HEALTH TECHNOLOGY ASSESSMENT INFORMATION SERVICE™

SPECIAL REPORT

Measures and CDS for Safer Opioid Prescribing: A Literature Review

ECRI Institute

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Executive Summary

The U.S. opioid epidemic continues to pose significant challenges for patients, families, clinicians, and public health policy. Opioids are responsible for an estimated 315,000 deaths (from 1999 to 2016) and have caused 115 deaths per day.[1] In 2017, the U.S. Department of Health and Human Services declared the opioid epidemic a public health crisis.[2] The total economic burden of opioid abuse in the United States has been estimated to be $78.5 billion per year.[3]

Although providing care for chronic opioid users is important, equally vital are efforts to prevent so-called opioid-naïve patients (patients with no history of opioid use) from developing regular opioid use, misuse, or abuse. However, much remains unclear regarding what role clinician prescribing habits play and what duration or dose of opioids may safely be prescribed without promoting long-term use.[4,5]

In 2013, ECRI Institute convened the *Partnership for Health IT Patient Safety,* and its component, single-topic-focused workgroups followed. For this subject, the Electronic Health Record Association (EHRA): Measures and Clinical Decision Support (CDS) for Safer Opioid Prescribing workgroup included members from the Healthcare Information and Management Systems Society (HIMSS) EHRA and the *Partnership* team. The project was oriented towards exploring methods to enable a synergistic cycle of performance measurement and identifying electronic health record (EHR)/health information technology (IT)–enabled approaches to support healthcare organizations' ability to assess and measure opioid prescribing.

To inform workgroup efforts, a rapid literature review was performed to identify risk factors for development of persistent opioid use for opioid-naïve patients and determine the impact of measurement and registry-based interventions (e.g., benchmarking or prescription drug monitoring programs [PDMPs]). Specifically, we asked the following key questions:

1. What resources or tools exist for creating or improving CDS for appropriate opioid prescribing for both opioid-naïve and opioid-exposed patients?
2. What evidence exists that measuring particular variables (e.g., prescribing habits) improves appropriate opioid prescribing?
3. What risk factors are associated with progression to opioid abuse for opioid-naïve patients?

We searched the literature for studies published from January 2010 to June 2018 and identified 51 relevant studies.

For Key Question 1, only limited evidence (15 studies, all pre/post) evaluated the impact of resources or tools for CDS, as follows: changing EHR defaults (for pills dispensed, opioids prescribed, and alternatives to narcotics), alerts, new prescribing guidelines and electronic-tablet-based decision aids. Overall, existing evidence suggests these interventions can be effective for reducing inappropriate opioid prescribing, although for many studies, the benefit was modest. Future work should clarify which settings and parameters within which these interventions could be most effective without adversely affecting clinical workflow.

For Key Question 2, 16 articles described health IT–related measurement interventions: Two studies found that benchmarking prescription rates for emergency room (ER) physicians significantly reduced opioid prescription rates. In one study of eight ERs in the Ochsner clinic system, within one year of implementing this intervention, the number of sites prescribing at rates below the national benchmark increased from 25% to 100%. Future work is needed to determine whether these results are generalizable to other ERs or to other settings (e.g., ambulatory care).

Two systematic reviews and fourteen studies assessed the impact of PDMPs, which allow physicians to check whether patients have existing opioid prescriptions. Evidence was insufficient to determine whether PDMPs reduce fatal or nonfatal overdoses. However, evidence from three controlled studies suggests PDMPs are associated with reductions in opioid prescribing. In particular, a large controlled study including data from 24 states found that PDMP implementation was associated with a 33% reduction (from 5.5% to 3.7%) in prescription rates of schedule II opioids in the ambulatory setting.[6]

For Key Question 3, 20 studies assessed risk factors for development of long-term opioid use or abuse in opioid-naïve patients. A history of depression, alcohol or substance abuse, smoking, or pain disorder was associated with increased risk. Similarly, increased opioid use (e.g., filling a prescription, number of refills, and duration of regular use) was associated with progression to long-term use and abuse across all settings. Higher morphine milligram equivalents

(MMEs) per dose increased risk, except for in surgical patients, where higher initial doses did not increase risk. Very limited evidence (from a single study) found that initiating opioid use with tramadol or a long-acting opioid instead of nalbuphine or schedule III or schedule IV opioid therapy increased risks of long-term use.

Awareness of these risk factors could serve many purposes, including the following:

- Allowing providers to address modifiable risk factors to reduce risk in opioid-naïve patients
- Facilitating alerts to physicians if patients are at higher risk when an opioid prescription is being considered
- Allowing for targeted monitoring of higher-risk opioid-naïve patients receiving opioids

Early identification of at-risk patients could promote more efficient deployment of prevention resources and potentially reduce the risks of long-term use or abuse.

Overall, this report identified a small, substantive evidence base suggesting health IT interventions can be effective for reducing opioid prescribing. Although evidence suggests that several interventions, including PDMPs and benchmarking prescribing rates, are associated with reductions in opioid prescribing, it remains unclear to what extent those reductions translate into important clinical outcomes such as reductions in opioid misuse, abuse, or overdoses. Notably, in one study, simply receiving an opioid prescription itself was associated with increased risk of long term opioid use,[7] suggesting that reduced prescribing could, in fact, have an impact. Going forward, further development of health IT interventions to reduce opioid prescribing represents one important strategy for decreasing long-term opioid abuse in opioid-naïve patients.

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Background

The U.S. opioid epidemic continues to pose significant challenges for patients, families, clinicians, and public health policy. Opioids have caused an estimated 315,000 deaths (from 1999 to 2016) and are responsible for an estimated 115 deaths per day.[1] In 2017, the U.S. Department of Health and Human Services (HHS) declared the opioid epidemic a public health crisis.[2] The total economic burden of opioid abuse in the United States has been estimated to be about $78.5 billion per year.[3]

Many public health strategies have focused on improving access to treatment for chronic opioid users. However, equally vital are efforts to prevent so-called opioid-naïve patients (patients with no history of opioid use) from developing regular opioid use, misuse, or abuse. Although mitigating risks for opioid-naïve patients is important, much remains unclear regarding important facts, such as what role clinicians' prescribing habits play or the duration or dose of opioids that may be safely prescribed without promoting long-term use.[4,5] Health information technology (IT)–based tools, such as the electronic health record (EHR) and clinical decision support (CDS), offer the potential to monitor and measure opioid prescribing patterns, promote safer opioid prescribing, and avert opioid misuse.

In 2013, ECRI Institute convened the *Partnership for Health IT Patient Safety,* and its component, single-topic-focused workgroups followed. For this subject, the Electronic Health Record Association (EHRA) Workgroup: Measures and Clinical Decision Support (CDS) for Safer Opioid Prescribing included members from the Healthcare Information and Management Systems Society (HIMSS) EHRA, and the ECRI *Partnership* team. The focus of the project was to define a synergistic cycle of performance measurement and EHR-enabled safer opioid prescribing that emphasized EHR/health IT–enabled approaches for healthcare organizations to assess and measure opioid prescribing.

To inform workgroup efforts, we performed a rapid literature review to summarize evidence for CDS interventions to improve appropriate opiate prescribing. Also, we identified evidence about whether measuring particular clinical variables could promote appropriate prescribing. We further identified existing evidence regarding which risk factors are associated with progression to long-term use or abuse for opioid-naïve patients. Specifically, we asked the following key questions:

1. *What resources or tools exist for creating or improving CDS for appropriate opioid prescribing for both opioid-naïve and opioid-exposed patients?*
2. *What evidence exists that measuring particular variables (e.g., prescribing habits) improves appropriate opioid prescribing?*
3. *What risk factors are associated with progression to opioid abuse for opioid-naïve patients?*

Besides surveying the evidence for these questions, we also performed an environmental scan to identify publically available, existing CDS artifacts aimed at improving appropriate opioid prescribing for opioid-naïve patients.

Methods

We conducted a systematic literature search of PubMed, MEDLINE, EMBASE, CINAHL, and Scopus, using a search strategy developed by a medical librarian. The search strategy identified studies published from January 2010 through June 2018 and used a combination of medical subject headings and keywords. Broad concepts were initially addressed: opioids, CDS systems, prescriptions, dosing, risk management, and prescription drug monitoring programs (PDMPs). Follow-up searches were conducted to further investigate the opioid-naïve population. The search strategies are available in Appendix A.

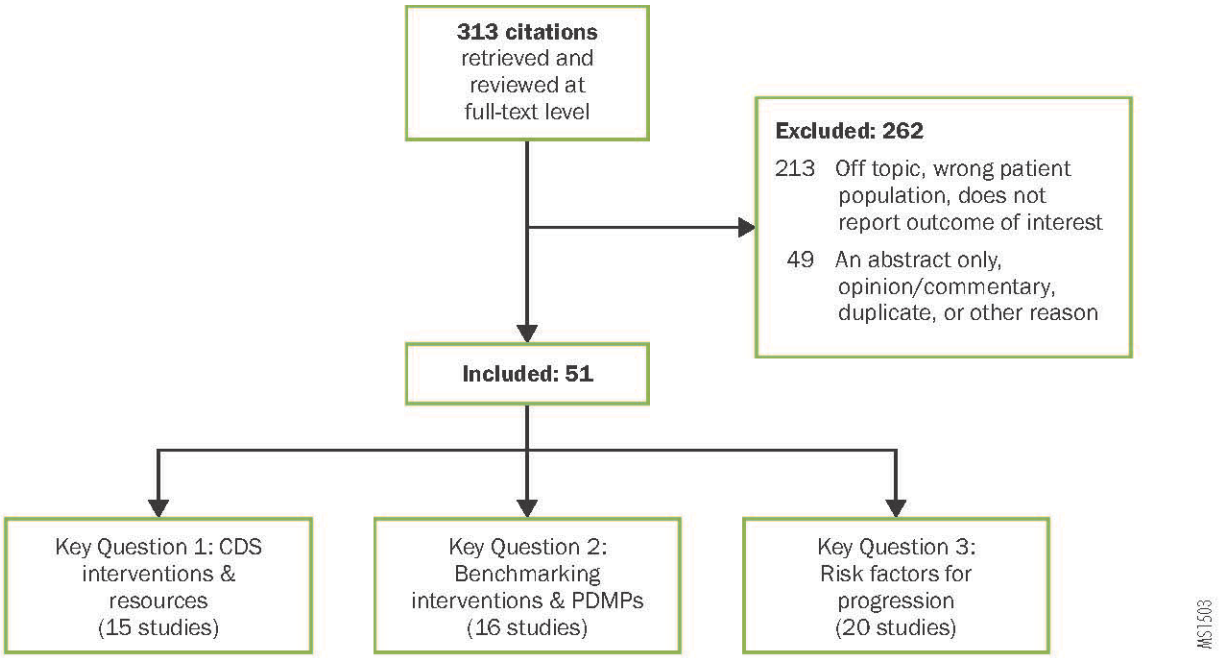
A physician analyst screened all studies using specified inclusion criteria. We excluded all studies performed in patients with long-term opioid abuse, opioid dependence, opioid misuse or abuse, cancer-related pain, or palliative care. We also excluded non-English language studies and studies performed outside the United States. Figure 1 shows the disposition of studies.

For Key Question 1, we included all studies assessing a CDS intervention to promote appropriate opioid prescribing. Specifically, studies must have reported change in prescribing rate or other clinical outcome (e.g. decreased opioid-

related adverse events). We also included studies assessing the impact of opioid prescribing guidelines if studies reported a change in opioid prescribing rates as an outcome. For Key Questions 1 and 2, we included all studies assessing an intervention of interest, even if the study did not specify an opioid-naïve patient population. However, for Key Question 3 (risk factors) we included only studies specifically addressing opioid-naïve patients and reporting outcomes of long-term opioid use, misuse, or abuse.

We had planned to assess all randomized controlled trials (RCTs), nonrandomized controlled trials, observational cohort studies, or case control studies using the U.S. Preventive Services Task Force (USPSTF) criteria for grading study quality.[8] However, aside from three studies (for Key Question 2), all included studies for Key Questions 1 and 2 used a pre/post study design. For pre/post or interrupted time series study designs, given the high risk of bias conferred by this study design, these studies were all considered low quality without further formal study quality assessment. Risk factor studies were assessed using the Newcastle-Ottawa scale.[9] All risk factor study quality assessments are available in Appendix C.

Figure 1. Flow Diagram of Studies for Key Questions



Results

Overall, we identified 51 studies for inclusion. Fifteen studies addressed Key Question 1 (resources for creating or improving CDS for appropriate opioid prescribing); 16 studies addressed Key Question 2 (measuring variables to improve opioid prescribing); and 20 studies addressed Key Question 3 (risk factors associated with progression to abuse).

Key Question 1: What resources or tools exist for creating or improving CDS for appropriate opioid prescribing for both opioid-naïve and opioid-exposed patients?

We identified 15 studies assessing resources, interventions, and tools for CDS to improve opioid prescribing. An overview of these interventions is provided in Table 1. The interventions consisted of altering EHR defaults (six studies), alerts and triggers (two studies), opioid prescribing guidelines (six studies), and an electronic-tablet-based tool for shared decision-making (one study). All studies used a pre/post study design (without a true control group). Below, we describe these interventions in further detail. Additional details are available in Appendix B. Also, we note that six studies[10-14] assessing

the impact of opioid guidelines on opioid prescribing rates were excluded because they did not describe implementation or dissemination using a health IT.

Table 1. Overview of tools for creating or improving CDS to promote appropriate opioid prescribing

Intervention Type	Intervention	Findings	Reference
Electronic health record (EHR) defaults (6 studies)	15-pill default (previously defaulted to 30 pills)	No change in 15-pill prescriptions or morphine milligram equivalents prescribed	Zivin et al. 2018[15]
	10-pill default (previously manually entered)	Increase in proportion of 10-tablet prescriptions; however, no change in mean number of oxy/APAP (oxycodone 5 mg/acetaminophen 325 mg) tablets prescribed per week, small reduction in median number of tablets prescribed	Delgado et al. 2018[16]
	No default (previously default of 20 tablets)	Median quantity of tablets decreased from 20 to 15 ($p < 0.001$)	Santistevan et al. 2018[17]
	Default starting doses of high-risk medications for geriatric patients	Increased use of default dose for opioids (29% to 35.2%), specifically fentanyl, morphine, and hydromorphone	Kim et al. 2017[18]
	Default to Tylenol and ibuprofen (instead of an order set containing narcotics)	Significant reduction in narcotic prescribing for tonsillectomy patients (82.2% to 15.4%, $p < 0.0001$) without increased use of emergency room (ER) services	Luk et al. 2016[19]
	Age-adjusted dosing and guided medication selection for elderly patients	Significantly higher acceptance of recommended actions for opiates with clinical decision support (CDS) tool active (36% vs. 26%, $p < 0.001$)	Griffey et al. 2012[20]
Alerts and triggers (2 studies)	Computerized physician order entry (CPOE) modified to organize opioids by route, efficacy; alerts firing to ask for explanation of higher-than-recommended dose; embedded links to dose calculator	Reduction in orders with potentially high doses of hydromorphone and morphine. Absolute decrease 3.6%, p value for trend <0.0001).	Lester et al. 2017[21]
	Pop-up alert with prescribing, reminding providers of opioid alternatives and risks	Significant reduction in patients discharged from emergency department (ED) with opioid discharge packs; decreased prescription of opioids to at-risk patients (21.8% to 13.9%)	Gugelmann et al. 2013[22]
Guidelines (6 studies)	New organizational guidelines for EDs deployed through multidisciplinary strategies	Absolute reduction of 3.6% for parenteral opioid use across 14 EDs; 1.5% decrease in oral opioids prescribed at discharge after 12 months	Ghobadi et al. 2018[23]
	Quality improvement project with education and guidelines for 4 urgent care clinics	Mean number of opioid prescriptions (per provider per week) declined (7.6 to 5.2 at 8 weeks, $p = 0.035$)	Young et al. 2018[14]
	New Ohio ER guidelines	Decrease in quantity of opioid prescriptions written by emergency room (ER) physicians	Weiner et al. 2017[11]
	Adoption of new guidelines	Significant reduction in opioids prescribed for patients with dental, back, neck, and chronic pain at 2 ERs (52.7% per-intervention to 33.8% at 12-18 months, $p < 0.001$)	Del Portal et al. 2015[12]

Intervention Type	Intervention	Findings	Reference
	Developed and implemented new guideline	Decreased opioid prescribed from 2 rural ERs (59% to 42%; absolute reduction of 17%)	Fox et al. 2013[13]
	Developed new guideline and implementation—included an online opioid dosing calculator to calculate totally daily morphine-equivalent dose from all opioid medications	35% decrease in proportion of patients receiving prescriptions for ≥120 mg/day	Franklin et al.(2012)[10]
Other decision aids (1 study)	Electronic-tablet-based tool for shared decision-making (for opioid prescriptions after cesarean delivery)	Significant reduction (50%) in number of pills prescribed compared to prior institutional benchmark	Prabhu et al. 2017[24]

Setting EHR Defaults

We included six studies that assessed using EHR defaults as a strategy to improve appropriate opioid prescribing. Five studies assessed the effect of changing the default number of pills dispensed or opiate dose. Evidence for the impact of these interventions was mixed. Delgado et al. (2018)[16] evaluated whether a new default setting of 10 opioid pills (previously, providers manually entered the number of pills) dispensed for emergency room (ER) patients would improve opioid prescribing at two urban emergency rooms (ERs). The study found a small reduction in median number of tablets prescribed, but no change in the mean number of Percocet tablets prescribed ($p = 0.42$)

Another study (Zivin et al., 2018)[15] also assessed changing the default number of pills dispensed, in this case from 30 pills to 15. However, this was not associated with significant change in number of prescriptions dispensing 15 pills or MMEs prescribed.

