengths: Controlled for patient MAT use, state and

	party provision, (2) standing order, (3) third party	Prescription Monthly database 2005-2015 – CDC Wonder	dispensed, opioid overdose deaths		Monthly database, CDC Wonder dataset	associated with an average increase of 78 prescriptions dispensed per state per quarter ($p < 0.001$) Standing orders associated with an average increase of 48 prescriptions dispensed per state per quarter ($p = 0.005$) Third party prescribing associated with an average increase of 72 prescriptions dispensed per state per quarter ($p < 0.001$)	year fixed effects Limitations: Increased Medicaid coverage of naloxone may confound finding
Multiple policies							
Al Achkar 2018	2013 opioid prescribing emergency rule	2011-2014	Total opioids dispensed in Indiana	Interrupted time series without comparison group	Indiana's Prescription Electronic Collection and Tracking Program (Indiana PDMP)	Emergency rule associated with an instantaneous decrease in daily MMEs per patient of opioids dispensed in both the recipient (-72.7, $p \leq 0.01$) and provider (-67.2, ≤ 0.01) fixed effects models. Emergency rules also associated with a trend decrease in daily MME per patient of opioids dispensed (-0.045, ≤ 0.01) in the recipient fixed effect model but not the provider fixed effect model Emergency rule associated with decrease in daily MEDs per patient dispensed for all opioids (-3.17, $p \leq 0.01$), hydrocodone (-3.68, $p \leq 0.01$), oxycodone (-2.03, p), methadone (-	Strengths: Patient and provider fixed effects

						6.19, p ≤ 0.01), and hydromorphone (-3.54, p ≤ 0.05). No statistically significant effect was noted for morphine, fentanyl, oxymorphone, and buprenorphine. The effect of the policy was greater for males (-3.68, p ≤ 0.01) than females (-2.80, p ≤ 0.01) and greater for 0-20 years (-27.26, p ≤ 0.01) than 20-40 years (-3.00, p ≤ 0.01), 40-60 years (-2.45, p ≤ 0.01), 60+ years (-2.04, p ≤ 0.01).	
Chang 2016	Florida PDMP and pain management clinic law implementation	2010-2012	57,031 prescribers who prescribed at least one opioid in Florida or Georgia in the 12-month pre-intervention period	Interrupted time series with comparison group	IMS 's LifeLink LRx claims	Florida's high-risk providers experienced large relative reductions in opioid patients (-539, 95% CI: -829, 243), opioid prescriptions as a percent of all prescriptions (-0.08, 95% CI: -0.20, -0.03), MME (−0.88 mg/month, 95% CI: −1.13, −0.62), and total opioid volume (−3.88 kg/month, 95% CI: −5.14, −2.62). Low-risk providers did not experience statistically significantly relative reductions in measures for opioid prescribing practices.	Strengths: Sensitivity analysis varying threshold of high-risk prescriber, interaction term for state and period, and interaction term for state and post-intervention Limitations: Dataset only contains retail prescription claims
Chang 2018	Florida PDMP and pain management clinic law implementation	2010-2012	2.76 million individuals who lived in Florida or Georgia, had at least 1 pharmacy claim	Interrupted time series with comparison group	QuintilesIMS LRx Lifelink Longitudinal prescription claims	Compared with Georgia, Florida high-risk patients experienced reductions in prescription opioid	Strengths: Model indicators for state, period (pre or post), month,

			each within the first and last 3 months of study period, and filled prescriptions from stress reporting data to QuintilesIMS within the first and last 3 months			utilization. Opioid shoppers (i.e. patients visiting >3 prescribers and >3 pharmacies to acquire opioids during any 90-day period) experienced a reduction in MME per transaction (-1.08 p < 0.01), total opioid volume (-0.55 p < 0.01), days supplied (-0.10, p not statistically significant), and opioid prescriptions (-0.19, p 0.01). Concomitant users (i.e. at least 30 days of concomitant opioids and benzodiazepines) experienced a reduction in MME (-1.07, p < 0.01), total opioid volume (-2.61, p < 0.01). Days supplied not significant. Chronic users (i.e. consuming more than 100 MMEs per day for more than 90 consecutive days) experienced a decline in MME (-1.20, p < 0.01) and total opioid volume (-4.58, p < 0.01), and opioid prescriptions (-0.71, p < 0.01). Days supply not statistically significant. Low-risk patients generally did not experience statistically significantly relative reductions	interaction term of state and month, interaction term for state and period indicator, and state and post-intervention month indicator Limitations: Dataset only contains retail prescription claims