A third study (Santistevan et al., 2018)[17] found that removing a default altogether (previously, the system default was 20 pills) was associated with a significant decrease in median number of pills dispensed (decrease from 20 to 15, $p < 0.001$).

The remaining three studies focused on particular patient populations. Two studies, Kim et al. (2017)[18] and Griffey et al. (2012),[20] assessed creating electronic medical record (EMR) defaults to reflect appropriate choice and dose of opioids for older adults receiving prescriptions in the ER. Both studies found statistically significant improvements in the proportion of patients treated with the recommended dose. However, the magnitude of improvement was relatively small for both studies (29% to 35.2%[18] and 23% to 31%[20] of orders, respectively).

However, the third of these studies (Luk et al., 2016)[19] evaluated the impact of a new order set for pediatric patients undergoing tonsillectomy at Kaiser Permanente ($n = 437$ patients). The previous order set offered narcotic options along with other analgesics. Study authors described a new order set that defaulted to Tylenol and ibuprofen instead. This intervention was associated with a dramatic reduction in narcotic prescribing (82% to 15%, $p < 0.0001$). Furthermore, this reduction in narcotics prescribed was not associated with an increase in visits to the ER (e.g., for inadequate pain control).

Alerts and Triggers

Two studies described multidisciplinary interventions that included pop-up alerts. A 2017 study by Lester et al.[21] evaluated the impact of a multifaceted intervention that included educational components (updating pocket cards for pain management and required educational modules for hospital staff) along with reorganizing computerized provider order entry (CPOE) screen for opioids. Opioids were organized by route, efficacy, and onset, with appropriate dose options. Orders for higher-than-recommended dosing would trigger an alert asking for an explanation. The module also included an embedded link to a dose conversion calculator. Over the four-year study periods there was a small, but significant

reduction in proportion of orders for high initial opioid doses for hydromorphone and morphine (absolute decrease 3.6%, p <0.0001).

Another study, by Gugelmann et al. (2013),[22] evaluated a similar intervention consisting of educational activities along with a pop-up CPOE alert at time of prescribing, reminding providers of opioid alternatives and risks. This intervention was associated with a reduction in overall number of opioid discharge packs prescribed: specifically, the percentage of discharged patients receiving an opioid discharge pack decreased from 21.8% to 13.9% for patients with risk factors for opioid dependence (psychiatric history, chronic pain, history of abuse, and age of more than 65 years).

Guidelines

Six studies assessed the impact of opioid prescribing guidelines. Guidelines varied from state to local institutional guidelines. All studies reported reductions in opioid prescribing after guideline introduction. For instance, a 2018 study by Ghobadi et al.[23] examined provider ordering patterns before and after the implementation of opioid treatment guidelines deployed through multidisciplinary strategies across 14 community emergency departments (EDs) at Kaiser Permanente. Each ED disseminated the guideline using different educational strategies. This intervention was associated with a modest, significant reduction in parenteral opioid use across all sites (3.6% percentage-point reduction [from 22.0% to 18.4%]) and a 1.5% percentage-point decrease in oral opioids prescribed at discharge after 12 months. Reductions were primarily seen in chronic opioid patients; there was no change for patients with acute fracture.

Another study (Weiner et al., 2017)[11] evaluated the impact of Ohio's new ED guidelines (released in 2012) by measuring the number of opioid prescriptions dispensed using the Ohio PDMP. Taking into account pre-intervention trends in prescribing, the study found the intervention was associated with an additional reduction of 11.2% (95% confidence interval [CI], -18.8% to -3.6%) in total monthly opioid prescriptions for more than three days.

Decision Aids

One small study (Prabhu et al., 2017)[24] assessed an electronic-tablet-based decision aid for providers and patients—to determine the quantity of opioids prescribed after cesarean delivery—in 50 patients. Compared with the prior institutional benchmark rate, the intervention was associated with a significant reduction (50%) in the number of opioid pills prescribed.

Key Question 2. What evidence exists that measuring particular variables (e.g., prescribing habits) improves appropriate opioid prescribing?

We identified two types of measurement-related interventions assessed in the literature: benchmarking interventions (two studies) and studies assessing the impact of PDMPs (two systematic reviews and six studies). Tables 2 and 3 summarize findings from these studies, and below we offer a brief narrative description. Further details are available in Appendix B, Tables B-4 and B-5.

Benchmarking

Two studies assessed benchmarking interventions. One study by Guarisco et al. (2018)[25] described the impact of benchmarking opioid prescription rates in eight EDs affiliated with the Ochsner clinic system. Initially, the intervention was piloted in a single ED, but it was subsequently deployed to additional EDs, given positive results. Opioid prescription rates were measured and benchmarked from the EHR (along with pill counts, and morphine milligram equivalents (MMEs) per prescription). Compared with two months pre-intervention, opioid prescription rates declined from 22% to 14% over the one-year post-intervention period, with some physicians reducing prescriptions rates by up to 70%. Although initially only 25% of sites had prescription rates below the national average, by the close of the study, 100% of sites were below the national average.

A second study (Burton et al., 2016)[26] assessed the impact of benchmarking in seven EDs staffed by the same practice. Initially, providers received "blinded" benchmarking reports for three months, after which benchmarking rate reports were unblinded and shared with colleagues (three months). Compared with results from nine months prior to the intervention, the mean quantity of pills prescribed significantly decreased from 16 pills to 13 pills (p <0.01). Similarly, the mean prescribing rate decreased from 20% to only 8% of visits, p <0.01.

Table 2. Studies assessing benchmarking interventions

Intervention	Findings	Reference
Measured and benchmarked opioid prescription rates from electronic health record (also pill counts, morphine milligram equivalents per prescription) at 8 emergency departments	At 1 year, opioid prescription rates decreased from 22% to 14% Initially, only 25% of sites had prescription rates below national benchmark; by study end, 100% were below national average	Guarisco et al. 2018[25]
Benchmarked opioid prescribing rates	Significant reduction in mean prescribing rate from 20% of visits to 8% (60% reduction, p <0.01)	Burton et al. 2016[26]

Prescription Drug Monitoring Program (PDMP) Databases

We identified fourteen studies (two systematic reviews and twelve studies) that evaluated the impact of PDMPs on opioid prescribing. Table 3 provides a summary of included studies.

Table 3. Systematic reviews and other studies assessing effect of prescription drug monitoring programs (PDMPs)

Type of Evidence	Purpose/Setting	Findings	Reference
Systematic reviews (2 studies)	Assessed effect of prescription drug monitoring program (PDMP) on fatal or nonfatal overdoses	Included 17 studies (3 nonfatal overdoses, 14 fatal overdoses) Insufficient evidence	Fink et al. 2018[27]
	Assessed efficacy of PDMPs	Mixed evidence	Finley et al. 2017[28]
Effect of PDMPs on overall prescription rates (9 studies)	Washington State	Analyzed Medicaid claims from 2013 to 2015 before and after automation of PDMP reports; no change in opioid prescribing	Sun et al. 2018[29]
	Pennsylvania	Analyzed data from 15 emergency departments (EDs; University of Pittsburgh health system) from July 2015 to March 2017; reduction in opioids prescribed	Suffoletto et al. 2018[30]
	Ohio	Analyzed dispensed medications from 2007 through 2017; there was a reduction in opioids dispensed	Winstanley et al. 2018[31]
	Iowa	Analyzed administrative claims data from 2004 to 2014 from large private health insurer: the PDMP was associated with 28% reduction on opioid prescription rates with large decline in morphine milligram equivalents per prescription	Ranapurwala et al. 2018[32]

	New York	Analyzed data from U.S. Drug Enforcement Agency's (DEA) Automated Reports and Consolidated Orders System (ARCOS), the New York State Department of Health Bureau of Narcotics Enforcement (BNE), and the Statewide Planning and Research Cooperative System (SPARCS). After implementation of Internet System for Tracking Over-Prescribing (I-STOP) there was a possible downward trend in prescribing (only 2 data points post-intervention)	Brown et al. 2017[33]
	Data from 24 states	Analyzed 2001 to 2010 data from National Ambulatory Medical Care Survey (NAMCS) on ambulatory care visits for pain. PDMPs were associated with 5.5% to 3.7% reduction (33%) in prescription rate of schedule II opioids	Bao et al. 2016[6]
	North Carolina	Analyzed data from 2009 to 2011. There was no association between mean days PDMP accessed by provider and prescription of schedule II opioids	Ringwalt et al. 2015[34]
	Florida	Analyzed 2010 to 2012 data from IMS Health LifeLink LRx to assess impact of Florida PDMP and pill-mill law, using Georgia patients as control At 12 months, compared with predicted prescribing rate, there was a modest 1.4% decline in opioid prescriptions	Rutkow et al. 2015[35] Note: this study examined the combined effect of PDMP and new legislation
	Multiple	Analyzed 2007 administrative claims data for Medicare patients; recipients living in states with an electronic or paper PDMP had higher odds of receiving an opioid analgesic prescription, but were less likely to receive a schedule II narcotic prescription (compared with states without a PDMP): adjusted odds ratio (AOR) 0.54 (95% confidence interval [CI] 0.53, 0.55) for electronic plus paper PDMP versus no PDMP	Simoni-Wastila et al. 2012[36]
Effect of PDMPs on individual provider decision-making for opioid prescribing (3 studies)	Single emergency department (ED; University of Pittsburgh)	23 providers were surveyed in 103 patient encounters. Querying PDMP had no impact on provider plans for opioid prescribing in 92 of 103 encounters.	Landau et al. 2018[37]
	Single ED (University of Toledo)	18 providers were surveyed around care for 179 patients with nonacute pain. After review of PDMP data, providers changed management plans in 41% (n = 74) of cases	Baehren et al. 2010[38]

	Two EDs (Massachusetts)	38 providers were surveyed in 544 patient encounters for back or dental pain or headache After review of PDMP data, providers changed management plans in 9.5% of cases (95% CI, 7.3% to 12.2%). • 3.0% (n = 16) no longer received a prescription • 6.5% (n = 35) received a prescription that was not previously planned	Weiner et al. 2013[39]

Impact on Prescribing Rates

Two systematic reviews assessed effects of PDMPs. Fink et al. (2018)[27] examined whether PDMP implementation was associated with changes in nonfatal and fatal overdoses, identified program features, and investigated the potential unintended consequences. Based on 17 studies (3 studies reporting nonfatal overdoses, 14 reporting on fatal overdoses), the authors concluded there was insufficient evidence to reach a conclusion regarding the effect of PDMP implementation on nonfatal or fatal overdoses. Similarly, there was insufficient evidence to reach conclusions regarding positive associations between specific administrative features and successful programs.

A second systematic review, by Finley et al. (2017),[28] assessed the impact of state-level policy and implementation characteristics and found mixed evidence. Features of PDMPs varied considerably across the United States, both with regard to legislated components and to strategies for implementation (e.g., use by providers prior to writing an opioid prescription may be mandatory or optional; the frequency with which data are reported to the program by participating pharmacies varies; ease of access, timeliness and accuracy of information, and the types of providers permitted to register are inconsistent).

We identified nine additional studies assessing PDMPs and reporting impact on opioid prescription rates or opioids dispensed. Overall, several studies found PDMPs significantly reduced opioid prescribing, with reductions reported in Florida, Iowa, Ohio, and Pennsylvania. However, one study of Medicaid patients in Washington State found an automated PDMP query intervention was not associated with any reduction in prescriptions or MMEs prescribed.[29]

Three studies[6,35,36] used a controlled study design, although notably for one study (Rutkow et al.),[35]) the Florida PDMP was implemented nearly simultaneously along with a pill-mill law, making it impossible to distinguish the impact of one without the other. All three studies reported PDMPs (or PDMPs plus pill-mill legislation[35]) were associated with a reduction in opioid prescriptions or opioid dispensed. In one of these studies, Bao et al. (2016)[6] assessed the impact of PDMP introduction in 24 states from 2001 to 2010, using data from the National Ambulatory Medical Care Survey (NAMCS). The study found that PDMPs were associated with a decrease from 5.5% to 3.7% (33% reduction) in prescription rates of schedule II opioids in the ambulatory care setting.

Provider Decision-Making

Three small studies assessed the impact of PDMPs on provider decision-making, with mixed results. Landau et al. (2018)[37] assessed ED providers' perception of possible abuse and intent to prescribe before and after querying the PDMP at the University of Pittsburgh. Reviewing information from the PDMP was associated with changes in a provider's plan to prescribe in only 11 of 103 encounters. In contrast, a 2010 study by Baehren et al.[38] found that after reviewing information from Ohio's PDMP, ED providers at the University of Toledo changed their plan for clinical management in 41% (74 of 179 cases). A third study, Weiner et al. (2013),[39] surveyed 38 providers in 544 patient encounters across 2 EDs. After querying the PDMP, providers changed their prescribing plan in 9.5% of cases. Notably, all studies included only low numbers of providers (range 18 to 38), likely limiting the generalizability of these findings.

Key Question 3: What risk factors are associated with progression to abuse for opioid-naïve patients?

Twenty studies described risk factors for progression of opioid-naïve patients to long-term/recurrent opioid use, opioid misuse, or opioid abuse. These studies were performed in a variety of clinical settings and are summarized in Table 4.

Half (ten studies) addressed surgery, with the remainder focused on hospital discharges (two studies), emergency room (one study), low back pain (one study) or patients from all settings (six studies). All studies were retrospective cohort studies using administrative claims data. In addition to assessing demographic variables, studies frequently assessed risk factors such as mental health comorbidities (depression, anxiety), history of smoking or other drug abuse, and characteristics of opioid prescribing or use (e.g., duration, number of refills, MMEs).

Table 4. Overview of studies assessing risk factors

Clinical Setting	Number of studies	Adult or Pediatric	Reference
Surgery (5 studies assessed a specific procedure type: spine surgery[40], hysterectomy[41], mastectomy[42], hand surgery[43], caesarean delivery[44])	10	Adult and pediatric[4] Adult[40,42-47] Pediatric[48]	Brat et al. 2018[4] Schoenfeld et al. 2017[40] Marcusa et al. 2017[42] Johnson et al. 2016[43] Bateman et al. 2016[44] Brummett et al. 2017[45] Swenson et al. 2017[41] Sekhri et al. 2018[46] Sun et al. 2016[47] Harbaugh et al. 2018[48]
Low back pain	1	Adult	Fritz et al. 2018[49]
Emergency room	1	Adult	Hoppe et al. 2015[50]
Hospital discharges	2	Adult	Calcaterra et al. 2016[51] Calcaterra et al. 2018[7]
All settings	6	Adult [52-54] Adult and pediatric[5,55,56]	Nelson et al. 2018[54] Halbert et al. 2016[52] Shah et al. 2017[53] Deyo et al. 2016[5] Jeffery et al. 2018[55] Hooten et al. 2015[56]

Surgery

Ten studies assessed risk factors in patients undergoing surgery (see Table 5 below). Of these, eight studies included only adults, one study included adults and children[4], and one study included only children.[48] Five studies identified patients with any type or multiple surgical procedures; the remaining five included patients undergoing spine surgery, hysterectomy, mastectomy with immediate reconstruction, hand surgery, or caesarean delivery. Further details regarding these studies can be found in Appendix B, Table B-7.

Patient characteristics

Most studies found a significant increased risk for patients with a history of depression[4,40,41,43-47], alcohol or substance abuse,[4,44-48] smoking,[4,43-46] or pain disorder.[4,44-46,48] However, one study in mastectomy patients (Marcusa et al., 2017)[42] found no association between depression or substance abuse and prolonged opioid use. Similarly, another study, in hand surgery patients (Johnson et al., 2016),[43] found that drug dependence, alcohol use, and history of pain were not associated with prolonged opioid use (prescription filled at 90 to 180 days after surgery).[43] In a third study, of multiple surgery types (Sekhri et al., 2018),[46] having back or neck pain did not increase risk of patients refilling a prescription within 30 days of surgery.

This suggests that while such patient factors are typically associated with increased risk, in particular patient subsets, risks may differ. These findings also indicate that progression of opioid use is not merely a function of the surgical procedure, but also a function of potentially treatable preexisting patient conditions.

Generally, patients with more comorbidities were also at higher risk for prolonged use or abuse.

Prescription characteristics

Interestingly, three studies (Brat et al., 2018[4], Sekhri et al.,[46] and Bateman et al., 2016[44]) found that the number of MMEs prescribed was not associated with progression to persistent use or abuse. Brat et al. included more than 1 million opioid-naïve patients (defined as seven or fewer days of opioid use in 60 days prior to surgery). Although 56% of patients filled opioid prescription postoperatively, only 0.2% of patients were diagnosed with misuse or abuse within 1 year. The MMEs of dose prescribed was statistically associated with this progression, but the effect was minimal (hazard ratio [HR], 1.008). Similarly, Sekhri et al. found that initial dose was not associated with increased probability of a single postoperative refill (within 30 days of surgery). The probability of refilling within 30 days remained 9.03% for patients receiving from 30 or fewer to 240 oral MMEs. This probability increased to only 10.08% for prescriptions with more than 300 oral MMEs (more than 60 pills).

Brat et al. found that the duration of opioid use and number of refills were strongly associated with increased risk for dependence, abuse, or overdose. After adjusting for covariates, each additional refill increased the hazard of misuse by 44% (95% confidence interval [CI], 40.8% to 47.2%, p <0.001). Similarly, each additional week of use was associated with 19.9% increase in hazard (95% CI, 18.5% to 21.4%, p <0.001). These increased risks tapered off after 11 weeks.

Procedure characteristics

Not surprisingly, risks of long-term use or abuse were higher for particular procedures (e.g., colectomy)[46,48] and more intense procedures.[40,41] For instance, Swenson et al. (2017)[41] found that women undergoing abdominal hysterectomy (compared to less invasive vaginal hysterectomy) were significantly more likely to develop chronic opioid use: adjusted odds ratio (AOR), 3.6 (95% confidence interval [CI], 2.0 to 6.4). The study included a small number of women with gynecologic malignancy (163 of 24,331 study subjects) who likely required an abdominal approach. However, only 1.4% (90 of 6,637) of abdominal hysterectomies were performed for gynecologic cancer, suggesting that many patients could benefit from greater use of minimally invasive hysterectomy. However, in contrast, Brummett et al. (2017)[45] found that having major (versus minor) surgery was not associated with increased risk.

Table 5: Risk factors for progression to long term or recurrent use, misuse, or abuse for patients undergoing surgery

Clinical setting	Outcome	Study patients	Risk factors		Reference
			Increased	Decreased or no effect	
All surgical procedures	International Classification of Diseases, ninth edition (ICD-9) code for opioid dependence, abuse, or overdose (prescription opioids only) over at least 1 year	1,015,115 patients (all ages)	• Duration of use • Number of refills • Regimen initiated with hydromorphone or oxycodone • Benzodiazepine • Presurgical diagnosis of bariatric surgery, tobacco, chronic pain, or depression	• Geography • Morphine milligram equivalents (MMEs)	Brat et al. 2018[4]
Minor and major surgery	Persistent opioid use (prescription filled 90 to 180 days after surgery)	36,177 patients (age 18 to 64) filling a perioperative opioid script	• Smoking, alcohol or substance abuse • Mood disorders, anxiety • Pain disorders (back or neck pain, arthritis) • Opioid prescription in 30 days prior to procedure • Higher opioid dose during surgical window • Younger age • More comorbidities	Major vs. minor surgery	Brummett et al. 2017[45]

Clinical setting	Outcome	Study patients	Risk factors		Reference
			Increased	Decreased or no effect	
Minor and major surgery	Refill of opioid prescription within 30 days of surgery	26,250 patients (age 18 to 64)	• Particular surgeries (colectomy, incisional hernia repair, reflux surgery, hysterectomy, hemorrhoidectomy, carpal tunnel repair) • Smoking history • Anxiety • Mood disorders • Adjustment disorder • Alcohol or substance abuse disorders • Arthritis or other pain conditions	• Number of comorbidities • Back, neck pain • Initial MME dose prescribed	Sekhri et al. 2018[46]
11 surgical procedures	Chronic opioid use (filling ≥10 prescriptions or ≥120 days' supply for postoperative days 91 to 365)	641,941 patients (age 18 to 64)	• Male, older age • Preoperative drug use (benzodiazepines, antidepressants) • Depression • Alcohol abuse • Drug abuse	• Antipsychotic use • Psychosis	Sun et al. 2016[47]
Spine surgery	Time to discontinuation of opioid use	9,991 TRICARE patients (age 18 to 64)	• Depression • Senior or junior enlisted (compared with officer) • Higher intensity procedures (lumbar interbody arthrodesis)	• Anxiety • Sex • Marital status	Schoenfeld et al. 2017[40]
Hysterectomy	Persistent opioid use: ≥2 opioid fills within 6 months of hysterectomy with ≥1 fill every 3 months and either total oral morphine equivalent ≥1,150 or days supplied ≥39	24,331 women (age 18 to 63)	• Depression/anxiety • Abdominal hysterectomy (compared with vaginal approach) • Gynecologic malignancy indication for surgery		Swenson et al. 2017[41]
Mastectomy with immediate breast reconstruction	Prolonged fills: filled opioid peri-operatively and refilled at 90 to 120 days postoperatively	4,113 patients filling a perioperative opioid prescription	• Younger age • Anxiety • More comorbidities • Complications during follow-up period (120 days)	• Depression • Substance abuse	Marcusa et al. 2017[42]
Hand surgery	Prolonged opioid use: Patients filled ≥1 opioid prescription peri-operatively (and ≥1 opioid prescriptions between 90 and 180 days after surgery.	77,573 adult patients	• Elective surgery (vs. trauma related) • More comorbidities • Mental health disorders • Smoking • Lower income • Younger age	• Drug dependence • Alcohol dependence • History of pain	Johnson et al. 2016[43]
Caesarean delivery	Persistent opioid use, defined as group of patients with highest probability of filling over time	80,127 women (age 12 to 55)	• Substance abuse • Smoking • Back pain • Migraines • Antidepressant use • Benzodiazepine use	• Type of opioid initially dispensed • Days' supply • Daily dose in MMEs	Bateman et al. 2016[44]

Clinical setting	Outcome	Study patients	Risk factors		Reference
			Increased	Decreased or no effect	
13 surgical procedures	Persistent opioid use (≥1 additional opioid prescriptions filled between 90 to 180 days after procedure)	88,637 opioid-naïve patients (age 13 to 21) filling perioperative opioid prescription	• Undergoing particular procedures (cholecystectomy, colectomy) • Female • Older age • Substance use disorder (in prior year) • Chronic pain diagnosis • Opioid prescription filled within 30 days before surgery		Harbaugh et al. 2018[48]

Other Clinical Settings

Ten studies addressed risk factors for prolonged opioid use or abuse in general clinical settings (i.e., no specific setting specified), patients discharged from the hospital (including surgical patients),[7,51] the emergency room versus non-ER,[55] and patients with low back pain.[49] Table 6 summarizes these studies. Additional details are provided in Appendix B, Table B-7.

Prescription factors

In contrast to studies focused on surgery (which found no increased risk with higher MMEs prescribed), three studies found that long-term opioid use or abuse was associated with higher MME prescriptions as well as number of refills and days' supply. Deyo et al. (2016) identified 536,767 opioid-naïve patients through the Oregon PDMP filling an opioid prescription.[5] The risk of long-term opioid use (six or more fills during one year of study) was significantly associated with higher MMEs dispensed: adjusted odds ratios (AORs), 1.99 to 5.21 for 800 to 3,999 MMEs (compared with 1 to 799 MMEs) for long-term opioids. This study also found increased risks for patients filling more prescriptions. Compared with patients filling a single prescription, those filling two prescriptions had an AOR of 2.25 (95% CI, 2.17 to 2.33) of long-term use.

Shah et al. (2017)[53] included more than 1.3 million cancer-free patients without a substance abuse diagnosis in the prior six months. Patients receiving a higher daily dose were significantly less likely to discontinue opioid use (defined as 180 continuous days or more without opioids after the end of their last prescription), Finally, Calcaterra et al. (2018)[7] found that higher MMEs per hospital day was associated with increased risk of progression to chronic opioid therapy for patients discharged from Denver Health Medical Center.

Shah et al. also found that compared with patients receiving nalbuphine or a schedule III or schedule IV opioid as their first opioid, those receiving tramadol or a long-acting opioid were less likely to discontinue use (tramadol HR, 0.89; 95% CI, 0.89 to 0.90; long-acting opioids HR, 0.79; 95% CI, 0.77 to 0.82).

Because EDs may commonly be considered contexts where patients are at high risk for receiving opioid prescriptions, Jeffery et al. (2018)[57] assessed whether opioid-naïve patients receiving an opioid prescription from the ER were more likely to progress to long-term opioid use than patients receiving a prescription in other clinical settings. Patients receiving the prescription from the ER were significantly less likely to develop long-term opioid use. For instance, patients with commercial insurance (and receiving the prescription from the ER) were 46% less likely to progress to long-term opioid use (adjusted risk ratio [ARR], 0.54; 95% CI, 0.53 to 0.56) than those receiving prescriptions outside of the ER. This finding was consistent across different dosages prescribed, as well.

Filling a prescription on discharge from either the ER (Hoppe et al., 2015)[50] or after hospital admission (Calcaterra et al., 2016)[51] was also associated with increased risk of long-term opioid use (AOR, 1.8; 95% CI, 1.3 to 2.3 and AOR, 4.9; 95% CI, 3.2 to 7.5, respectively). Further, Calcaterra et al. (2018)[7] found that simply receiving a prescription for opioids at discharge was associated with increased risk for progression to chronic opioid therapy: AOR, 2.33 (95% CI, 1.78 to 3.04).

Patient characteristics

We identified studies reporting increased risks for patients with a history of mental health problems (mood disorders,[52] anxiety[49]), prescription for psychotropic medications,[54] chronic pain,[7] smoking,[49,54] substance[56] or benzodiazepine abuse,[49] and Medicaid insurance.[7,49]

Nelson et al. (2018)[54] retrospectively analyzed outpatient data from 552,193 active duty Army soldiers with no opioid prescriptions for 6 months. Only 2.5% of these patients developed chronic opioid use; male gender, tobacco use and being prescribed psychotropic medications were all associated with increased risk of chronic opioid use. However, the strongest predictor of chronic opioid use was total number of prior opioid prescriptions received.

Fritz et al. (2018)[49] followed 707 opioid-naïve patients prescribed and filling an opioid prescription within 14 days of a new consultation for low back pain at the University of Utah. Nearly one-quarter (24.3%) of patients progressed to long-term use at one year. Factors associated with increased risk included a history of smoking (AOR, 1.50; 95% CI, 1.0 to 2.3) or benzodiazepine use (AOR, 1.87; 95% CI, 1.0 to 3.5), anxiety (AOR, 1.69), older age (AOR, 1.03), and Medicaid insurance (AOR, 2.84), which is a proxy for lower socioeconomic status.

Another study, of more than 27,000 patients hospitalized at the Denver Health Medical Center over six years (Calcaterra et al., 2018),[7] also found that Medicaid patients were at higher risk of receiving chronic opioid therapy than were patients with commercial insurance at one year. In addition, a history of chronic pain diagnosis in the prior three years increased risks as well: AOR, 1.79 (95% CI, 1.41 to 2.26).

A fourth study, by Halbert et al. (2016),[52] used survey data from the Medical Expenditure Panel Survey (MEPS) from 2005 to 2011 to evaluate the impact of mood disorders on risks of long-term opioid use in more than 33,000 opioid-naïve patients with pain (not related to cancer). Compared with patients who did not have a mood disorder, patients with a mood disorder were more likely to start opioids. Patients with mood disorders were also more likely to transition to long-term opioid therapy; this was true for these patients with either acute or chronic pain (AOR, 2.4; 95% CI, 1.6 to 3.4, and AOR, 2.7; 95% CI, 2.0 to 3.6, respectively).

Another small study, Hooten et al. (2015),[56] included 293 randomly selected opioid-naïve patients from Olmsted County, Minnesota, who had received (and filled) a new opioid prescription. Of the 6% who progressed to long-term use at one year (more than 90 days prescribing and 120 or more total days' supply or 10 or more prescriptions), patients with a history of substance abuse (including alcohol and benzodiazepine abuse) were at significantly higher risk of progression: AOR, 8.72 (95% CI, 2.76 to 27.55).

Table 6. Risk Factors for Progression from Opioid-Naïve to Long-Term Opioid Use, Misuse, or Abuse

Setting	Risk factors studied		Study details (N)	Reference
	Increased risk	Decreased risk or no effect		
Low back pain				
Low back pain	Older age Medicaid recipient Anxiety Smoking Primary care visit Benzodiazepine prescription	*Decreased risk*: Physical therapy visit	707 patients receiving new consultation for low back pain and receiving opioid prescription within 14 days of visit Data source: University of Utah Health Plans administrative claims data (from Jan 1, 2012, to Jun 30, 2015)	Fritz et al. 2018[49]

Setting	Risk factors studied		Study details (N)	Reference
Emergency room				
Acute mild-moderate painful condition and treated in emergency room (dental/tooth pain, back pain, neck pain, knee pain, headache, fracture or sprain)	Filling opioid prescription after discharge from emergency room (ER)		2,499 patients treated from Sep 1, 2011, to Feb 1, 2012 Data source: Hospital emergency department (ED) and Colorado prescription drug monitoring program (PDMP)	Hoppe et al. 2015[50]
Hospital discharges				
All surgical and medical discharges from hospital	Opioid receipt within 72 hours of discharge		6,689 patients discharged from hospital in 2011 Data source: Denver Health data	Calcaterra et al. 2015[51]
All hospital discharges	Older age Higher milligrams of morphine per hospital day Higher number of opioid prescriptions filled in prior year Receiving nonopioid analgesics in prior year 3 year history of chronic pain diagnosis ≥1 hospitalization within 12 months of discharge No healthcare encounters in prior year Medicaid insurance		276,705 hospitalized patients (not receiving chronic opioid therapy or opioid agonist therapy in 1 year prior to index discharge), 2008 to 2014 Chronic opioid therapy defined as ≥90-day supply of oral opioid (with less than 30-day gap in supply) within a 180-day period or receipt of ≥10 opioid prescription over 1 year after index discharge Data source: Denver Health data warehouse	Calcaterra et al. 2018[7]
All settings				
General (outpatient)	Psychotropic medications prescribed Tobacco use Higher number of total opioid prescriptions	Female Non-white race	552,193 active duty Army soldiers (with no opioid prescription in 6 months prior to outpatient visit), Jan 2011 to Sep 2014 Chronic opioid therapy defined as 3 consecutive months with opioid prescriptions Data source: Defense Manpower Data Center (DMDC); Military Health System Data Repository (MDR); MDR Pharmacy Detail Transaction Service	Nelson et al. 2018[54]
General	Mood disorders (increased new opioid use and transition to long-term opioid use)		33,450 adults with noncancer pain Data source: Medical Expenditure Panel Survey household component (MEPS-HC) from 2005 to 2011	Halbert et al. 2016[52]

Setting	Risk factors studied		Study details (N)	Reference
General	Higher number of refills Cumulative dose during initial month		536,767 opioid-naïve patients filling an opioid prescription. Data source: Oregon PDMP (Oct 1, 2012, to Sept 10, 2013	Deyo et al. 2016[5]
General	Opioid prescriptions from non-ED settings increase risk for prolonged use (across multiple dosages)		3,656,781 opioid fills (for patients with no opioid fills in prior 6 months) Data source: OptumLabs Data Warehouse, 2009 to 2015	Jeffery et al. 2018[55]
General	Higher days' supply (initial prescription) Higher average daily dose Initiating treatment with long-acting opioids or tramadol (compared with schedule III or IV opioids, or nalbuphine)		1,353,902 cancer-free patients (no substance abuse diagnosis for 6 months prior to prescription) with at least 1 opioid prescription Data source: Intercontinental Marketing Services Lifelink plus nationally representative health insurance claims database of commercially insured patients including inpatient, outpatient, and pharmacy claims) from Jun 2006 to Dec 2014	Shah et al. 2017[53]
General	Substance abuse		Random sample of 293 patients from Olmsted County, Minnesota (Jan 1 to Dec 31, 2009) Data source: Rochester Epidemiology Project (REP) and Mayo Clinic and Olmsted Medical Center records Opioid-naïve (no prescription for 6 months) with new opioid prescription	Hooten et al. 2015[56]

Strengths and Limitations of the Evidence Base

Randomized controlled trials (RCTs) represent the highest quality study design for assessing efficacy of interventions. However, nearly all studies addressing Key Questions 1 and 2 were retrospective pre/post studies. Pre/post study designs are problematic for inferring efficacy because they lack a parallel control group and are, therefore, unable to account for secular trends. Also, pre/post studies are susceptible to the Hawthorne effect, in which behavior changes when people know they are being observed. Nevertheless, for pragmatic reasons, this study design is often used to assess the effect of quality improvement efforts.