						in opioid utilization.	
Delcher 2015	Florida PDMP: (1) binary indicator for PDMP implementation, (2) continuous query rate indicator	2003-2012	Florida state population	Interrupted time series with comparison group	Florida medical examiners commission	PDMP associated with a -24.8 death reduction in oxycodone caused mortality the month after implementation ($p = 0.008$). Every one PDMP query per health care provider associated with a decline in oxycodone-caused deaths by 0.229 persons per month ($p = 0.002$).	Strengths: Intervention dose evaluated through query rate, model incorporated effects of simultaneous Florida and national opioid related policies Limitations: Significant correlation between PDMP indicators and indicators for other opioid related policy
Dowell 2016	Opioid prescribing policies, pain clinic laws and mandated provider review of PDMP before prescribing opioids	2006-2013	38 states and DC	Controlled pre-post	IMS Health's National Prescription Audit; National Vital Statistics System Multiple Cause of Death mortality files	Combined policies (pain clinic law and PDMP mandatory access requirement) reduced prescribing rates by 80.1 ($p < 0.01$) MMEs prescribed per state residents per year and prescription opioid overdose deaths per 100,000 state residents by -1.198 ($p < 0.01$). Implementation of pain clinic laws alone did not significantly reduce opioid prescribing or prescription opioid overdose death rates. Neither the combined nor pain clinic laws were associated with a statistically significant reduction in heroin death rate.	Strengths: State and year fixed effects, intervention dose Limitations: IMS Health data does not capture direct opioid dispensing
Johnson 2014	2010-2012 Florida PDMP and pain management	2003-2012	Drug overdose death rates per 100,000 FL resident	Uncontrolled pre-post	Florida Department of Health	From 2010-2012, decrease in overdose death rates due to	Limitations: No covariates for other national opioid relevant

	clinic law implementation and other policy initiatives					oxycodone (-52.1%), methadone (-27.2%), and hydrocodone (-23.1%). All values are statistically significant at $p < 0.001$. From 2010-2012, increase in overdose deaths due to morphine (56.2%), hydromorphone (189.9%), and heroin (122.4%). All values are statistically significant at $p < 0.001$.	policies and prescriber or patient characteristics included in model
Kennedy-Hendricks 2016	2010-2012 Florida PDMP and pain management clinic law implementation and other policy initiatives	2003-2012	State monthly overdose death rate	Controlled pre-post	Florida Department of Health, North Carolina State Center for Health Statistics	Prescription opioid overdose mortality per 100,000 populations in Florida was -0.55 (95% CI: -0.79, -0.29) from March-October 2010, -1.79 (95% CI: -2.55, -0.93) from January-December 2011, and -3.02 (95% CI: -4.31, -1.57) from January-December 2012) lower than what would have been expected had the changes in mortality rate trends in Florida been the same as changes in trends in North Carolina. While both Florida and North Carolina experienced sharp increases in heroin overdose during the first half of 2011, Florida's increase in mortality rates from heroin from early 2011 to late 2012 was substantially less	Strengths: Model predictors include month, state, and a month-state interaction Limitations: Confounding associated with simultaneous implementation of other opioid relevant policies in Florida and North Carolina

						than North Carolina's.	
Rutkow 2015	2010-2012 Florida PDMP and pain management clinic law implementation and other policy initiatives	2010 -2012	Retail prescriptions dispensed in FL and Georgia	Interrupted time series with comparison	IMS Health LifeLink LRx (IMS Incorporated) data	Laws associated with 2.5 kg/month reduction in total opioid volume and a 0.45 mg/month decline in mean MME in Florida compared to Georgia. No effect on mean days' supply per transaction or total number of opioid prescriptions dispensed. Significant decreases in MME per transaction attributable to the laws were limited to those with the highest levels of opioid use at baseline. Strongest change in total opioid volume and mean MME per transaction were among providers with the highest baseline prescription volume.	Strengths: Sensitivity analyses varying policy window and open cohort Limitations: No indicators for prescriber or patient characteristics
Sun 2017	Washington mandated hospital best practices to reduce ED visits by Medicaid beneficiaries, including several practices targeting opioid misuse (e.g. implementation of opioid prescribing guidelines)	2011-2013	ED visits by Medicaid beneficiaries in Washington who were not dual eligible, under 15 years of age, and did not have a history of active cancer nor hospice or nursing home care in the prior year	Interrupted time series without comparison	Medicaid medical and pharmacy claims data	Mandates associated with a 1.5% reduction (95% CI: -2.8%, -0.2%) in opioid dispensed within 3 days of visits in the overall cohort. Mandates associated with a -4.7% reduction (95% CI: -7.2%, -2.3%) in opioid dispensed within 3 days of visit in the prior risk opioid use cohort. Mandates associated with a -3.6% reduction (95% CI: -5.6, -	Strengths: Covariates for demographics and physical and mental health conditions Limitations: Findings can not be attributed to particular mandate