Assessing efficacy of large-scale public health interventions such as PDMPs with an RCT trial design presents many challenges and may simply be unfeasible. However, taken altogether, the quality of studies assessing PDMPs was moderate. Although several studies of PDMPs used a pre/post comparison (and thus are susceptible to the problems described above) many were also large, population-based studies performed using administrative claims data. Three PDMP studies used a controlled trial design.

For instance, Bao et al.,[6] used a pre/post comparison but also used states that had not yet implemented PDMPs as control groups. Another study, by Simoni-Wastila et al.,[36] compared opioid prescribing in states with PDMPs to states without. Many studies found that PDMPs had a favorable effect. However, one study that specifically assessed efficacy in a higher risk Medicaid population (Sun et al.)[29] found no benefit. This suggests that benefits may have limited generalizability for particular populations.

Overall, most studies assessing risk factors (Key Question 3) were high-quality, retrospective, observational cohort studies using administrative data from local institutions or large national administrative databases. Using such large validated datasets has characteristic strengths—namely, the ability to capture a large population of interest, often across a large geographic area. Administrative datasets rely on accuracy of diagnosis codes (e.g., for depression, smoking, or other clinical diagnoses) because verifying their accuracy through chart review is not feasible. In fact, aside from the small study by Hooten et al. (2015),[56] these studies did not include verification of diagnosis coded through the claims data. Nevertheless, all included studies offered clearly defined criteria for opiate-naïve populations and outcome measures, and most included large populations. Thus, overall, the overall quality of studies assessing risk factors among opioid-naïve patients was high.

Discussion/Conclusion

Overall, low quality evidence suggests a variety of CDS interventions could be helpful for decreasing opioid prescriptions, and moderate quality evidence suggests that PDMP and benchmarking appear to be effective, at least in particular settings. CDS interventions assessed included changing EHR defaults (for pills dispensed, opioids prescribed, and alternatives to narcotics), alerts, new prescribing guidelines, and electronic-tablet-based decision aids.

Evidence for changing defaults for pills dispensed was mixed; limited available evidence suggests that altering default dosing and opioid choices to reflect appropriate dosing for older adults can have a significant, but small effect on opioid prescribing. Notably, these studies were predominantly performed in the ED context (four of six). In the single study that assessed defaults to nonnarcotic alternatives in the postoperative setting, authors reported a dramatic reduction in narcotic prescriptions (82% to 15%) without increased use of emergency services for pain.[19]

More work is needed to clarify how factors such as baseline performance (e.g., opioid prescribing rates) and particular clinical context (e.g., surgery versus ED) should impact CDS design. Interventions such as alerts or triggers inherently disrupt workflow, and deploying these without careful consideration of benefits versus harms could cause increased frustration for clinical staff without significantly improving clinical care. Future work should clarify which settings and parameters within these interventions could be most effective without adversely affecting clinical workflow.

Two studies found that benchmarking prescription rates for ER physicians had a significant impact on opioid prescription rates. In fact, in one study of eight ERs in the Ochsner clinic system, within one year of implementing this intervention, the number of sites prescribing at rates below the national benchmark increased from 25% to 100%. Future work is needed to determine whether these results are generalizable to other ERs or other settings (e.g., ambulatory care).

With regard to PDMPs, evidence was insufficient to determine whether PDMPs reduce fatal or nonfatal overdoses. However, evidence from a handful of large studies suggests PDMPs are associated with reductions in opioid prescribing. In particular, a large controlled study including data from 24 states found that PDMP implementation was associated with a 33% reduction (from 5.5% to 3.7%) in prescription rates of schedule II opioids in the ambulatory setting.[6] Similarly, another large controlled study found that Medicare patients were less likely to be prescribed a schedule II narcotic in states with a PDMP. However, the negative results from Sun et al.[29] suggest these results may not be generalizable to Medicaid patients.

With regard to risk factors for progression to chronic opioid use, misuse or abuse, a history of depression, alcohol or substance abuse, smoking, or pain disorder was associated with increased risk. Similarly, increased opioid use (e.g., filling a prescription, number of refills, and duration of regular use) was associated with progression to long-term use and abuse across all settings. Higher MMEs per dose increased risk, except for surgical patients, where higher initial doses did not increase risk. Very limited evidence (from a single study) found that initiating opioid use with tramadol or a long-acting opioid instead of nalbuphine or schedule III or schedule IV opioid therapy increased risks of long-term use.

Awareness of these risk factors could serve many purposes, including the following:

- Allowing providers to address modifiable risk factors to reduce risk in opioid-naïve patients
- Facilitating alerts to physicians if patients are at higher risk when an opioid prescription is being considered
- Allowing for targeted monitoring of higher-risk opioid-naïve patients receiving opioids

Early identification of at-risk patients could promote more efficient deployment of prevention resources and potentially reduce the risks of long-term use or abuse.

Overall, this report identified a small, substantive evidence base suggesting health IT interventions can be effective for reducing opioid prescribing. Although evidence suggests that several interventions—including monitoring prescriptions with PDMPs and benchmarking provider opioid prescribing rates—are associated with reductions in opioid prescribing, it remains unclear to what extent those reductions translate into important clinical outcomes such as reductions in opioid misuse, abuse, or overdoses. Notably, in one study, receiving an opioid prescription itself was associated with increased risk of long-term opioid use,[7] suggesting that reduced prescribing can, in fact, affect clinical outcomes.

At a minimum, providing fewer opioid prescriptions is likely to reduce opioids available for diversion. Going forward, further development of health IT interventions to reduce opioid prescribing represents one important strategy for decreasing long-term opioid abuse in opioid-naïve patients.

Appendix A. Search strategies

We conducted a systematic literature search of PubMed, MEDLINE, EMBASE, CINAHL, and Scopus, using a search strategy developed by a medical librarian. The search strategy identified studies published from January 2010 to June 2018 and used a combination of medical subject headings and keywords. Broad concepts were initially addressed: opioids, clinical decision support systems, prescriptions, dosing, risk management, and prescription drug monitoring programs. Follow-up searches were conducted to further investigate the opioid-naïve population. Specific search strategies available upon request.

Sources searched: Databases (5), PubMed; EMBASE; MEDLINE; CINAHL, Scopus

1. Ovid Medline Strategy

Set #	Concept	Search Statement
1	Opioids	exp Analgesics, Opioid/ or exp Narcotics/ or (opiate$ or opioid$ or acetyldihydrocodeine or alfentanil or allylprodine or alphamethylfentanyl or alphaprodine or benzylmorphine or betaprodine or bezitriamide or buprenorphine or butorphanol or bremazocine or carfentan$ or codeine or contin or dextromoramide or dextropropoxyphene or dezocine or diacetylmorphine or diamorphine or dihydrocodeine or dihydromorphine or dihydromorphinone or dihydromorphone or dimorphone or diphenoxylate or dipipanone or enadoline or ethylketazocine or ethylmorphine or etonitazene or etorphine or fentanil$ or fentanyl or heroin$ or hydrocodon$ or hydromorphin$ or hydromorphon$ or ketazocine or ketobemidone or lefetamine or levomethadon or levomethadyl or levomethorphan$ or levorphanol or loperamide or meperidine or meptazinol or methadone or methadyl or methylmorphine or morphin$ or nalbuphine or narcotic$ or nicocodeine or nicomorphine or normorphine or noscapin$ or ohmefentanyl or opium or oripavine or oxycodone or oxycontin or oxymorphone or papaveretum or papaverin or pentazocine or percocet or peronine or pethidine or phenazocine or phencyclidine or pholcodine or piritramid$ or prodine or promedol or propoxyphene or remifentanil or sufentanil or tapentadol or thebaine or tilidine or tramadol).tw.
2	Clinical Decision Support	"Medical Informatics"/ or "Medical Informatics Applications"/ or exp "Decision Making, Computer-Assisted"/ or exp "Decision Support Techniques"/ or exp "Management Information Systems"/ or "Decision Support Systems, Clinical"/ or "Health Information Systems"/ or "Integrated Advanced Information Management Systems"/ or exp "Medical Records Systems, Computerized"/ or "Reminder Systems"/ or "User-Computer Interface"/ or "Software"/ or (CDS or CDSS or "decision support" or "decision making" or decision aid$ or CPOE or (order adj2 (entry or set$)) or "computer-assisted" or informatic$ or "natural language" or NLP or "app" or "apps").tw. or ((computerized or computer or electronic$ or personal or digital or online or on-line) adj3 (record? or chart$ or order? or note? or system? or alert$ or prompt$ or reminder? or intervention? or suggestion? or templat$ or guideline? or audit? or measure? or decision?) or EHR? or EMR? or EPHR? or PHR?).tw. or ((electronic adj2 (prescrib$ or prescript$ or pharmacopoeia or medication$)) or "e-prescribing" or "e-prescription" or "e- prescriptions" or ePMR?).tw.
3	Prescribing guidance	(((over or guideline$) adj2 prescrib$) or ((refill$ or provider$ or prescrib$ or chart$) adj3 (rate? or data or histor$ or review$ or algorithm$)) or registry or registries).tw.
4	Dashboard and trigger tools	(dashboard$ or nudge$ or (trigger$ adj3 (tool$ or record? or chart$ or order? or note? or system? or alert$ or prompt$ or reminder? or intervention? or suggestion? or templat$ or guideline? or audit? or measure? or decision?))).tw.
5	Risk Management	"Risk Assessment"/ or "Risk Factors"/ or ((risk adj3 (index or mitigat$ or model? or categor$)) or RIOSORD or VHA-RIOSORD or PainCAS or eCQM).tw.

6	PDMP	(Prescription Drug Monitoring Program$ or PDMP$ or prescription monitoring program$ or "PMP InterConnect" or "PMP Gateway" or "Automated Rx Reporting System" or OARRS or NarxCare or NarxCheck or Appriss or "I-STOP").tw.
7	Patient-Provider Contracts	(pain or opioid$ or controlled substance or "patient–provider") adj4 (contract? or agreement?).tw.
8	Dose	("aggregate dose" or (dose or morphine or opioid$) adj2 (convert$ or conversion or chart$ or equianalges$ or equivalen$ or guide or guidance)).ti,ab.
9	Combine sets	#1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8)
10	Apply limits	#9 with Filters: Publication date from 2010/01/01; English

2. Ovid Medline Strategy

Set #	Concept	Search statement
1	Opioids	exp Analgesics, Opioid/ or exp Narcotics/ or (opiate$ or opioid$ or acetyldihydrocodeine or alfentanil or allylprodine or alphamethylfentanyl or alphaprodine or benzylmorphine or betaprodine or bezitriamide or buprenorphine or butorphanol or bremazocine or carfentan$ or codeine or contin or dextromoramide or dextropropoxyphene or dezocine or diacetylmorphine or diamorphine or dihydrocodeine or dihydromorphine or dihydromorphinone or dihydromorphone or dimorphone or diphenoxylate or dipipanone or enadoline or ethylketazocine or ethylmorphine or etonitazene or etorphine or fentanil$ or fentanyl or heroin$ or hydrocodon$ or hydromorphin$ or hydromorphon$ or ketazocine or ketobemidone or lefetamine or levomethadon or levomethadyl or levomethorphan$ or levorphanol or loperamide or meperidine or meptazinol or methadone or methadyl or methylmorphine or morphin$ or nalbuphine or narcotic$ or nicocodeine or nicomorphine or normorphine or noscapin$ or ohmefentanyl or opium or oripavine or oxycodone or oxycontin or oxymorphone or papaveretum or papaverin or pentazocine or percocet or peronine or pethidine or phenazocine or phencyclidine or pholcodine or piritramid$ or prodine or promedol or propoxyphene or remifentanil or sufentanil or tapentadol or thebaine or tilidine or tramadol).tw.
2	Opioid Naive	("opioid naive" or "opioid free" or new opioid recipient$ or new opioid use$ or new opiate recipient$ or new opiate use$ or "not previously received" or naivety).tw.
3	Prescribing	Risk Assessment/ or Risk Factors/ or exp Prescriptions/ or Inappropriate Prescribing/ or Prescription Drug Overuse/ or "Practice Patterns Physicians"/ or (prescrib$ or prescript$ or overprescrib$ or refill$ or misuse$ or risk factor$ or risk assessment$).tw.
4	Combine sets	#1 and #2 and #3
5	Apply limits	#4 with Filters: Publication date from 2010/01/01; English

Appendix B: Evidence Tables

Table B-1. Clinical Decision Support Interventions

Study Characteristics	Intervention	Clinical Setting, Methods	Study Findings
Electronic health record (EHR) defaults			
Zivin et al. 2018[15] Study design: Pre/Post	15-pill default for new schedule II opioid prescriptions in EHR at 2 health systems (previously defaulted to 30-day supply)	**Setting**: 2 health systems (West Virginia and Connecticut) **Methods**: Compared prescription data from Feb to April 2016 (pre) vs. May to July 2016 (post) for adults with no prior opioid script in 90 days	Analyzed prescription data from 448 prescribers, totaling 6,390 prescriptions • The intervention was associated with an overall non-statistically significant increase in 15 pill prescriptions • No change in morphine milligram equivalents (MMEs) prescribed before or after
Delgado et al. 2018[16] Study Design: Pre/Post	Default supply quantity (10 pills) for opioids prescribed at discharge (previously, providers would manually enter the quantity)	**Setting**: Emergency departments (EDs) for 2 urban EDs (Presbyterian Medical Center, Hospital of the University of Pennsylvania) **Methods**: Pre/post study comparing prescription data before and after introduction of EPIC (EHR system)	After the default implementation, no change in the mean number of oxycodone/acetaminophen (Percocet) tablets prescribed per week across the 2 EDs (p = 0.42), but the median number decreased by a small amount, from 11.3 to 10 (p = 0.004) in the HUP ED and 12.6 to 10.9 (p <0.001) in the PMC ED Small decrease in number of prescriptions written for <10 tablets • Implementation of a default of 10 tablets versus no default was associated with a strong increase in the proportion of prescriptions written for 10 tablets • Deploying defaults that included lower than baseline default opioid quantities for acute pain was potentially a widely scalable approach for changing prescribing behavior while still preserving clinician autonomy
Santistevan et al. 2018[17] Study Design: Pre/Post (retrospective)	Removal of default supply quantity: (previously default of 20 tablets)	**Setting**: Single academic ED (University of Wisconsin) **Methods**: Compared before and after default setting introduced (1/2013 to 11/3/2014, with intervention introduced 1/17/2014) Patients: All adults discharged home (from ED) with prescriptions for tablet forms of hydrocodone and oxycodone and their	4,104 patients received discharge prescriptions for opioids in the 54 weeks pre-intervention, and 2,464 in the 43 weeks post-intervention • Median quantity of opioid tablets prescribed decreased from 20 to 15 (P <0.0001) after removal of the default quantity • Proportion of patients who received prescriptions on discharge that contained 20 tablets decreased from 0.5 to 0.23 (95% confidence interval [CI], 0.21 to 0.14; P <0.001) after default quantity removed • Default value of 20 tablets for opioid prescriptions may be an example of the electronic medical record's (EMR) ability to reduce

		acetaminophen-containing combination formulations	practice variability in medication orders actually counteracting optimal patient care
Kim et al. 2017[18] Study Design: Pre/Post	Default starting doses of high risk medications on computerized provider order entry (CPOE) templates for older adults	**Setting**: 2 academic EDs in Seattle, Washington **Methods**: Compared before and after defaults implemented in Sep 2015 (analyzed 4 month comparable periods in 2015 and 2016). Primary outcome measure was the difference in the frequency of the recommended starting dose (risk difference) before and after the CPOE template modification for opioids, benzodiazepines, and nonsteroidal anti-inflammatory drugs (NSAIDs). Patients' age: ≥65	• 1,002 patients treated pre-intervention, 944 treated post-intervention • Adjusting the default starting doses of high-risk medications for older adults significantly increased the frequency of administration of the recommended doses • Greatest increase was observed for opioids (29% to 35.2%); significant changes for fentanyl, morphine, and hydromorphone; no changes for oxycodone, benzodiazepines, or NSAIDs
Luk et al. 2016[19] Study Design: Pre/Post	Order set defaulted to Tylenol and ibuprofen Prior order set offered options of weight-based narcotic prescriptions for acetaminophen with codeine and acetaminophen with hydrocodone; new order set defaulted to weight-based Tylenol and ibuprofen	**Setting**: Pediatric Surgery Group Practice at Kaiser Permanente **Methods**: Retrospectively compared opioid orders before and after introduction of new order set Pre-intervention (Jun 2011 to Nov 2012) vs. Post-intervention (Jan 2013 to June 2014) Patients: Tonsillectomy patients age <7	• 437 cases overall (197 pre-intervention, 240 post-intervention) • Age-based narcotic protocol significantly decreased physician narcotic prescribing from 82.2% to 15.4% (P < .0001) without increased use of emergency department services
Griffey et al. 2012[20] Study Design: Pre/Post (Retrospective)	Age-adjusted dosing and guided medication selection (of 72 medications, including opioids) when prescribing potentially inappropriate medications for the elderly	**Setting**: Emergency Department (single, large urban ED); this support tool was already active for inpatient orders **Methods**: Compared opiate prescriptions across 4 sequential periods of computerized decision support (CDS) being ON or OFF (6 or 7 week blocks) Patients: Adults age ≥ 65	2,398 Orders (1407 patients) • Acceptance of recommended actions for opiates was higher with tool ON compared to off (36% vs. 26% or orders, p <0.001). • Although overall acceptance rates were higher with tool on (compared to off) 31% vs. 23%, the use of recommendations was low • Fewer adverse drug events were observed when CDS was active

Alerts and triggers			
Lester et al. 2017[21] Study design: Pre/post	Multidisciplinary intervention: • CPOE: Organized opioids by route, efficacy, onset, and appropriate dose options; alerts reminding intravenous (IV) to oral conversation and asking for explanation for higher-than-recommended dosing; embedded links to dose conversion calculator • Updated pocket cards (pain management) • Education: Modules required for house staff	**Setting**: Acute care hospital **Methods**: Compared before and after the intervention from 2011 to 2015	• Significant reduction in the percentage of orders of potentially high initial doses of opioids of hydromorphone and morphine after implementing an electronic alert (absolute decrease 3.6%, p<0.001) • From 2011 to 2015, there was an absolute decrease of 3.6% in intramuscular (IM) orders of opioids (P value for trend <.0001)
Gugelmann et al. 2013[22] Study Design: Pre/Post (Prospective)	Multiple interdisciplinary educational modalities: • Lectures, journal clubs, case discussions • Pop-up CPOE alert at time of prescribing, reminding prescribers of opioid alternatives and risks	**Setting**: 2 large urban EDs in the same health system **Methods**: Compared before and after multidisciplinary intervention including pop-up CPOE alert Specifically, 6 to 9 months pre-intervention vs. 8 to 11 months (due to staggered start dates) post-intervention by using each institution's individual controlled substance pharmacy inventory. This data was cross referenced with order entry from the EMR Primary outcome: Monthly rate of clinician orders for an opioid "discharge pack" (4 tablets of oxycodone 5 mg–acetaminophen 325 mg) for discharged patients; secondary outcome, decreased prescribing to patients with risk factors for opioid abuse	• Orders for opioid discharge packs decreased from 13.9% to 8.4% and 4.7% to 1.9% at the primary and affiliate hospitals, respectively (P <.0001) • Dispensing among individuals at risk for opioid dependence at the primary ED decreased from 21.8% to 13.9% Opioid discharge pack orders decreased: • From 19.3% to 12.2% in individuals <65 years • From 19.4% to 12.2% in individuals with a history of a psychiatric disorder or psychotropic medication use • From 23.7% to 15.1% among patients with a chronic pain condition; and from 21.8% to 13.9% among individuals with any of the 4 risk factors analyzed (i.e., psychiatric history, chronic pain, history of abuse, age >65)

Table B2. Impact of Opioid Guidelines

Study Characteristics	Intervention	Clinical Setting, Methods	Study Findings
Ghobadi et al., 2018[23] Study Design: Retrospective Pre/Post	New organizational guidelines for opioid use adopted by 14 emergency departments (EDs). Each ED disseminated guidelines through different educational strategies (lectures, fliers, etc.)	**Setting**: 14 integrated EDs (Kaiser Permanente) **Methods**: Compared before and after introduction of new organizational guidelines. Jan 1, 2013, to Dec 31, 2014 Primary outcome: Proportion of adult ED encounters with parenteral opioids ordered	• 1,039,957 encounters (508,337 pre- and 531,620 post-intervention) • Modest reduction in parenteral opioid use in the ED (22% to 18.4%, for absolute reduction 3.6%; p, NR.) • Reduction in parenteral opioid use in chronic pain patients: (odds ratio [OR] = 0.81, 95% confidence interval [CI] = 0.72–0.91). • No reduction in parenteral opioid use for patients acute fractures Slight reduction in proportion of patients prescribed oral opioids at discharge: OR = 0.98, 95% CI = 0.98–0.99; At 12 months, 16.5% → 15% (absolute decrease 1.5%).
Young et al. 2018[14] Study Design: Retrospective pre/post	Evidence-based quality improvement project in 4 urgent care clinics (provider education, guidelines for opioid prescribing, and monitoring of prescribing behavior)	**Setting:** 4 privately owned urgent care centers (pediatric and adult) **Methods**: Guidelines consisted of need to query Rhode Island PDMP, assess for other prescriptions that could cause adverse reactions (such as benzodiazepines), and limit all prescribing to 7 days' supply; compared 8 weeks prior to guidelines to 5 to 8 weeks post-adoption	• These clinics were staffed by 14 providers • The mean number of opioid prescriptions written per provider per week declined from 7.6 (8 weeks prior) to 5.8 (at 4 weeks) and 5.2 (at 8 weeks), p = 0.035
Weiner et al., 2017[11] Study Design: Pre/Post (retrospective)	State emergency room (ER) guidelines (Apr 2012) influence on inappropriate opioid prescribing and the number and type of opioid prescriptions dispensed	**Setting**: ED **Methods**: Compared opioid prescriptions from Ohio prescription drug monitoring program (PDMP) written by ED physicians from Jan 1, 2010, to Dec 31, 2014. Specifically, the 5 most commonly prescribed opioids (hydrocodone, oxycodone, tramadol, codeine, and hydromorphone). Primary outcome: Monthly statewide prescription total of opioids written by emergency physicians in Ohio Patients: All patients age 5 to 99.	• During the 60-month study period, there were 2,798,918 prescriptions for the 5 most commonly prescribed opioids, written by 1,855 emergency physicians in Ohio. • Prescribing guidelines were associated with a decrease in the quantity of opioid prescriptions written by emergency physicians • Taking into account pre-guideline trend, authors estimated an additional decline of 0.89% (95% CI, −1.1% to −0.70%) for prescriptions and 0.90% for morphine milligram equivalents per month (95% CI, −1.25% to −0.56%) relative to what would be expected according to the pre-guideline rate of change. • For prescriptions greater than 3 days' duration, the adjusted model estimated a level decline of 11.2% (95% CI, −18.8% to -3.6%) for total monthly prescriptions • Guidelines occurred in parallel with other opioid-related interventions; findings suggested an additional effect of the guidelines on prescribing behavior

Del Portal et al. 2015[12] Study Design: Pre/Post (Retrospective)	Adoption by university of opioid prescribing guideline based on Oregon College of Emergency Physician guideline	**Setting:** 2 ERs (Philadelphia); one tertiary care academic medical center and an affiliated community hospital ER **Methods:** Compared opioid prescription rates before and after adoption of opioid prescribing guideline (based on Oregon College of Emergency Physicians guideline); compared 6-12 months before guideline to 6 months immediately after guideline adopted and 12-18 months after adoption of the guideline **Primary Outcome**: Proportion of patients seen for dental, neck/back, or chronic pain who were prescribed an opioid upon discharge from the ED	• 13,187 patients include (age >18 and discharged from ED during study periods with a variety of discharge diagnoses related to dental pain, neck or back pain, or chronic pain. • There was a significant reduction in proportion of patients prescribed opioids after introduction of the guideline: o 52.7% (pre-intervention) to 29.8% (0-6 months post) and 33.8% (12-18 months post), p <0.001 for both time points o There were significant reductions for each type of pain: dental (63.3%, decreased to 38.1% and 45.7%; p <0.001); back/neck pain, 49.1%, decreased to 27.1% and 29%)
Fox et al. 2013[13] Study Design: Pre/Post (Retrospective)	Developed and implemented a local opioid prescribing guideline as part of quality improvement project	**Setting:** 2 rural community ERs **Methods:** Compared opioid prescribing rates for all patients ≥16 with dental pain 12 months before and after guideline. Patients were excluded if they were admitted, transferred, underwent oral incision/drainage or received intravenous antibiotics.	• 668 patients included (mean age 34, range 16 to 87) • The rate of opioids prescribed fell from 59% to 42% for an absolute reduction of 17% (95% CI, 7% to 25%)
Franklin et al.(2012)[10] Study Design: Pre/Post (Retrospective)	The Agency Medical Director's Group (AMDG), representing all Washington State public payers, developed an Interagency Guideline on Opioid Dosing which was implemented as an online educational pilot in April 2007. Guideline included a web-based opioid dosing calculator physicians could use to calculate totally daily morphine-equivalent dose from all opioid medications.	**Setting:** Washington State workers compensation **Methods:** Using data from the Washington State Department of Labor & Industries and the Medical Information Payment System (MIPS), compared the total number of prescriptions for all opioids annually from 2003 to 2010 and combined with prior study data to assess trends from 1996 to 2010.	• The number of paid prescriptions for schedule II opioids for all claimants in the WA workers compensation increased from 1996 (22,867) to 2006 (66,544) and then plateaued from 2006 to 2008 and declined in 2009 (63,808) and 2010 (52,499). • Compared with the 2 quarters immediately prior to release of guideline (2006 quarter 4 and 2007 Quarter 1), the last 2 quarters of 2010 showed a 35% decrease in proportion of patients receiving prescriptions for ≥120 mg/day

Table B3. Other Decision Aids (outside of EHR)

Study Characteristics	Intervention	Clinical Setting, Methods	Study Findings
Prabhu et al. 2017[24] Study Design: Observational	Electronic-tablet-based tool for shared decision-making for opioid prescribing after cesarean delivery	**Setting**: Obstetric Surgery **Methods**: Compared median usage in these population to institutional standard (40 tablets)	• 50 patients were included • Prescribing intervention was associated with about a 50% decrease in the number of pills prescribed postoperatively compared with the standard prescription of the institution Median (interquartile range) number of 5-mg oxycodone tablets selected was 20.0 (15.0–25.0),lower than the 40 tablets usually prescribed (P<0.001, Wilcoxon test)

Table B-4. Benchmarking Interventions

Study Characteristics	Intervention	Clinical Setting, Methods	Study Findings
Guarisco et al. 2018[25] Study Design: Pre/Post	Measured and benchmarked provider opioid prescription rates from electronic health record (EHR): opioid-classified prescription count pill counts, and morphine milligram equivalents (MMEs) per prescription Piloted at 1 emergency department (ED), then deployed in 8 EDs	**Setting**: Ochsner Clinic System EDs **Methods**: Compared prescribing rate pre-intervention (Apr 2016 to Jun 2016) vs. post-intervention (Jul 2016 to Jul 2017) Outcome measure: Prescribing rate (percentage of patients discharged from the ED with opioid prescriptions)	• Opioid prescription rates declined in aggregate for the emergency services from 22% to 14% during the 1-year project timeline • Some physicians demonstrated a 70% reduction in prescription rate • Provider performance transparency using unblinded and transparent data analytics can efficiently and significantly alter provider practice • Initially only 25% of sites with prescription rates below the national benchmark (17%); by study end, 100% below national average
Burton et al. 2016[26] Study Design: Pre/Post (Prospective)	Benchmarking of prescribing rates: • Retrospective analysis over 9 months prior • Blinded benchmarking (3 months) • Unblinded (and shared with colleagues) benchmarking (3 months)	**Setting**: 7 EDs staffed by the same practice **Methods**: Compared prescribing rate from baseline (over 9 months) to after blinded and then unblinded reports of prescribing rates	• 47 physicians with 149,884 ED patient encounters • Mean quantity of pills prescribed per prescription significantly decreased from first to last stage of improvement initiative: 16 pills in Stage 1; 14 pills in Stage 2 (18% reduction, $p < 0.01$);13 pills in Stage 3 (18% reduction, $p < 0.01$) • The group mean prescribing rate (per visit) decreased through each stage: 20% in Stage 1; 13% in Stage 2 (46% reduction, $p < 0.01$); 8% in Stage 3 (60% reduction, $p < 0.01$)

Table B-5. Databases and Registries (PDMPs)

Study Characteristics	Study Purpose, Methods	Setting	Study Findings
Systematic Reviews, Scoping Reviews			
Fink et al. 2018[27] Study Design: Systematic Review	**Purpose**: To assess associations between prescription drug monitoring program (PDMP) and fatal or nonfatal overdoses **Methods**: N/A	N/A	• 17 studies identified: 3 nonfatal overdoses, 14 fatal overdoses • Evidence that implementation either increases or decreases nonfatal or fatal overdoses is largely insufficient, as is evidence regarding positive associations between specific administrative features and successful programs • Future studies should consider the variation in features to develop a set of empirically based best practices that result in the greatest reduction in prescription opioid-related harm and mitigate potential consequences, such as heroin-related harm
Finley et al. 2017[28] Study Design: Scoping Review	**Purpose**: To assess efficacy of PDMPs **Methods**: N/A	N/A	• Characteristics vary considerably across states in both legislated components and strategies for implementation • Clinicians may use the program as a tool for communication and interaction with patients • Evidence for the impact of state-level PDMPs remains mixed
Individual Studies			
Suffoletto et al. 2018[30] Study Design: Pre/Post	**Purpose:** To determine whether implementation of state-mandated PDMP in a single health system through an e-mail awareness campaign altered opioid prescribing among ED providers **Methods:** Analyzed data from 15 EDs from one health system before and after PDMP implementation (Jul 2015 to Mar 2017)	Pennsylvania	122,732 adult patients cared for in a participating ED (University of Pittsburgh Medical Center system) • Mandated documentation of PDMP query before prescribing opioids • 1,373 unique providers prescribed at least 1 opioid • From August (pre-PDMP) to September 2016 (post-PDMP), the opioid prescribing rate decreased from 12.4% (95% CI = 10.8%-14.1%) to 10.2% (95% CI = 8.8%-11.8%), equivalent to a relative reduction of 17.7% • For oxycodone prescriptions there were 6,523 prescribed over 6 months pre-PDMP compared with 4,524 (6 months post-PDMP) for a 30.6% reduction
Sun et al. 2018[29] Study Design: Pre/Post	**Purpose:** To assess whether automated prescription drug monitoring program intervention in emergency department (ED) settings	Washington state	• 86 EDs in Washington State from January 1, 2013, to September 30, 2015; the PDMP was automated queried and providers could access the information without having to enter their credentials • 1,187,237 qualifying ED visits (898,162 pre-intervention; 289,075 post-intervention)

	is associated with reductions in opioid prescribing and quantities **Methods:** Analyzed Medicaid claims before and after automation of PDMP reports; excluded age <15, cancer diagnosis, subjects with Medicare insurance; hospice or palliative care patients; encounters that resulted in hospital admission		• There was no change in prescribing rates or morphine milligram equivalents (MMEs) prescribed
Winstanley et al. 2018[31] Study Design: Pre/Post	**Purpose**: To assess association between mandated use of PDMP and reduction in quantity of opioids and benzodiazepines dispensed; reduction in days' supply, morphine milligram equivalents (MMEs) per prescription, and number of multiple provider episodes **Methods**: Analyzed all dispensed medications from 2007 through the first quarter of 2017 (Mar 31, 2017).	Ohio	From Nov 2014 through Mar 2017, there were 4.7 million fewer opioids dispensed and 1.6 million fewer benzodiazepines dispensed. Absolute quantity of opioids dispensed decreased by 8.9% and benzodiazepines decreased by 7.5%. • Significant decrease in the monthly quantity of opioids and benzodiazepines dispensed • Modest increase in the mean days' supply of opioids; and no change in the MME dose • Mandate was effective in reducing the quantity of opioids and benzodiazepines dispensed
Ranapurwala et al. 2018[32] Study Design: Pre/Post	**Purpose**: To assess Prescription Monitoring Program's (PMP) impact on prescribing patterns: average daily dosage in MMEs, MMEs per prescription, average days' supply per prescription, and prescription rate per 1,000 insured person-years (PY) **Methods**: Retrospective study using de-identified administrative claims data from 2003–2014 from a large private health insurer in the state of Iowa to evaluate impact of Iowa's PMP on opioid pain reliever (OPR) prescribing patterns	Iowa	• Compared with the pre-intervention trend, post-intervention, the PMP was associated with a 28% decrease in opioid prescription rates or a decline of 155 OPRs/1,000 PY (pre-intervention it was increasing, and decreased post-intervention) • Large decline in MMEs per day and MMEs per prescription • Days' supply kept increasing post-PMP implementation, albeit at a slightly slower rate • Implementation may have resulted in declines in opioid prescribing, and this impact varies by patient age and sex