						1.7%) in opioid dispensed within 3 days of visit in chronic opioid use cohort.	
Surratt 2014	2010-2012 Florida PDMP and pain management clinic law implementation and other policy initiatives	2009-2012	Florida agencies participating in the Drug Diversion program	Un-controlled pre-post	Researched Abuse Diversion and Addiction-Related Surveillance System	Significant declines in diversion rates were observed for oxycodone (-1.31, $p < 0.05$), methadone (-0.23, $p < 0.01$), morphine (-0.13, $p < 0.05$). No significant decline for fentanyl, hydrocodone, hydromorphone, buprenorphine.	Strengths: Geographic specific diversion rates Limitations: Reporting bias associated with non-representative sample

Appendix 3: Hierarchy of types of public health law research designs [a]

Experimental	**Randomized controlled trial**	**Experiments in which units are assigned exposure to a legal intervention or no exposure randomly.**
Quasi-experimental	Interrupted time series	Study observes outcomes at multiple time points pre- and post- a specific legal intervention. Stronger designs include a comparison group now exposed to the legal intervention.
	Regression discontinuity	Study evaluates an outcome for a population on either side of a pre-defined cutoff.
	Difference-in-difference (or) controlled pre-post	Study observes outcomes before and after a legal intervention compared to a group not exposed to the legal intervention.
Observational	Uncontrolled pre-post	Study observes outcomes before and after a legal intervention but without a comparison not exposed to the legal intervention. Stronger designs adjust for potential confounding.
	Uncontrolled post-only	Study observes outcomes after a legal intervention but without a comparison not exposed to the legal intervention. Stronger designs adjust for potential

		confounding.
	Cross-sectional design	Study measures outcome variable at one point in time after the intervention. Stronger designs adjust for potential confounding.

[a] This classification system intends to provide a simplified hierarchy of design types to assist policymakers in assessing public health law research. It is neither exhaustive of all study designs nor does it incorporate study quality variation within the same research design. For instance, it is possible that a well-designed and analyzed quasi-experimental or observational studies may be more appropriate for causal inference than a poorly conducted randomized controlled trial. For readers interested in limitations of specific studies, see Appendix 5.

Appendix 4: GRADE Summary of Findings[a,b]

Policy	Outcome	Number of studies by design		Quality of evidence	Notes
		Study design	Number		
Continuing medical education requirements	Prescribing/dispensing	Uncontrolled pre/post	1	Very low *due to limitations in study design*[c]	One evaluation Failure to adequately control confounding (e.g., no control group, minimal covariates)
Laws related to pain management clinics	Prescribing/dispensing	ITS without comparison	1	Very low *due to inconsistency in results*	While differences in direction, in and of themselves, do not constitute a criterion for inconsistency of results, the magnitude of effects vary across studies
		Controlled pre-post	3		
	Patient behavior	Controlled pre-post	1	Very low[c]	One evaluation
	Patient health	Controlled pre-post	2	Low	

Opioid prescribing guidelines	Prescribing/dispensing	ITS with comparison	1	Low	
		Uncontrolled pre-post	3		
	Patient health	Uncontrolled pre-post	1	Very low[c]	One evaluation
Anti-doctor shopping laws	Prescribing/dispensing	Controlled pre-post	2	Very low *due to limitations in study design*	Failure to adequately control confounding in one evaluation
	Patient behavior	Controlled pre-post	1	Very low[c]	One evaluation
	Patient health	Controlled pre-post	1	Very low[c]	One evaluation
Drug supply management policies	Prescribing/dispensing	Controlled pre-post	3	Moderate *due to magnitude and consistency of effect*	Consistency among rigorous evaluations in statistically significant decline in high-dose, increase in low-dose, and no change total opioids
		Uncontrolled pre-post	1		
	Patient behavior	Controlled pre-post	2	Very low[c]	One evaluation
	Patient health	Controlled pre-post	1	Very low *due to limitations in study design*	Failure to adequately control confounding in cross-sectional evaluation (e.g., no control group, minimal covariates), leaving one rigorous study
		Cross-sectional	1		