Brown et al. 2017[33] Study Design: Pre/Post	**Purpose:** To assess the effect of Internet System for Tracking Over-Prescribing (I-STOP) on the supply and/or prescribing of opioids, opioid overdose/morbidity; and heroin overdose morbidity **Methods**: Analyzed data from Drug Enforcement Agency's (DEA) Automated Reports and Consolidated Orders System (ARCOS), the New York State Department of Health Bureau of Narcotics Enforcement (BNE), and the Statewide Planning and Research Cooperative System (SPARCS) from 2010 through 2015	New York PDMP, I-STOP	• I-STOP was implemented on August 27, 2013; mandated clinician review of the controlled substance database prior to prescribing opioids • Possible downward trend in prescriptions filled (only 2 data points post-intervention); insufficient data to draw a conclusion • Prescription overdose morbidity was rising pre-implementation and leveled off post-implementation • However, heroin overdose morbidity increased during the study period
Bao, et al. 2016[6] Study Design: Observational Cohort Study	**Purpose**: To assess PDMP's effect on the prescribing of opioids and other pain medication to manage pain **Methods**: Used National Ambulatory Medical Care Survey (NAMCS) data from 2001 to 2010 for all ambulatory care visits including pain as a reason for visit. Data from 24 states which implemented a PDMP during this time frame were included. Used states that had not yet implemented PDMP as controls.	Ambulatory care	• Overall, 26,275 ambulatory visits for pain occurred in these 24 states during this time period • Implementation of programs during the period 2001–2010 was associated with more than a 30% reduction (5.5% to 3.7%) in the rate of prescribing of schedule II opioid analgesics • Effect was immediate following the launch of providers' and dispensers' access to a program database and was sustained in the second and third years afterward
Rutkow et al. 2015[35] Study Design: Comparative interrupted time-series	**Purpose**: To quantify the effect of Florida's PDMP and pill-mill laws on overall and high-risk opioid prescribing and use **Methods**: Comparative interrupted time-series using IMS Health LifeLink LRx data on a closed cohort of prescribers, retail pharmacies, and patients from Jul 2010 through Sep 2012 in Florida (intervention	Florida, Georgia	Florida's pill-mill law required dispensing clinics to register with the state and have a physician-owner, created inspection requirements, and established prescribing and dispensing requirements and prohibitions for physicians at these clinics. Implementation began in 2010, with additional elements that became effective in Jul 2011 and prohibited prescriber dispensing of certain drugs Florida PDMP implemented in Sep 2011. • 2.6 million patients, 431,890 prescribers, and 2,829 pharmacies was associated with approximately 480 million prescriptions in Florida and Georgia, 7.7% of which were for opioids

	state) compared with Georgia (control state); included patients with 1 prescription during study period; excluded patients filling any prescription at store not consistently reporting data; excluded patients not filling prescription in first 3 months and last 3 months of study period		• One year after implementation, the interventions were associated with a 2.52% reduction in total opioid volume, 5.64% reduction in mean MME per transaction, no change in days' supply per transaction, and 1.35% reduction in total number of opioid prescriptions dispensed
Ringwalt et al. 2015[34] Study Design: Observational	**Purpose**: To assess PDMP's association with decline in prescriptions for controlled substances and in particular, opioid analgesics after 3 years of use by providers **Methods**: Analyzed data from PDMP from 2009 to 2011	North Carolina	• No association between mean days PDMP accessed by each provider or mean number of provider's registered for PDMP and decreased prescription of schedule II opioids • Did find a slight positive relationship between the growth in the use of the PDMP and the number of prescriptions filled for opioids • Concerns that PDMPs may constrain prescribing behavior with regards to controlled substances were unsupported
Simoni-Wastila et al. 2012[36] Study Design: Retrospective Cohort	**Purpose:** To compare opioid prescriptions in states with PDMPs vs. no PDMP **Methods:** Analyzed data from 2007 Coordination of Benefits (COB) MarketScan administrative claims data of Medicare eligible and their dependents	Multiple states	• 2,175,012 Medicare beneficiaries and their dependents • 834,489 (38.4%) of the sample filled at least one analgesic in 2007; among analgesic users, 75.3% used at least one class II opioid analgesic • Recipients living in states with an electronic or paper PDMP had higher odds of receiving an opioid analgesic prescription, but were less likely to receive a schedule II narcotic prescription (compared with prescribing in states without a PDMP): AOR 0.54 (95% CI 0.53, 0.55) for electronic + paper PDMP compared to no PDMP

Table B-6. Do PDMPs Change Prescribing Behaviors?

Study Characteristics	Study Purpose, Methods	Setting	Study Findings
Landau et al. 2018[37] Study Design: Pre/Post	**Purpose**: To assess prescription drug monitoring program's (PDMP) influence on emergency department (ED) providers' opioid prescribing process **Methods**: Assessed ED providers' perceptions of possible abuse and plan for prescribing (e.g., intent) before and after accessing PDMP	ED providers, University of Pittsburgh	• 23 providers, 103 patient encounters • Consistent with prior studies, findings indicated that program data rarely alters plans to prescribe an opioid among providers (for 92 of 103 encounters providers did not alter plans after PDMP review) • When changes in prescribing plan were made, this was reflected by changes in cognitions both related to perceived patient need for opioids and concern for drug abuse and/or diversion
Baehren et al. 2010[38] Study Design: Pre/Post	**Purpose**: To assess influence of Ohio's PDMP (Ohio Automated Rx Reporting System [OARRS]) PDMP data on clinical management of ED patients with non-acute painful conditions Patients: Non-acute pain **Methods:** Survey of providers before and after using PDMP from Jun to Jul 2018	ED (University of Toledo)	• 18 providers, 179 patients • After review of the OARRS data, providers changed the clinical management in 41% (N = 74) of cases • The use of data from a statewide narcotic registry frequently altered prescribing behavior for management of patients with complaints of non-traumatic pain
Weiner et al. 2013[39] Study Design: Pre/Post	**Purpose:** To compare emergency provider impression of drug-seeking behavior according to clinical evaluation with objective criteria from the Massachusetts Prescription Drug Monitoring Program. Patients: Back pain, dental pain, headache patients age 18 to 64 **Methods**: Survey providers before and after using PDMP from Jun 2011 to Jan 2013 Opioid seeking defined as: ≥4 opioid prescriptions from ≥4 providers in 12 months, as recorded in the PDMP	2 urban EDs (Massachusetts)	• 38 providers, 544 patients (no provider was allowed to have more than 54 patients included) • Overall, the plan changed (in either direction) for 9.5% of patients (95% CI 7.3% to 12.2%), with 3.0% (n = 16) no longer receiving a prescription after PDMP evaluation and 6.5% (n = 35) receiving a prescription that was not previously planned

Table B-7. Evidence Tables for Risk Factors for Progression from Opioid Naïve to Long-Term Use, Misuse, or Abuse

Reference	Setting	Study Details (n)	Risk Factor	Comment
	Surgery			
Brat et al. 2018[4]	All surgical procedures	1,015,115 patients (all ages) undergoing surgery Data source: Aetna administrative claims (medical and pharmacy), 2008 to 2016 **Opioid naïve**: Total opioid use in 60 days prior to surgery was ≤7 days **Outcome**: ≥1 year; International Classification of Diseases, ninth edition (ICD-9) code for opioid dependence, abuse, or overdose (prescription opioids only) over entire study period Additional inclusion/exclusion criteria: For inclusion patients had to have at least 6 months of medical insurance and 3 months of pharmacy insurance before surgery along with 90 days of pharmacy coverage and 1 year of medical coverage after surgery; Excluded patients with presurgical evidence of opioid or other nonspecific forms of misuse in 6 months prior to surgery Median follow-up: 2.67 years	After surgery 56% filled a prescription for postoperative opioid (90% filled within 3 days). Misuse was identified in 0.6% with 0.2% occurring within 1 year of surgery. Duration of use: After adjustment for covariates: each additional week of opioid use was associated with 19.9% increase in hazard (95% confidence interval [CI], 18.5% to 21.4%, p<0.001). Number of refills: Rate of misuse more than doubled with those with 1 refill Regimen initiated with hydromorphone (adjusted hazard ratio [AHR]: 1.76, 95% CI, 1.37 to 2.26) or oxycodone (AHR: 1.24, 95% CI, 1.02 to 1.48) Benzodiazepine (AHR: 1.77, 95% CI, 1.64 to 1.93) Other factors associated with increased risk: presurgical diagnosis of bariatric surgery, tobacco, chronic pain, and depression *No effect*: Geography Morphine milligram equivalents (MMEs) of dose (statistically significant, but only a small effect (AHR 1.008))	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Brummett et al. 2017[45]	Minor and major surgery (13 common elective surgical procedures)	36,177 patients (age 18 to 64) who filled an opioid prescription 1 month prior to surgery or within 2 weeks of discharge Data source: Clinformatics Data Mart, 2013 to 2014 **Opioid naïve**: No opioid scripts 12 months to 1 month before surgery **Persistent opioid use**: Prescription filled 90 to 180 days after surgery Additional inclusion/exclusion criteria: Excluded patients with another code for anesthesia during 6 month postoperative period	In 1 year preoperative period: Smoking (adjusted odds ratio [AOR] 1.35, 95% CI 1.21 to 1.49) Alcohol or substance abuse (AOR 1.34, 95% CI 1.05 to 1.72) Charlson comorbidity Index: 1.10 (95% CI 1.08 to 1.13) Mood disorders (AOR 1.15, 95% CI 1.01 to 1.30) Anxiety (AOR 1.25, 95% CI 1.1 to 1.42) Pain disorders Back pain: AOR 1.57, 95% CI 1.42 to 1.75) Neck pain: AOR 1.22 (95% CI 1.07 to 1.39) Arthritis: AOR 1.56 (95% CI 1.40 to 1.73) Opioid prescription in 30 days prior to procedure: AOR 1.93 (95% CI 1.71 to 2.19) Total opioid dose during surgical window of ≥300 mg (≥75th percentile): AOR 1.14 (95% CI 1.03 to 1.27) Age 30 to 49 compared with 18 to 29 (AOR 0.72 to 0.76) *No significant association detected*: Major vs. minor surgery: AOR 1.09 (95% CI 0.96 to 1.23) Persistent opioid use: minor surgery 5.9% vs. major surgery 6.5%, odds ratio (OR) 1.12 (95% CI 1.01 to 1.24)	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Sekhri et al. 2018[46]	Minor and major surgery	26,250 patients (age 18 to 64) 81.2% (minor surgery), 18.8% (major surgery) Data source: Optum Insights Claims Data (2013 to 2014) **Opioid naïve**: No opioid prescription filled for 12 months prior to surgery **Outcome**: Refill within 30 days Additional inclusion/exclusion criteria: Patient must have filled 1 opioid prescription within 30 days of surgery; however, patients refiling prescriptions twice within 30 days were excluded (assumed to continue prescriptions regardless of initial prescription amount)	8.67% of patients refilled prescriptions within 30 days of surgery Undergoing a particular surgery: Colectomy, (AOR 2.8, incisional hernia repair (2.6), reflux surgery (3.1), hysterectomy (2.2), hemorrhoidectomy (3.1), carpal tunnel repair (1.2) Increased risk (adjusted for age, sex education, race and geographic area): • History of smoking: AOR: 1.41 (95% CI 1.2 to 1.5) • Anxiety: AOR 1.3 (95% CI 95% CI 1.1 to 1.4) • Mood disorders: AOR 1.27 (95% CI 1.1 to 1.4) • Adjustment disorder: AOR 1.19 (95% CI 0.98 to 1.4) • Alcohol or substance abuse disorders: AOR 1.43 (95% CI 1.1 to 1.8) • Arthritis: AOR 1.23 (95% CI 1.1 to 1.3) • Other pain conditions: AOR 1.19 (95% CI 1.0 to 1.3) *No significant association detected*: • Mean Charlson comorbidity index • Back, neck pain Initial MME dose prescribed was not associated with probability of a single postoperative refill. Probability of refill only increased slightly (from 8.67%) to 9.03% with 240 to 200 opioid milli equivalents (OMEs, 48 to 60 pills)) and to 10.08% for >300 OMEs (>60 pills)	

Reference	Setting	Study Details (n)	Risk Factor	Comment
	Specific Surgery Types			
Swenson et al. 2017[41]	Hysterectomy	24,331 women (age 18 to 63) undergoing hysterectomy, with no opioid prescription from 243 to 31 days prior to surgery Data Source: Optum Clinformatics DataMart, from Jan 1, 2011, to December 31, 2014 **Opioid naïve**: No opioid prescription for 243 days to 31 days prior to surgery **Outcome**: "New persistent opioid use" defined as ≥2 opioid fills within 6 months of hysterectomy with ≥1 fill every 3 months and either total oral morphine equivalent ≥1,150 or days supplied ≥39 Additional inclusion/exclusion criteria: Excluded patients with any other surgical procedures during this period; included patients with continuous insurance enrollment 8 months prior and 6 months post-procedure	Prevalence of new persistent opioid use was 0.5% (n = 122) • Non-vaginal hysterectomy (e.g., abdominal or laparoscopic): Compared with patients with vaginal hysterectomy, patients receiving abdominal hysterectomy were significantly more likely to develop persistent opioid use: AOR 3.6 (95% CI 2 to 6.4) • Depression/anxiety: AOR 2.6 (95% CI 1.7 to 4.0) • Indication for hysterectomy was malignancy: AOR 7.6, 95% CI 3.4 to 17.2) Only 90 of 6,637 abdominal hysterectomies were performed in patients with gynecologic malignancy	Included 63 patients with gynecologic cancer (0.25% of overall study population)
Sun et al. 2016[47]	11 Surgical procedures: total knee arthroplasty, total hip arthroplasty, laparoscopic cholecystectomy, open cholecystectomy, laparoscopic appendectomy, open appendectomy, cesarean delivery, functional endoscopic sinus surgery, cataract surgery, transurethral prostate resection, simple mastectomy	641,941 opioid naïve surgical patients (privately insured patients age 18 to 64) Data Source: MarketScan, from Jan 1, 2001, through Dec 31, 2013. **Opioid naïve**: No opioid prescription for 12 months prior to procedure **Outcome**: Chronic opioid use (defined as filling either ≥10 prescriptions or ≥120 days' supply for post-operative days 91 to 365) Additional inclusion/exclusion criteria: Excluded patients undergoing 2 or more procedures	Male: AOR 1.34 (standard error [SE] 0.06) Age>50: AOR 1.74 (SE 0.09) **Pre-operative drug use**: Preoperative use of benzodiazepines : AOR 1.82 (SE 0.1) Antidepressants: AOR 1.65 (SE 0.09) **Comorbidities**: Depression: AOR 1.15 (SE 0.07) Alcohol abuse: AOR 1.83 (SE 0.2) Drug abuse: AOR 3.15: (SE 0.53) No significant association found: Antipsychotic use, psychosis	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Schoenfeld et al. 2017[40]	Spine surgery: • discectomy • decompression • lumbar posterolateral arthrodesis • lumbar interbody arthrodesis	9,991 patients (age 18 to 64) Mean age: 46.4 ± 11.0 Data source: TRICARE from 2006 to 2014 **Opioid Naïve**: No opioid prescriptions within 6 months prior to procedure **Outcome**: Time to discontinuation of opioid use Additional inclusion/exclusion criteria: Excluded patients with history of trauma or cancer within 1 year prior to procedure; excluded patients eligible for Medicare or Medicaid Higher intensity surgical procedures defined as lumbar interbody arthrodesis and posterolateral arthrodesis	84% filled at least 1 opioid prescription after surgery Increased risk: (AHRs for discontinuation of opioid use) • Depression: 0.84 (95% 0.77 to 0.90) • Senior enlisted (compared to officer): 0.94 (95% CI 0.89 to 0.99) • Junior enlisted (compared to officer): 0.80 (95% CI 0.72 to 0.90) • Decompression (compared to lumbar interbody arthrodesis): 1.34 (95% CI 1.25 to 1.43) • Discectomy (compared to lumbar interbody arthrodesis): 1.43 (95% CI 1.36 to 1.50) Higher intensity procedures increased risk of prolonged opioid use No significant effect identified: Anxiety, sex, marital status	
Marcusa et al. 2017[42]	Mastectomy with immediate breast reconstruction	4,113 patients who filled an opioid prescription 30 days preoperative to 30 days postoperative Data source: Truven Health MarketScan research databases (inpatient, outpatient and prescription drug services), from Jan 2010 to Aug 2014 **Opioid naïve**: No opioid prescriptions for 1 year to 30 days before surgery **Outcome**: Prolonged fills: Filled opioid perioperatively and refilled at 90 to 120 days post-op Additional inclusion/exclusion criteria: Excluded women who underwent procedures requiring anesthesia in the postoperative period (120 days)	90% filled an opioid prescription in the perioperative period and 10% continued to fill 90 days after surgery Anxiety (psychiatric condition existing within 1 year before surgery) (AOR: 1.6, 95% CI 1.1 to 2.1) >3 comorbidities (Elixhauser index): AOR: 1.8 (95% CI 1.3 to 2.5) Complications during follow-up period (120 days): AOR 1.5 (95% CI 1.2 to 1.9) *Decreased risk:* Age ≥65: AOR 0.5 (95% CI 0.2 to 0.9) No significant effect detected: Depression, substance abuse	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Johnson et al. 2016[43]	Hand surgery	77,573 adult patients undergoing elective or trauma-related hand surgery Data source: Truven Health MarketScan research databases, from 2010 to 2012 **Opioid naïve**: No diagnosis code of opioid dependence or abuse; and no opioid prescription 1 to 12 months before surgery **Outcome**: Prolonged opioid use: Patients filled ≥1 opioid prescription perioperatively (30 days prior to 2 weeks post-op) and ≥1 opioid prescriptions between 90 and 180 days after surgery. Additional inclusion/exclusion criteria: None	77% filled at least 1 perioperative opioid prescription. AORs for prolonged opioid use: *Increased risk*: Elective (vs. trauma-related surgery: 1.2 (95% CI 1.1 to 1.3) • Elixhauser comorbidity index 2: 1.4 (95% CI 1.3 to 1.5) • Elixhauser comorbidity index 3: 1.6 (95% CI 1.4 to 1.7) • Elixhauser comorbidity index >3: 2.2 (95% CI 2 to 2.3) • Mental health disorders: 1.1 (95% CI 1.1 to 1.2) • Smoking: 1.6 (95% CI 1.0 to 2.6) *Decreased risk*: Median household income in area residing >60,000: 0.8 (95% CI 0.7 to 0.9) >70,000: 0.7 (95% CI 0.6 to 0.9) Age ≥ 65: 0.8 (95% CI 0.7 to 0.9) *No significant effect detected*: Drug dependence, alcohol dependence, history of pain	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Bateman et al. 2016[44]	Cesarean delivery	80,127 women (age 12 to 55) undergoing cesarean delivery Data source: Clinformatics Data Mart, from 2003 to 2011 **Opioid naïve**: No opioid prescriptions for 1 year prior; no diagnosis code of opioid dependence or abuse in baseline period **Outcome**: Persistent opioid use, defined as group of patients with highest probability of filling over time Determined by trajectory analysis: Did a woman fill opioid medication during each of 12 consecutive 30-day periods of follow-up; estimated probability of group membership for each patient; patients were assigned group with highest membership probability	For groups 1 to 3 (n = 76,557 or 95.5%), fewer than 10% of group members filled an opioid prescription in each month of follow-up period. In group 4 (n = 3,285, 4.1%), estimated proportion filling an opioid prescription in the first month of follow up was 28%, but fell to <10% at month 4. In group 5: n = 285, 0.36%, (persistent user group), estimated proportion filling at month 1 was 37%, and increased to month 12: 61%. Overall, opioid-naïve women who filled a prescription for opioid analgesic after cesarean delivery have a small risk (about 1 in 300) of becoming persistent users of prescriptions opioids in 1 year after delivery. AORs of persistent opioid use: • Substance use: Age 20-29 (vs. 30-39): 1.4 (95% CI 1.09 to 1.8) • Cocaine use: 6.11 (95% 1.03 to 36.3) • Other illicit substances: 2.78 (95% CI 1.12 to 6.91) • Smoking: 3.04 (95% CI 2.03 to 4.55) • Back pain: 1.74 (95% CI 1.33 to 2.29) • Migraines: 2.14 (95% CI 1.58 to 2.9) • Antidepressant use: 3.19, 95% CI 2.4 to 4.2) • Benzodiazepine use: 3.7 (95% CI 2.6 to 5.2) No significant effect detected: Type of opioid initially dispensed, days' supply, or daily dose in morphine equivalents.	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Harbaugh et al. 2018[48]	Patients undergoing 1 of 13 operations in the U.S. (including tonsillectomy, inguinal hernia repair, epigastric hernia repair, appendectomy, colectomy, open epicondylar fracture repair)	88,637 opioid-naïve patients age 13 to 21 who filled an opioid prescription in perioperative period Data source: Truven Health MarketScan research databases (capturing patients with employer based insurance) from Jan 1, 2010 to Dec 31, 2014 **Opioid naïve**: No opioids prescriptions from 12 months to 1 month prior to surgery **Outcome**: Persistent opioid use (≥1 additional opioid prescriptions filled between 90 to 180 days after procedure) Additional inclusion/exclusion criteria: Included if (1) continuous insurance coverage during 12 months before the procedure through 6 months after; (2) No additional surgical procedure or anesthesia during 6 months after procedure; (3) Opioid naïve without prior prescription fills during 11 months before the 30 days before surgery Perioperative period defined as 30 days prior to 2 weeks after procedure	Persistent opioid use was found in 4.8% of patients (range 2.7% to 15.2% across procedures); Procedures with significant increased risk: • Cholecystectomy: AOR 1.13 (95% CI 1 to 1.26) • Colectomy: 2.33 (95% CI 1.01 to 5.34) Female: AOR: 1.2 (95% CI 1.14 to 1.31) Older age: AOR: 1.07 (95% CI 1.05 to 1.08) Substance use disorder (in prior year): AOR 1.41 (95% CI 1.12 to 1.77) Chronic pain diagnosis: AOR 1.48 (95% CI 1.33 to 1.66) Opioid prescription filled within 30 days before surgery: AOR 1.26 (95% CI 1.17 to 1.36)	

Reference	Setting	Study Details (n)	Risk Factor	Comment
	Other condition			
Fritz et al. 2018[49]	Low back pain	707 patients (age 17 to 64) receiving new consultation for low back pain and receiving opioid prescription within 14 days of visit Mean age: 38.1 ± 11.6; 76.9% Medicaid 64.8% primary care visits; 28.1% emergency department Data source: University of Utah Health Plans administrative claims data (from Jan 1, 2012, to Jun 30, 2015) **Opioid naïve**: No opioid prescription 90 days preceding index visit **Outcome**: Long term opioid use (≥120 days or >90 days with ≥10 fills over 1 year follow-up period) Additional inclusion/exclusion criteria: Excluded patients who did not fill an opioid prescription in 14 days after index visit; Included patients with no low back pain (LBP) related claims within 90 days preceding index visit; index visit setting (primary care, nonsurgical specialist (e.g., physical medicine and rehabilitation), emergency department, or surgical specialist; excluded patients with red flag condition potentially requiring urgent management or increased likelihood of opioids prescribing (e.g., malignant neoplasm, fracture of spine or pelvis, osteomyelitis, or cauda equine syndrome). Excluded patients with significant mobility limitations or health condition impacting ability to access care occurring with any claim in the 90 days prior to 1 year following index visit including paraplegia, quadriplegia, or wheelchair dependence.	76.9% of patient received at least 1 additional opioid fill beyond early care period and 24.3% were categorized as long term use over 1 year. Increased risk for long-term opioid use (AORs): • Age (years) 1.03 (95% CI 1.02 to 1.05) • Medicaid 2.84 (95%CI 1.62 to 5) • Anxiety: 1.69 (95% CI 1.12 to 2.5) • Smoking: 1.53 (95% CI 1.03 to 2.28) • Primary care visit: 1.66 (95% CI 1.12 to 2.46) • Benzodiazepine: 1.87 (95% CI 1.01 to 3.48) *Decreased Risk*: • Physical therapy (PT) visit: 0.44 (95% CI 0.22 to 0.89) *No significant effect detected*: Sex, depression, substance abuse, Charlson comorbidity, obesity	

Reference	Setting	Study Details (n)	Risk Factor	Comment
	Emergency Room			
Hoppe et al. 2015[50] Excluded <8, pregnancy, and admitted patients	Acute mild-moderate painful condition and treated in emergency room (dental/tooth pain, back pain, neck pain, knee pain, headache, fracture or sprain)	2,499 patients ≥18 years with acutely painful condition discharged from the emergency department (ED) Data source: University of Colorado Hospital ED and Colorado prescription drug monitoring program (PDMP), from Sep 1, 2011, to Feb 1, 2012 **Opioid Naïve**: No opioid script filled for 1 year prior to emergency room (ER) visit **Outcome**: Recurrent opioid use (filling any opioid prescription within 60 days of first anniversary of index ED visit; e.g. 305 to 425 days after visit) Additional inclusion/exclusion criteria: Excluded pregnancy, and patients admitted; for patients with multiple visits, only initial visit was included Of note: study authors were unable to detect whether patients filled scripts outside of 60 days before or after 1 year anniversary of ED visit; or if it was filled outside of the states	Rates of recurrent use (opioid-naïve patients): • 12% overall recurrent use Long term risk was: • 17% for patients who filled their ED opioid prescription, • 10% for patients who did not receive an opioid prescription on discharge; • 8% for patients who received, but did not fill ED opioid prescription *Increased risk:* AOR • Filling opioid prescription after discharge from ER: 1.8 (95% CI 1.3 to 2.3) (reference = patients who were not given an opioid prescription) Decreased risk: • Hispanic (vs. White): 0.58 (95% CI 0.40 to 0.82) *No significant effect detected*: Age, sex, insurance type	

Reference	Setting	Study Details (n)	Risk Factor	Comment
	Hospital Discharges			
Calcaterra et al. 2016[51]	All surgical and medical discharges from hospital	6,689 patients discharged from academic safety hospital in Denver (Jan 1, 2011, to Dec 31, 2011) **Opioid naïve**: No opioid prescription filled at a Denver health affiliated pharmacy 1 year prior to hospital discharge **Outcome**: Risk of chronic opioid use and opioid refills 1 year after discharge; chronic opioid use defined as an opioid use episode lasting >90 days with a total of 120+ day supply of opioids or >10 opioid prescriptions dispensed over 1 year Additional inclusion/exclusion criteria: Included opioid-naïve medical and surgical patients; excluded age <15, in correctional care (prison, jail or police custody), died during hospitalization, ≥2 visits to Denver Health in 3 years preceding their index hospitalization, on hemodialysis, or undocumented. Excluded patients with <2 visits to Denver Health (as patients less likely to receive follow up care within this system)	Opioid receipt within 72 hours of discharge 25% had opioid receipt (filled prescription for opioid); 75% did not Patients filling an opioid prescription within 72 hours of discharge were significantly more likely to have chronic opioid use at 1 year (compared to patients not filling an opioid prescription): AOR: 4.9 (95% CI 3.22 to 7.45) Also, patients filling an opioid prescription had a higher mean opioid refills within 1 year (1.8 (SD 7.5) vs. 0.6 (SD 3.7), p<0.001.	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Calcaterra et al. 2018[7]	All hospital discharges	27,705 hospitalized patients discharged Data source: Denver Health Medical Center (from 2008 to 2014) **Opioid naïve**: No chronic opioid therapy or opioid agonist therapy in 1 year prior to index discharge **Outcome**: Chronic opioid therapy (COT) defined as: ≥90 day supply of oral opioid (with less than 30 day gap in supply) within a 180 day period or receipt of ≥10 opioid prescription over 1 year following index discharge Additional inclusion/exclusion criteria: Excluded patients on COT, age <15 or >85, prisoners, in jail or police custody, died after discharge, had <2 healthcare visits to Denver Health, undocumented persons receiving emergent hemodialysis or undocumented obstetric patients. Excluded subsequent hospital discharges Goal: To create model to predict future COT among hospitalized patients without COT	Only 1,457 (5.3%) of patients were on COT at 1 year after index discharge. Multiple logistic regression model correctly predicted 79% of COT patients and 78% of no COT patients. Prescribed opioids at discharge: AOR 2.33 (95% CI 1.78 to 3.04) Higher milligrams of morphine per hospital day (ref = 0) • 0.01 to <10: AOR 1.65 (95% CI 1.09 to 2.52) • 10 to 50: AOR 2.08 (95% CI 1.47 to 2.93) • 51 to 100: AOR 2.23 (95% CI 1.49 to 3.35) • 100+: AOR 3.37(95% CI 2.1 to 5.4) Higher number of opioid prescriptions filled in prior year: AOR 9.87 (95% CI 6.3 to 15.4) for 4 to 9 filled prescriptions compared to 0. Receiving non-opioid analgesics in prior year: AOR 1.92 (95 CI 1.49 to 2.48) Filled prescription for benzodiazepine in the past year: AOR: 1.89 (95% CI 1.26 to 2.82) History of chronic pain diagnosis in prior 3 years: AOR 1.79 (95% CI 1.41 to 2.26) Number of hospitalizations in 1 year after index discharge: AOR 1.51 (95% CI 1.39 to 1.64) Medicaid insurance: with Medicaid as the reference, patients with commercial insurance had lower odds of long-term use: AOR 0.3 (95% CI 0.25 to 0.73); the point estimate was also lower for Medicare patients, although this did not reach statistical significance (AOR 0.73, 95% CI 0.52 to 1.03). Model was adjusted for age and insurance type	