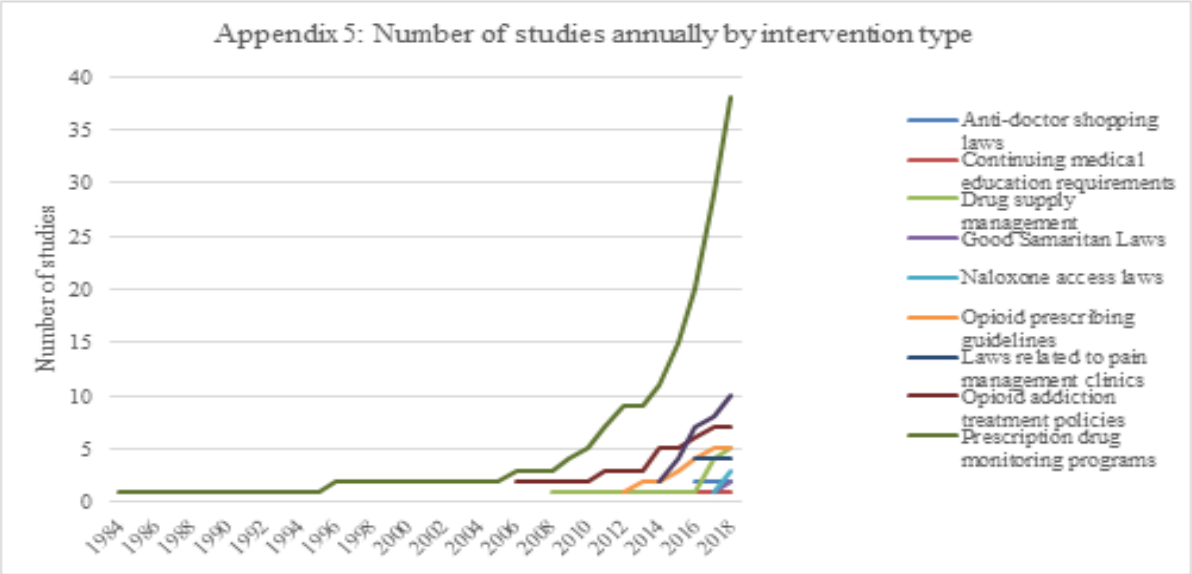
Prescription drug monitoring programs	Prescribing/dispensing	ITS with comparison	1	Low	
		Controlled pre-post	8		
		Uncontrolled pre-post	3		
		Cross-sectional	4		
	Patient behavior	Controlled pre-post	2	Very low *due to inconsistency in results*	Differences in outcomes measures changes policy effect within studies
	Patient health	ITS with comparison	2	Very low *due to inconsistency in results*	While differences in direction, in and of themselves, do not constitute a criterion for inconsistency of results, the magnitude of effects, as well as direction, vary greatly across studies
		ITS without comparison	1		
		Controlled pre-post	10		
Good Samaritan Laws	Patient health	Controlled pre-post	2	Low	
Policies affecting opioid addiction treatment	Patient health	ITS without comparison	1	Very low *due to inconsistency in results*	Significant differences in outcomes measures across studies
		Uncontrolled pre-post	2		
		Cross-sectional	4		
Naloxone access laws	Prescribing/dispensing	Controlled pre-post	2	Low	Some inconsistency in results remain due

					to outcome measurement, specifically third-party prescribing
	Patient health	Controlled pre-post	1	Very low[c]	One evaluation

[a] GRADE grades of evidence: high quality – further research is very unlikely to change our confidence in the estimate of effects; moderate quality – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality - further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality – we are very uncertain about the estimate.

[b] The GRADE approach automatically rates observational studies a low quality of evidence score. Since all of our included articles use an observational approach, compared to a randomized trial, all policy/outcome pairs are initially given a low quality of evidence score. Policy/outcome groups can be rated up or down. If the quality of evidence score is moved up or down from the law rating, we provide an explanation following the score.

[c] Policy/outcome pair with only one study. We acknowledge that the GRADE framework rates the quality of evidence for each outcome, not each study. Thus, the quality of evidence score for policy/outcome pairs with only one evaluation are inherently limited due to the sole evaluation. Consequently, we rated all policy/outcome pairs with one evaluation a very low GRADE quality of evidence score.



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