Reference	Setting	Study Details (n)	Risk Factor	Comment
	All settings			
Nelson et al. 2018[54]	Outpatient (ambulatory) care	552,193 active duty United States Army soldiers. 15.1% female; mean age 30.5 (± 7.55); 75% white Data source: Defense Manpower Data Center (DMDC) Master File: Demographic and military service data; DMDC Transaction File; Military Health System Data Repository (MDR); MDR Clinical Data Repository Vitals File; MDR Pharmacy Detail Transaction Service from January 2011 to September 2014 **Opioid naïve**: No opioid prescription in previous 6 months prior to index outpatient visit **Outcome**: Chronic opioid use (defined as 3 consecutive months of receiving opioid therapy) Additional inclusion/exclusion criteria: Patients were observed until they had less than 3 months of observed time; reasons for leaving the dataset include discharge from the military or death. Based on study's reported 6.73 million person-months of observation on 552,193 individuals, the mean length of time followed would be 12.2 months per person	13,891 (2.5%) of individuals developed chronic opioid use Increased risk for developing chronic opioid use: • 3+ prior opioid prescription received: AOR 4 (95% CI 3.8 to 4.2) • Tobacco use: AOR 1.5 (95% CI 1.5 to 1.6) • ≥ 2 Psychotropic medications: AOR 1.7 (95% CI 1.6 to 1.8) Decreased risk: • Non-white race • Younger age • Female gender	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Halbert et al. 2016[52]	General	33,450 adults with noncancer pain Data source: Survey data from 7 consecutive Medical Expenditure Panel Survey household component (MEPS-HC) from 2005 to 2011 **Opioid naïve**: Reporting no opioid use during first survey period **Outcome**: Longer-term opioid use (receiving ≥3 opioid prescriptions during consecutive survey periods) Additional inclusion/exclusion criteria: Included adults ≥18 with 2 full years of follow up and reporting at least 1 acute or chronic pain condition. Excluded adults with any cancer diagnosis or hospice care.	6,276 (weighted estimate 18.8%) reported mood disorder. 16,475 with likely acute pain condition. Of these patients, 2,995 (17.6% weighted) started opioid therapy for that condition, and 209 (1.2% weighted) continued to longer term opioid therapy. 25,100 chronic pain condition. Of these 2,545 (9.7% weighted) started new opioid therapy for that condition, and 610 (2.4%) weighted continued to longer term opioid therapy. Mood disorders (increased new opioid use and transition to long-term opioid use) Of patients with acute pain, patients with mood disorders were more likely to transition to long term opioid use compared to patients without mood disorders: weighted percentage 11.7% vs. 0.3%, p<0.01 This was also true for patients with chronic pain conditions: Weighted percentage 36.8% vs. 19.9%, p<0.01. Compared with patients without mood disorders, patients with mood disorders were more likely to start opioids: • Acute pain (AOR 1.16, 95% CI 1.03 to 1.30) • Chronic pain (AOR 1.21, 95% CI 1.08 to 1.35) Compared with patients without mood disorders, patients with mood disorders were more likely to transition to long term opioid therapy • Acute pain: AOR 2.35 (95% CI 1.63 to 3.38) • Chronic pain: AOR 2.65 (95% CI 1.97 to 3.55) (Adjusted for age, sex, race, education, access to usual care provider and body mass index [BMI])	

Reference	Setting	Study Details (n)	Risk Factor	Comment

Deyo et al. 2016[5]	General	536,767 opioid naïve patients (all ages) filling an opioid prescription.
		Data source: Oregon PDMP, linked to death certificates and statewide hospital registry (Oct 1, 2012 to Sep 30, 2013)
		Opioid naïve: No opioid prescription in prior year or hospitalization for opioid related diagnosis or receiving a high cumulative opioid dose (≥4000 MMEs) in initiation month from Oct 1, 2012, to Sep 10, 2013
		Outcome: Long-term opioid use (≥6 prescription fills during 1 year study interval)
		Additional inclusion/exclusion criteria: Included all opioid-naïve patients filling an opioid prescription; excluded patients with address outside Oregon
			26,785 (5%) opioid naïve patients filling a prescription became long term opioid users
			Number of prescriptions filled (all included patients), ref=1
			• 2: AOR 2.25 (95% CI 2.17 to 2.32)
			• 3: AOR 2.60 (95% CI 2.47 to 2.73)
			• ≥4: AOR: 3.21 (95% CI 3.03 to 3.40)
			(Adjusted for urban/rural, categorical age)
			Number of prescriptions filled (all included patients) (Percentage becoming long term opioid users):
			• 1: 2.9%
			• 2 (10.6%)
			• 3 (16.7%)
			• ≥ 4: 26.1%
			Also increased risk with increased MMEs dispensed: (AOR ranged from 1.43 to 16)
			Subset analysis: age >11 and <45, and not dying within 1 year of index prescription (to exclude palliative care or cancer patients)
			Number of prescriptions filled:
			• Short acting opioids (ref =1)
			  o 2: AOR 2.25 (95% CI 2.17 to 2.33)
			  o 3: AOR: 2.62 (95% CI 2.49 to 2.76)
			  o ≥4: AOR: 3.32 (95% CI 3.11 to 3.53)
			• Long acting opioids (re=1)
			  o 2: AOR: 2.04 (95% CI 1.31 to 3.17)
			  o 3: AOR 1.88 (95% CI 1.06 to 3.33)
			  o ≥4: AOR: 1.77 (95% CI 0.96 to 3.24)
			Increasing morphine equivalents dispensed:
			Long acting opioids (ref = 1-799)
			• 800 to 1599: AOR: 1.99 (95% CI 1.16 to 3.42)
			• 1600 to 2399: AOR: 4.89 (95% CI 2.7 to 8.84)
			• 2400 to 3199: AOR 6.84 (95% CI 3.67 to 12.75)
			• 3200 to 3999: AOR: 5.21 (95% CI 2.57 to 10.56)
			Also significant increased risk for short acting opioids (AOR ranged from 1.42 to up to 16.30)
			Adjusted for urban/rural, categorical age	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Jeffery et al. 2018[55]	General	3,656,781 opioid fills (all ages) for patients with no fills in prior 6 months) Data source: OptumLabs Data Warehouse administrative claims data (privately insured and Medicare Advantage), Jan 1, 2009, to Dec 31, 2015 **Opioid Naïve**: No opioid fills in prior 6 months **Outcome**: Consortium to Study Opioid Risks and Trends Criteria: episodes of opioid prescribing lasting longer than 90 days and 120 or more total days' supply or 10 or more prescriptions in the year after index fill. Also concordance with practice opioid prescribing guidelines from Centers for Disease Control and Prevention (CDC) guidelines Additional inclusion/exclusion criteria: Excluded prescription fills from patients with hospice claims or ≥2 physician visits for cancer diagnosis in prior 3 months; excluded fills for patients with less than 6 months of insurance enrollment prior to index fill; excluded if patients had <12 months of follow-up after index fill Tramadol was classified as an opioid.	Opioid prescriptions from non-ED settings increase risk for prolonged use (across multiple dosages) In all beneficiary populations, prescriptions attributed to the ED were less likely to progress to long-term opioid use. Progression to long-term opioid (LTO) use in ED vs. non-ED settings: • Commercial insurance: 46% less likely in ED (adjusted risk ratio [ARR] 0.54 (95% CI 0.53 to 0.56) • Aged Medicare beneficiaries: 56% less likely in ED (ARR 0.44 (95% CI 0.42 to 0.46) • Disabled Medicare: 58% less likely (ARR 0.42 (95% CI 0.39 to 0.45) "Across nearly all care settings and beneficiary populations, a nonconcordant prescription was associated with a greater risk of progression to LTO use (ARR range from 1.09 (95% CI 0.93 to 1.26) for disabled Medicare beneficiaries treated in the ED to 5.42 (95% CI 4.79 to 6.05) for aged Medicare beneficiaries treated in unknown settings." Statistically significant increases for all populations except disabled Medicare/ED.	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Shah et al. 2017[53]	General	1,353,902 cancer-free patients (age ≥14) with no substance abuse diagnosis for 6 months prior to prescription) with at least 1 opioid prescription Data source: Random 10% sample from Intercontinental Marketing Services Lifelink plus nationally representative health insurance claims database of commercially insured patients including inpatient, outpatient and pharmacy claims) from June 1, 2006 to Dec 31, 2014 **Opioid naïve**: at least 6 months of continuous pharmacy and medical enrollment without an opioid prescription before their first opioid prescription **Outcomes**: Opioid discontinuation (at least 180 continuous days without opioid use from the end date of the last opioid prescription) Additional inclusion/exclusion criteria: Only included patients age ≥14 at time of first prescription; excluded patients with any cancer (except nonmelanoma skin cancer) or substance abuse disorder diagnosis in 6 months prior to first prescription; excluded patients with first opioid prescription of Suboxone (because indicated for substance abuse disorder treatment); excluded patients with missing or invalid demographic information (e.g., type of payer, age sex); excluded patients with only pharmacy benefits	Probability of continued opioid use at 1 year was 5.3% across all subjects AHR <1 indicates a lower likelihood of opioid discontinuation. Higher days' supply (initial prescription), ref = 1-2 • 3-4: AHR 0.7 (95% CI 0.7 to 0.71) • 5-7: AHR: 0.48 (95% CI 0.47 to 0.48) • 8-10: AHR 0.37 (95% CI 0.37 to 0.38) • 11-14: AHR: 0.32 (95% CI 0.31 to 0.33) • 15-21: AHR 0.29 (95% CI 0.28 to 0.29) • ≥22: AHR 0.20 (95% CI 0.19 to 0.20) Higher average daily dose (ref = 0-24 MMEs) • 25 to 49: AHR: 0.97 (95% CI 0.96 to 0.97) • 50 to 89 : AHR 0.95 (95% CI 0.94 to 0.95) • ≥ 90: AHR: 0.91 (95% CI 0.91 to 0.92) Drug patient initiated with (compared to schedule III, IV opioid or nalbuphine) • Initiated with tramadol (hazard ratio [HR] = .89; 95% CI, .89–.90) or long-acting opioids (HR = .79; 95% CI, .77–.82) Adjusted for year of opioid initiation, region, primary payer, gender, age, mental health conditions, benzodiazepines, or nonbenzodiazepine gamma aminobutyric acid receptor modulator in previous 6 months and muscle relaxant in prior 6 months	

Reference	Setting	Study Details (n)	Risk Factor	Comment
Hooten et al. 2015[56]	General	293 patients (all ages) from Olmsted County, Minnesota, receiving a new opioid prescription (with no prior for 6 months) and authorizing use of medical records for research Data source: Random sample of outpatient prescriptions from Rochester Epidemiology Project (REP) and Mayo Clinic and Olmsted Medical Center records (Jan 1 to Dec 31, 2009) **Opioid naïve:** No prescription for 6 months with new opioid prescription **Outcome:** • Short term (opioids prescribed ≤90 days); Episodic (opioids prescriptions extend beyond 90 days, but total days supple <120, and total # of prescriptions <10; • Long term (>90 days of prescribing and ≥120 total days' supply or ≥10 prescriptions) Additional inclusion/exclusion criteria: Included patients followed for at least 1 year patient initial prescription date Full chart reviews by nurse abstractor were conducted on the random sample of 299 patients, of which 98% had a new prescription for opioid medication	6% progressed to long-term prescribing pattern Patients with history of substance abuse (alcohol, marijuana, methamphetamine, benzodiazepine, or cocaine) were more likely to have long term (compared to short term) use: AOR: 8.72 (95% CI 2.76 to 27.55) Adjusted for sex, age, race, education, depression/anxiety, nicotine use and comorbidities No effect was found for smoking and other psychiatric diagnosis	Method of random selection not explained

Appendix C. Study Quality Assessment

Table C-1: Risk Factor Studies: Newcastle-Ottawa Scale

	Selection				Comparability		Outcome		
Lead author and year	Exposed cohort representative	Nonexposed cohort representative	Exposure (risk factor) ascertained	Outcome of interest not present at start of study	Cohorts comparable on basis of design/analysis	Blinded outcome assessors (N/A) Outcome adequately assessed	Adequate follow-up duration	Multivariable regression	Summary
Bateman et al. 2016[44]	Yes	Yes	Administrative data	No opioid prescription for 12 months prior; also, no diagnosis code of opioid dependence or abuse	Yes	Opioid prescriptions	1 year	Yes	Low
Brat et al. 2018[4]	Yes	Yes	Administrative data	Excluded if code for opioid abuse in 6 months before surgery	Yes	International Classification of Diseases, ninth edition (ICD-9) code for misuse	At least 1 year	Yes	Low
Brummett et al. 2017[45]	Yes	Yes	Administrative data	No opioid scripts for 12 months to 1 month prior to surgery	Yes	Opioid prescriptions	90 to 180 days	Yes	Low
Calcaterra et al. 2018[7]	Yes	Yes	Administrative data	No chronic opioid therapy or opioid agonist therapy in 1 year prior to index discharge	Yes	Opioid prescription	1 year after discharge	Yes	Low

	Selection				Comparability		Outcome		
Lead author and year	Exposed cohort representative	Nonexposed cohort representative	Exposure (risk factor) ascertained	Outcome of interest not present at start of study	Cohorts comparable on basis of design/analysis	Blinded outcome assessors (N/A) Outcome adequately assessed	Adequate follow-up duration	Multivariable regression	Summary
Calcaterra et al. 2016[51]	Yes	Yes	Administrative data	No opioid prescription filled at a Denver Health–affiliated pharmacy 1 year prior to discharge	Yes	Opioid prescriptions	1 year after discharge	Yes	Low
Deyo et al. 2016[5]	Yes	Yes	Administrative data	No opioid prescription in the prior year or hospitalization for opioid-related diagnosis or receiving high cumulative opioid dose in initiation month	Yes	Opioid prescription	1 year	Yes	Low
Fritz et al. 2018[49]	Yes	Yes	Administrative data	No opioid prescription for 90 days prior to index visit	Yes	Opioid prescriptions	1 year	Yes	Low
Halbert et al. 2016[52]	Yes	Yes	Administrative data	No opioid use reported during first survey period	Yes	Opioid prescription	2 years	Yes	Low

	Selection				Comparability		Outcome		
Lead author and year	Exposed cohort representative	Nonexposed cohort representative	Exposure (risk factor) ascertained	Outcome of interest not present at start of study	Cohorts comparable on basis of design/analysis	Blinded outcome assessors (N/A) Outcome adequately assessed	Adequate follow-up duration	Multivariable regression	Summary
Harbaugh et al. 2018[48]	Yes	Yes	Administrative data	No opioid prescriptions for 12 months to 1 month prior to surgery	Yes	Opioid prescription	180 days post-operative	Yes	Low
Hooten et al. 2015[56]	Yes	Yes	Random sample of administrative data	No opioid prescription in prior 6 months	Yes	Opioid prescription	1 year	Yes	Low
Hoppe et al. 2015[50]	Yes	Yes	Administrative data	No opioid prescription filled for 1 year prior to emergency room (ER) visit	Yes	Opioid prescription	425 days after ER visit	Yes	Low
Jeffery et al. 2018[55]	Yes	Yes	Administrative data	No opioid prescriptions fills in prior 6 months	Yes	Opioid prescription	1 year	Yes	Low
Johnson et al. 2016[43]	Yes	Yes	Administrative data	No diagnosis code of opioid dependence or abuse; also, no opioid prescription 1-12 months prior to surgery	Yes	Opioid prescriptions	180 days postoperative	Yes	Low

	Selection				Comparability		Outcome		
Lead author and year	Exposed cohort representative	Nonexposed cohort representative	Exposure (risk factor) ascertained	Outcome of interest not present at start of study	Cohorts comparable on basis of design/analysis	Blinded outcome assessors (N/A) Outcome adequately assessed	Adequate follow-up duration	Multivariable regression	Summary
Nelson et al. 2018[54]	Yes	Yes	Administrative data	No opioid prescriptions for 6 months prior to index outpatient visit	Yes	Opioid prescriptions	At least 3 months; based on study's reported 6.73 million person-months of observation on 552,193 individuals, the mean length of time followed would be 12.2 months per person	Yes	Low
Marcusa et al. 2017[42]	Yes	Yes	Administrative data	No opioid prescriptions for 1 year to 30 days prior to surgery	Yes	Opioid prescriptions	180 days post-operative	Yes	Low
Schoenfeld et al. 2017[40]	Yes	Yes	Administrative data	No opioid prescriptions for 6 months prior to procedure	Yes	Opioid prescriptions	Time to discontinuation of opioids (8 year window)	Yes	Low
Sekhri et al. 2017[46]	Yes	Yes	Administrative data	No opioids for 12 months prior to surgery	Yes	Opioid refill within 30 days	30 days post-operative	Yes	Low

	Selection				Comparability		Outcome		
Lead author and year	Exposed cohort representative	Nonexposed cohort representative	Exposure (risk factor) ascertained	Outcome of interest not present at start of study	Cohorts comparable on basis of design/analysis	Blinded outcome assessors (N/A) Outcome adequately assessed	Adequate follow-up duration	Multivariable regression	Summary
Shah et al. 2017[53]	Yes	Yes	Administrative data	At least 6 months of continuous pharmacy enrollment without an opioid prescription before their first opioid prescription	Yes	Opioid prescription/ Discontinuation	1 year	Yes	Low
Sun et al. 2016[47]	Yes	Yes	Administrative data	No opioid prescription for 12 months prior to procedure	Yes	Opioid prescriptions	Up to 365 days	Yes	Low
Swenson et al. 2017[41]	Yes	Yes	Administrative data	No opioid scripts for 8 months to 30 days prior to surgery	Yes	Opioid prescriptions	6 months postoperative	Yes	Low

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